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Neha A Nimbark
Department of Obstetrics and Gynecology, Parul Institute of Medical Sciences and Research, Vadodra, Gujarat, India

Corresponding Author:
Neha A Nimbark
Department of Obstetrics and Gynecology, Parul Institute of Medical Sciences and Research, Vadodra, Gujarat, India

Morbidity of metabolic syndrome in endometrial cancer versus at a tertiary care hospital

Neha A Nimbark

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Abstract
Objective: To investigate the morbidity of metabolic syndrome (MS) in endometrial cancers patients (EC) and explore the relationship between endometrial cancers and metabolic syndrome.
Methods: 50 cases of endometrial cancers were enrolled as study group, 100 cases of uterine fibroids were enrolled as control group. Clinical characteristics of the two groups were compared. Morbidity of metabolic syndrome in both groups was calculated. Minitab version17 software was used for statistical analysis
Results: Compared with the control group, systolic blood pressure, diastolic blood pressure, body mass index (BMI), abdominal circumference, the fasting blood glucose, fasting blood insulin, plasma triglycerides, morbidity of metabolic syndrome (47.50% *vs.* 19.25%) in study group were significantly increased (all P<0.05). The level of high-density lipoprotein cholesterol in study group was lower than it in control group (P<0.05).
Conclusion: The morbidity of MS in endometrial cancers patients is higher.

Keywords: endometrial cancers, metabolic syndrome, morbidity, clinical characteristics

Introduction
In India, endometrial cancer is third most common gynecologic malignancy. In India, the total number of estimated new cases of endometrial cancer in 2018 is 13,328 with an estimated 5010 deaths [1]. The age standardized incidence rate (ASIR) of endometrial cancer in India is 2.1/100,000 women [1]. Uterine fibroids are the most common benign gynecological neoplasm. The metabolic syndrome (MS) (also known as syndrome X or dysmetabolic syndrome) is a confluence of clinical risk factors that tend to occur together for cardiovascular disease and type 2 diabetes and comprises of a growing problem around the world. Metabolic syndrome (MS) is a clustering of at least three of the five following medical conditions: central obesity, high blood pressure, high blood sugar, high serum triglycerides, and low serum high-density lipoprotein (HDL) [2]. Obesity, diabetes and hypertension are often associated with endometrial cancer. These conditions are commonly referred to as the Metabolic Triad of Endometrial Cancer. The incidence of MS is increasing year by year; on the other hand, more and more studies support the emerging hypothesis that MS may be an important etiologic factor for the development and progression of endometrial cancer [3]. So we aimed to investigate the morbidity of MS in EC patients and to explore the relationship between EC and MS. This study was retrospectively analyzed the clinical data of patients suffered from EC in our hospital and reported as follows.

Materials and Methods
Study population
This is a retrospective case control study of 50 cases of Endometrial Carcinoma who were treated in a single unit of the hospital from April 2010 to March 2012 (2 years) conducted at the Department of Gynecological Oncology G.C.R.I, Ahmedabad. These 50 cases (study group) with newly diagnosed histological proven disease and had full clinical and pathological data in our hospital. 100 cases (control group) with fibroids were randomly selected from the same period. Two groups had no family history of hereditary diseases, without addiction of smoking and alcohol, and had no history of exposure to oral contraceptive pills or hormone replacement therapy within 1 year.

Methods
Cases and controls were interviewed during their hospital stay by trained interviewers using a

well structured questionnaire, including information on socio-demographic characteristics, anthropometric measures, lifestyle habits (e.g. tobacco smoking, alcohol drinking, and dietary habits), personal history of selected medical conditions, family history of cancer, menstrual and reproductive factors, and use of oral contraceptives pills (OCP) and hormone replacement therapy (HRT). Data of age at menarche, age at incidence, menopausal status and parity in two groups were analyzed. All patients were measured and recorded for blood pressure, weight, height, waist circumference (2 cm above the umbilicus), Body mass index (BMI) was computed according to Quetelet's index (weight/height^2, kg/m^2).The fasting plasma glucose, fasting insulin, HbA1c and lipids were tested by sampled intravenous blood preoperatively. Metabolic syndrome was diagnosed reference to guidelines of the International Diabetes Federation criteria, namely, central obesity as the core of a group of metabolic syndrome, for Asian women, must comply with the waist circumference ≥ 80 cm, and at least meet two of the following four items: triglycerides ≥ 150 mg/dl or have received treatment, high-density lipoprotein cholesterol < 50 mg/dl or have received corresponding treatment, blood pressure: systolic blood pres-sure ≥ 130 mmHg and (or) diastolic blood pressure ≥ 85 mmHg or have received corresponding treatment or have been diagnosed hypertension previously, hyperglycemia: fasting plasma glucose ≥ 100 mg/dl or have been diagnosed with impaired glucose tolerance, type 2 diabetes or have received treatment.

Statistical methods

Minitab version 17 software was used for statistical analysis. The measurement data was presented as $x \pm s$ [x refers to a sample mean and s refers to the standard deviation of a sample] and was compared using t test. The data was compared using the χ^2 test. P<0.05 was considered statistically significant.

The clinical features in endometrial cancers and fibroids patients: As shown in the Table 1, there were no significant difference about age at menarche, age at incidence, menopausal status and parity between both groups (all P>0.05).

Table 1: Comparison of the clinical features between two groups ($x \pm s$) where x is mean and s is standard deviation for Age and Parity; n(%) where n is for number of women is pre and post menopausal status.

Group	N=	Age at menarche (years)		Age at incidence (years)		Menopausal status N (%)		Parity (number of times)	
		X	s	*x*	s	Pre	post	*x*	s
Case group	50	12.22	3.7	47.8	9.1	18(36)	32(64)	2.8	0.9
Control group	100	12.50	2.9	49.2	7.5	42(42)	58(58)	3.19	1.56

Results of physical examination in endometrial cancers and fibroids patients: As shown in the Table 2, compared with the control group, systolic blood pressure, diastolic blood pressure, body mass index (BMI) and waist circumference in study group were significantly increased (all Results of physical examination in gynecologic cancers and fibroids patients ($x \pm s$) [a]P<0.05.

Table 2

Group	N	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Body Mass Index (kg/m^2)	Waist Circumferance (cm)
Case	50	130±11[a]	87±11[a]	28±3.2[a]	89±8[a]
Control	100	114±13	75± 8	24±1.9	78±5

(P<0.05).

Results of laboratory examinations in endometrial cancers and fibroids patients: Compared with the control group, the fasting blood glucose, fasting blood insulin, plasma tri-glycerides and HbA1c in study group were significantly increased (Table 3) (P<0.05). The level of high-density lipoprotein cholesterol in study group was lower than it in control group (Table 3) (P<0.05).

Table 3: Results of laboratory examinations in EC and fibroids patient (x± s)

Group	N	Fasting Glucose (mg/dL)	Fasting Insulin (μIU/ml)	Triglycerides (mg/dL)	HDL High-Density Lipoprotein (mg/dL)	HbA1c Levels (%)
Case	50	117.12± 52.2	8.9±4.7[a]	282.55 ±170[a]	48.22±15	6.5±1.5[a]
Control	100	84.68±16.22	5.3±3.0	138.18±109	60.5±17.78	5.7±2

[a]P<0.05 ;
HDL: high-density lipoprotein

Morbidity of metabolic syndrome in endometrial cancers and fibroids patients

As shown in the Table 2, compared with the control group, morbidity of metabolic syndrome in study group was significantly higher than that it in control group (47.50% *vs.* 19.25%) (P<0.05).

Discussion

Endometrial cancer is the most common cancer of the female reproductive tract and the 4th most common cancer in women in the developed world [4]. Endometrial cancer is the most common cancer of the female reproductive tract and the 4th most common cancer in women in the developed world [4]. In India, it is third most common gynecologic malignancy [5]. Data from population based registries under the National Cancer Registry Program indicate that the leading sites of cancer among women are the cervix uteri, breast, and oral cavity [6]. About 50-60% of all cancers among women in India are related mainly to the four organs; cervix uteri, breast, corpus uteri, and ovaries [6].

Metabolic syndrome (syndrome X, insulin resistance) is a multiplex risk factor that arises from insulin resistance accompanying abnormal adipose deposition and function.

Obesity, diabetes and hypertension often coexist in patients with endometrial cancer, which increases the risk of endometrial cancer, also known as the "triple syndrome of endometrial cancer." In 2005, the International Diabetes Foundation (IDF) published new criteria for metabolic syndrome [7]. Although it includes the same general criteria as the other definitions (image 1), it requires that obesity, but not necessarily insulin resistance, be present. Of the various definitions for the metabolic syndrome, the NCEP ATP III definition is the easiest to apply clinically and epidemiologically, because it uses straightforward criteria that are measured readily [8]. Adult overweight/obesity is one of the strongest risk factors for endometrial cancer, accounting for approximately 40% of endometrial cancer incidence in developed countries [9]. The prevalence of metabolic syndrome in the United States (according to National Cholesterol Education Program/Adult Treatment Panel III criteria) has been estimated at 23% among non-diabetics in the Third National Health and Nutrition Examination Survey (NHANES) [10]. Endometrial cancer development is strongly linked to lifestyle factors [11].

	NCEP-III: US National Cholesterol Education Program Adult Treatment Panel III	IDF (2005)
Absolutely required	None	Central obesity (waist circumference[§]): ≥94 cm (M), ≥80 cm (F)
Criteria	Any three of the five criteria below	Obesity, plus two of the four criteria below
Obesity	Waist circumference: >40 inches (M), >35 inches (F)	Central obesity already required
Hyperglycemia	Fasting glucose ≥100 mg/dl or Rx	Fasting glucose ≥100 mg/dl
Dyslipidemia	TG ≥150 mg/dl or Rx	TG ≥150 mg/dl or Rx
Dyslipidemia (second, separate criteria)	HDL cholesterol: <40 mg/dl (M), <50 mg/dl (F); or Rx	HDL cholesterol: <40 mg/dl (M), <50 mg/dl (F); or Rx
Hypertension	>130 mmHg systolic or >85 mmHg diastolic or Rx	>130 mmHg systolic or >85 mmHg diastolic or Rx

Image 1: Definitions of metabolic syndrome

This study analyzed retrospectively the clinical statistics in our hospital. The age of menarche, age of incidence, menopausal status and parity in the study group and control group were compared, and the differences between the study group and control group were not different. Systolic blood pressure, diastolic blood pressure, BMI, waist circumference, fasting glucose, fasting insulin, HbA1c and triglycerides in study group were significantly higher than it in control group. High-density lipoprotein cholesterol in study group was significantly lower than the other group. The incidence of MS in study group was significantly higher than it in control group. Those results suggested that excluding the contribution of age and female hormones, MS plays a role in onset and development of EC. Insulin resistance (IR) is considered to be the most crucial preliminary to MS. In a large population-based case-control (515 cases/962 controls) study in Alberta, Canada, Friedenreich *et al*. reported that metabolic syndrome was significantly more prevalent among cases (62%) than controls (38%) and A statistically significant increased risk for endometrial cancer was observed for metabolic syndrome (OR = 1.53; 95% CI: 1.17-2.00), as well as for some of the individual components of metabolic syndrome including waist circumference ≥ 88 cm (OR = 1.57; 95% CI: 1.18-2.08), hypertension (OR = 1.57; 95% CI: 1.18-2.09), and fasting blood glucose ≥ 100 mg/dL (OR = 1.31; 95% CI: 1.03-1.67) [12]. In our study, the morbidity of MS in the patients with endometrial cancer were significantly higher than it in control group, it suggested that MS may be a potential contributing factor of occurrence and development of this gynecological cancer. Endometrial cancer is considered to be the most closely associated with MS in all gynecological malignancies, Rosato *et al.* analyzed 454 cases of endometrial cancer and 798 cases of healthy control, and the multivariate OR values of endometrial cancer with type 2 diabetes, hypertension, hyperlipidemia and BMI >30 kg/m were 22.18, 1.77, 1.20 and 3.83 respectively, and there was a direct correlation between MS and endometrial cancer [13]. In a pooled analysis of seven cohort studies in northern Europe (cohort ~290,000 women, 917 endometrial cancer cases), Bjorge and colleagues reported increased risk of endometrial cancer per unit increase in metabolic syndrome score (RR (95% CI) 1.37 (1.28–1.46)), which was calculated using the sum of Z-scores for measured BMI, blood pressure, glucose, total cholesterol, and triglycerides, quantified in pre-diagnostic specimens (primarily non-fasting) [14]. In line with previous epidemiological data, we observed a strong association between endometrial cancer risk and obesity, as measured by both BMI and waist circumference [15].

In a case-control study within the SEER-Medicare linked database it was examined whether metabolic factors, individually or combined, were associated with endometrial cancer. Endometrial cancer risk was associated with metabolic syndrome [OR (95% CI): 1.39 (1.32–1.47)] and its component

factors: overweight/obesity [1.95 (1.80–2.11)], impaired fasting glucose [1.36 (1.30–1.43)], high blood pressure [1.31 (1.25–1.36)], and high triglycerides [1.13 (1.08–1.18)]. After adjusting for overweight/obesity, the increased risks associated with the metabolic syndrome factors remained [3]. A prospective case control study reported that women newly diagnosed with endometrial cancer have a higher prevalence of incident hyperglycemia, total: HDL cholesterol ratio, and three or more cardiovascular risk factors than women without endometrial cancer [16]. A meta-analysis of six studies reported that metabolic syndrome is closely associated with increased risk of endometrial cancer in women (relative risk: 1.89, 95% CI 1.34–2.67) [17]. A new research reported that there was a very high prevalence of metabolic syndrome in women newly diagnosed with endometrial cancer [18]. A case–control study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC) examined the relation between prediagnostic plasma lipids, lipoproteins, and glucose, the metabolic syndrome (MetS; a cluster of metabolic factors) and endometrial cancer risk suggest that metabolic abnormalities and obesity may act synergistically to increase endometrial cancer risk, the mean age of women at baseline was 56.9 years when compared with control subjects, women who developed endometrial cancer during follow-up were more likely to be obese, nulliparous, report having hypertension, have a later age at menopause or earlier age at menarche, and were less likely to have used OCs in the past [19]. The presence of the MetS (metabolic syndrome) at baseline was associated with a 2.1-fold increased endometrial cancer risk using the NCEP definition and a 1.7-fold increased risk using the IDF definition [19]. Another prospective study reported a 1.9-fold increased risk (95% CI 0.84–4.34) associated with a cluster of similar metabolic abnormalities (excluding obesity) [20].

Our results were similar with the relevant literature; the incidence of MS in EC patients was significantly higher than it in control group. Our results suggested that MS increases the incidence of EC, and possibly plays a potential role in occurrence and development of EC. So larger sample may be helpful for increase evidence-based studies but further research remains to be confirmed to reveal the underlying mechanism in the future.

Conclusion

In a word, there is relevance between EC and MS. The clinicians should fully understand that the incidence of EC may be increased with increased prevalence of MS, and should be aware of the importance of control of excessive weight, high blood pressure, high blood glucose, deranged lipids and insulin resistance of female. Gynecologists should counsel high-risk group, and detect a variety of risk factors associated with MS. So those measures should have positive significance to prevention and control of this gynecological malignancy.

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