Prevalence and Characteristics of Polycystic Ovary Syndrome (PCOS) in Filipino Women Diagnosed with Endometrial Cancer: A Five-year Retrospective Study

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Objective: To determine the prevalence and characteristics of PCOS among Filipino women diagnosed with endometrial cancer.
Methodology: A review of women with histopathologically-confirmed endometrial carcinoma treated at the Philippine General Hospital from June 2010 to June 2015 was performed. Data were extracted regarding age at diagnosis of endometrial cancer, gravidity, parity, menstrual history, presence of polycystic ovaries on ultrasound, body mass index, abnormal blood glucose, histologic type and stage of the disease at the time of diagnosis of endometrial cancer.
Results: Sixty-one out of 487 (12.53%) endometrial cancer patients were identified to have PCOS. Thirty-four percent of those identified were diagnosed with endometrial cancer at ages 30 to 39 (p=0.00). Majority were nulligravid (80.33%) and nulliparous (81.97%). There was direct correlation with obesity with highest prevalence seen in Obese Type II (62.30%, p=0.00). Prevalence of diabetes mellitus in those identified PCOS was statistically significant (78.69%, p=0.00). Prevalence of endometrial Type I cancer and Stage I disease were 78.69% and 62.30%, respectively, but both were not statistically significant.
Conclusion: There is increased prevalence of PCOS in endometrial cancer patients who are at the premenopausal age group (30-39 years old) and they are likely nulligravid, nulliparous, obese, with a history of abnormal blood glucose.

Key words: endometrial carcinoma, Polycystic Ovary Syndrome (PCOS), prevalence

Introduction

To date, endometrial cancer is the most common gynecologic malignancy and is the leading cause of cancer-related deaths in women worldwide.[1,2] Although more prevalent in Western countries, there has been increasing trend of endometrial cancer cases seen in Asian countries in recent years.[3] In the Philippines, endometrial cancer ranks third after cervical and ovarian cancer. Endometrial cancer is statistically a disease in the postmenopausal period with a mean age of diagnosis at 61 years.[4] However, studies have shown endometrial cancer in 20-25% of premenopausal women with 5% of all cases diagnosed at less than 40 years old.[1,2,5] Interestingly, the increased proportion of endometrial cancer seen in young women is associated with early stage disease, well-differentiated Type 1 cancer, with good tumor prognosis.[6] There is a window of opportunity to identify those at risk for endometrial cancer at an early stage and avoid hysterectomy, particularly in reproductive age women with primary infertility.[7] Increasing evidence also show increased risk in those with menstrual irregularities, an indication of chronic anovulation that is related to hyperandrogenism.

A recent systematic review revealed up to three folds risk of endometrial cancer with obesity.[8] In addition, other studies show that insulin resistance, the presence of elevated free insulin-like growth factor-I, and Type 2 diabetes mellitus were observed to be strongly associated with the disease.[9] These risk factors point to one common entity that combines most, if not all, of the clinical and metabolic causes of endometrial cancer, the Polycystic Ovary Syndrome (PCOS).

A recent meta-analysis of pooled data from five comparative studies on endometrial cancer revealed that the risk of developing endometrial cancer was three times higher in women with PCOS compared to those without the disease.[10] Therefore, young premenopausal women with PCOS in particular, are at higher risk.[7,8,11,12]

PCOS is the most common female endocrinologic disorder affecting 4-18% of reproductive-age women.[2,13] Women with PCOS classically manifest with signs of hyperandrogenism, menstrual irregularities, and polycystic ovaries. The chronic anovulatory state induced by elevated androgen levels in PCOS leads to persistent progesterone deficiency. In effect, there is prolonged and unopposed endometrial exposure to the proliferative and anti-apoptotic effects of estrogen that leads to endometrial hyperplasia and even cancer development.[9,13,14] PCOS is associated with Metabolic syndrome that includes obesity, hyperinsulinemia, and diabetes mellitus. All these have direct and indirect mechanisms that predispose to neoplastic changes in the endometrium.[15,16] This is supported by several studies that explain this relationship.1,9,10 Women with PCOS, thereby, have several risk factors for endometrial cancer10 especially in the young premenopausal subgroup.[7,8,13] To date, there are only a few epidemiological studies that support the hypothesis that PCOS predisposes to endometrial cancer in premenopausal women.[7,8,11,17] It is the aim of this study to further investigate the association of PCOS and endometrial cancer in the population of Filipinas. It has public health significance given the 4-18% prevalence of PCOS in the reproductive age group. Identification of the subgroups at greatest risk will allow early cancer detection and make conservative, nonsurgical, hormonal therapy, fertility-sparing treatment options available especially for patients still desirous of pregnancy. Furthermore, primary preventive measures such as lifestyle changes can be advocated to women with PCOS and address modifiable risk factors for Metabolic Syndrome and endometrial cancer.

Review of Related Literature

Globally, there has been an increasing trend of endometrial cancer cases in recent years.[16] This trend is projected to double in the next 20 years. The rising incidence is attributed mostly to Type 1 endometrial cancer or the estrogen-dependent histologic type.[19] Hyperstimulation of the endometrium by estrogen unopposed by progesterone via anovulation, hyperandrogenism, insulin resistance, and obesity results in endometrial hyperplasia leading to cancer development.[14] These clinical and metabolic characteristics are features seen with a high prevalence in PCOS women. In a 2014 systematic review, women affected with PCOS had a three-fold risk of endometrial cancer with risk escalating three times in obese women.[16]

Using the definition of the 2003 Revised Rotterdam Criteria, polycystic ovary syndrome is a condition of ovarian dysfunction which has hyperandrogenism and a distinct polycystic ovarian morphology as its cardinal features.[20] Its clinical manifestations include menstrual irregularities, signs of excess androgens, and obesity. Metabolic derangements such as insulin resistance, impaired glucose tolerance, and diabetes mellitus are also common features in PCOS. Insulin resistance is a significant determinant of endometrial cancer.[9]

Despite endometrial cancer being a disease in the postmenopausal women, 5% of affected women belong to the younger age group below 40 years old. Many of them suffer from subfertility, obesity, and features attributable to PCOS.

Since surgery is the definitive treatment for endometrial cancer, this has reproductive significance for those women with PCOS. Despite the theoretical risk, there are limited

epidemiological evidences both local[21] and abroad relating PCOS and its associated metabolic attributes in young women with endometrial cancer.

This is the first study conducted involving endometrial cancer patients being evaluated for a possible association with PCOS. No similar study has been done locally.

Objectives

General Objective:

To determine the prevalence of PCOS among women diagnosed with endometrial cancer.

Specific Objectives:

- To determine the prevalence of PCOS in the different age groups of women with endometrial cancer
- To determine the prevalence of PCOS in women diagnosed with endometrial CA with and without the associated metabolic features of obesity and/or diabetes mellitus or impaired glucose tolerance.
- To determine the prevalence of PCOS in the different histologic types of endometrial cancer
- To determine the prevalence of PCOS in endometrial cancer by cancer stage
- To determine the prevalence of PCOS with and without the associated metabolic features of obesity and/or diabetes mellitus or impaired glucose tolerance in the different endometrial cancer stage

Materials and Methods

Research Design

This is a 5-year prevalence study that involved a chart review to evaluate the relationship between PCOS and histologically confirmed endometrial cancer using data of patients treated in a tertiary hospital in the Philippines from the period of June 1, 2010 to June 30, 2015.

Patient Population

The study population consisted of all registered endometrial cancer patients treated at the Philippine General Hospital within June 1, 2010 to June 30, 2015. Women included in the study had no other known co-existing gynecologic or non-gynecologic malignancy at the time of diagnosis of endometrial cancer. Excluded from the study were women with no preoperative transvaginal or transabdominal ultrasound, those who underwent incomplete surgical staging for the endometrial cancer at another institution, and those with incomplete data.

Sample Size

The study included all patients diagnosed with endometrial cancer, treated at the Philippine General Hospital from the period of June 1, 2010 to June 30, 2015 who fulfilled the inclusion and exclusion criteria.

Description of Study Procedure

After obtaining approval from the Expanded Hospital Research Office (EHRO), a detailed chart review of all endometrial cancer patients treated at the Philippine General Hospital from the period of June 1, 2010 to June 30, 2015 was conducted. Medical records of those who met the inclusion and exclusion criteria were reviewed and the following individual clinical parameters were extracted and recorded in a patient data form including: age at diagnosis of endometrial cancer, gravidity, parity, educational background, menstrual history, presence of polycystic ovaries on ultrasound, body mass index, personal history of diabetes mellitus or impaired glucose tolerance, surgical pathology report, and stage of the disease at the time of diagnosis of endometrial cancer.

PCOS was evaluated following two out of the three set conditions in the 2003 Revised Rotterdam criteria namely presence of oligo- and/or amenorrhea and polycystic ovarian morphology. Clinical and biochemical signs of hyperandrogenism cannot be extracted from the charts because it was not recorded and was not

included in the criteria. According to the study done by Manalo et al18, Filipino PCOS women are less androgenic compared to other racial groups. Therefore, hyperandrogenism as criterion could underestimate the exact pool of PCOS women gathered if included in this study.

The presence of metabolic features such as BMI was defined according to the Asia Pacific Obesity Classification and blood sugar abnormalities like Diabetes mellitus or impaired glucose tolerance were based on the 2006 WHO recommendations. Cancer stage at the time of diagnosis of endometrial cancer was classified according to the 2009 FIGO Surgical Staging System. Flowchart of the methodology is provided in Figure 1.

Data Analysis

After data collection, the information was encoded in the datasheet. Data were processed using the open software CDC Epi Info 7.0. Baseline demographic characteristics of the population such

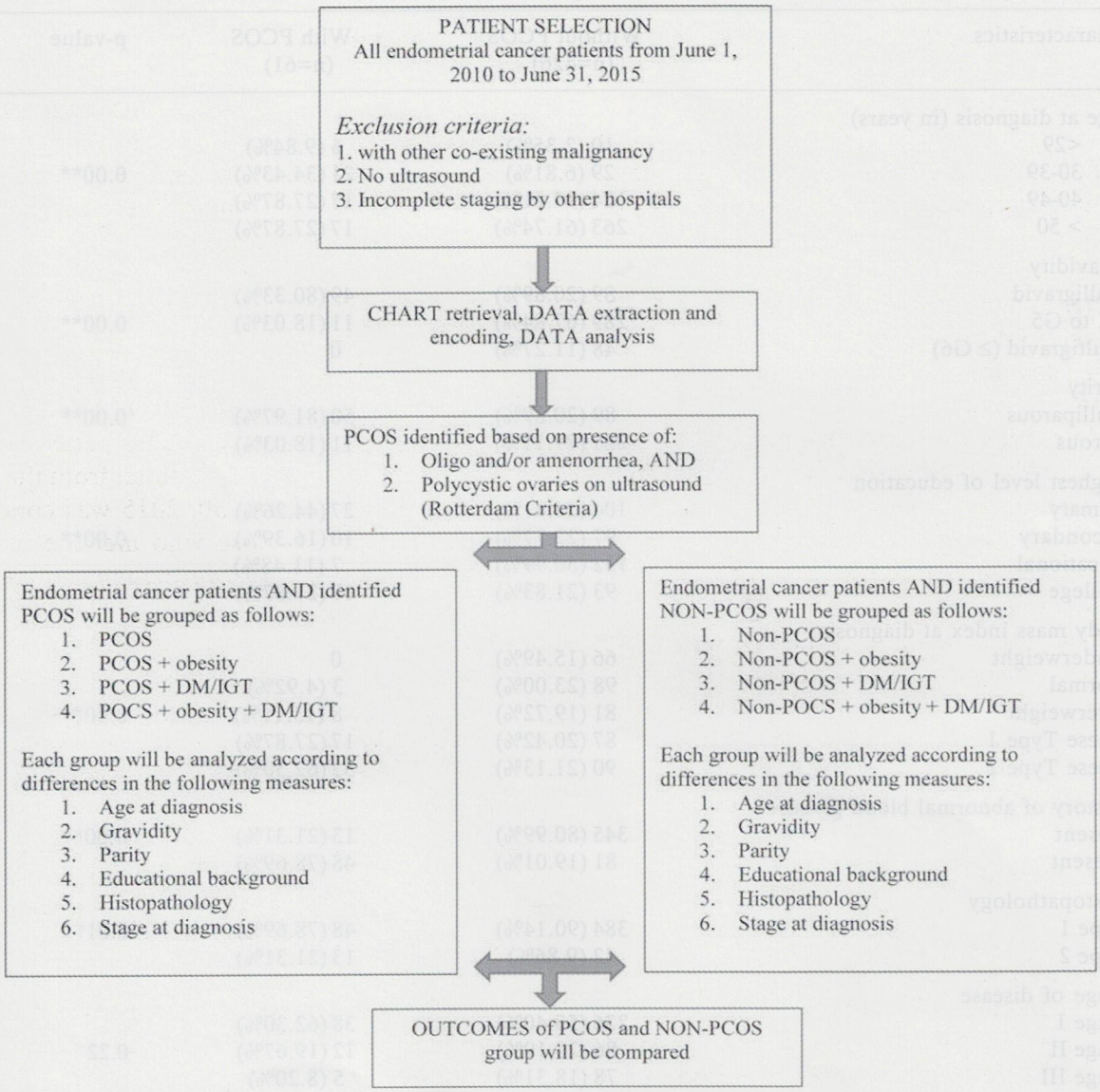

Figure 1. Flowchart of the methodology, data collection and analysis.

as age, gravidity, parity, and body mass index were expressed using frequency and percentage for categorical variables, or mean and standard deviation for continuous ones.

Measures of disease prevalence and prevalence differences were computed from the data on the presence of obesity, diabetes mellitus or impaired glucose tolerance test among endometrial carcinoma with PCOS. Categorical data were analyzed using the Pearson's chi squared test while continuous data were analyzed using the independent t-test, or their non-parametric equivalents if needed. Statistical significance was set as $p < .05$.

Results

A total of 910 charts of endometrial cancer patients were retrieved from the registry of a tertiary hospital in the Philippines from the period of June 1, 2010 to June 30, 2015 (Figure 2). Of these, only 487 (53.52%) met the inclusion criteria while 423 (46.48%) were excluded because patients

Table 1. Baseline characteristics of the eligible study population with endometrial cancer.

Characteristics	Without PCOS (n=426)	With PCOS (n=61)	p-value
Age at diagnosis (in years)			
<29	10 (2.35%)	6 (9.84%)	
30-39	29 (6.81%)	21 (34.43%)	0.00**
40-49	124 (29.11%)	17 (27.87%)	
> 50	263 (61.74%)	17 (27.87%)	
Gravidity			
Nulligravid	89 (20.89%)	49 (80.33%)	
G1 to G5	289 (67.84%)	11 (18.03%)	0.00**
Multigravid (≥ G6)	48 (11.27%)	0	
Parity			
Nulliparous	89 (20.89%)	50 (81.97%)	0.00**
Parous	337 (79.11%)	11 (18.03%)	
Highest level of education			
Primary	104 (24.41%)	27 (44.26%)	
Secondary	97 (22.77%)	10 (16.39%)	0.00**
Vocational	132 (30.99%)	7 (11.48%)	
College	93 (21.83%)	17 (27.87%)	
Body mass index at diagnosis			
Underweight	66 (15.49%)	0	
Normal	98 (23.00%)	3 (4.92%)	
Overweight	81 (19.72%)	8 (13.11%)	0.00**
Obese Type 1	87 (20.42%)	17 (27.87%)	
Obese Type 2	90 (21.13%)	33 (62.30%)	
History of abnormal blood glucose			
Absent	345 (80.99%)	13 (21.31%)	0.00**
Present	81 (19.01%)	48 (78.69%)	
Histopathology			
Type 1	384 (90.14%)	48 (78.69%)	0.01*
Type 2	42 (9.86%)	13 (21.31%)	
Stage of disease			
Stage I	236 (55.40%)	38 (62.30%)	
Stage II	86 (20.19%)	12 (19.67%)	0.22
Stage III	78 (18.31%)	5 (8.20%)	
Stage IV	26 (6.10%)	6 (9.84%)	

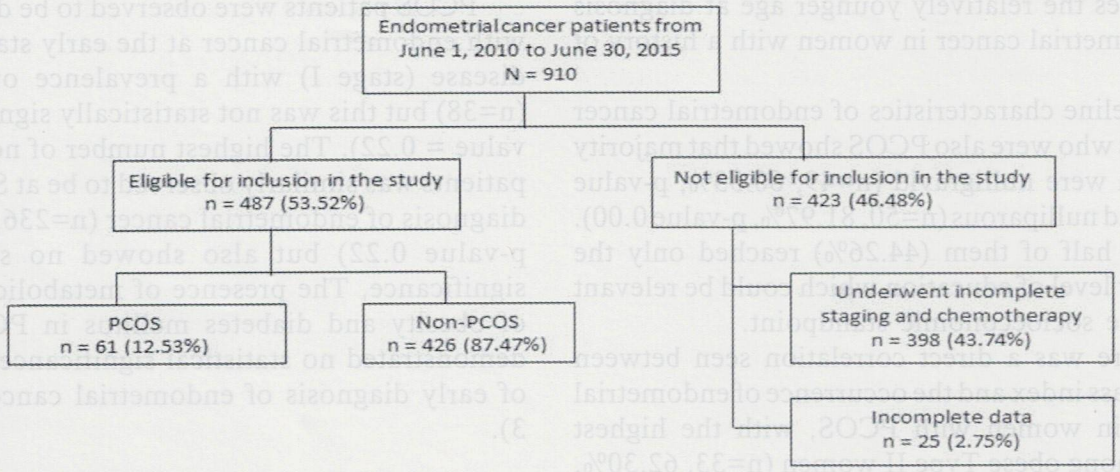

Figure 2. Analysis status of eligible study subjects, endometrial cancer patients evaluated for PCOS from June 1, 2010 to June 30, 2015.

were either already subjected to a previous operation and underwent incomplete surgical staging, and/or for chemotherapy, or had incomplete data to allow for analysis.

A total of 61(12.53%) subjects out of the 487 endometrial cancer patients eligible for study met the aforestated definition of PCOS having both menstrual irregularity and polycystic ovarian morphology on ultrasound (Table 2). The prevalence of PCOS among the total number of population is 15.27% compared to the 12.53% prevalence of PCOS in eligible subjects. This shows no significant difference and may allow for statistical analysis of the eligible group despite the exclusion of a number of patients from the study.

Table 2 shows the basaline characteristics of the study population. Most of these patients with PCOS were first diagnosed with endometrial cancer at ages between 30 and 39 (n=21, 34.43%, p-value 0.00). In contrast, endometrial cancer patients without PCOS had a mean age of diagnosis at ages beyond 50 (n=476, 61.74%, p-value 0.00). This

Table 2. Prevalence of PCOS among women diagnosed with endometrial cancer who were treated at the Philippine General Hospital, June 1, 2010 to June 30, 2015.

	ALL patients	Patients eligible for inclusion in the study
Eligible for Inclusion in the Study	Yes: 487 (53.52%) No: 423 (46.48%)	Yes: 487 No: 0
Experience of Operation or Chemotherapy	Yes: 398 (43.74%) No: 512 (56.26%)	Yes: 0 No: 0
Incomplete Data	Yes: 7 (0.77%) No: 903 (99.23%)	Yes: 0 No: 0
Menstrual History	Regular: 746 (81.98%) Irregular: 164 (18.02%)	Regular: 415 (85.22%) Irregular: 72 (14.78%)
Polycystic ovaries on ultrasound	Yes: 144 (15.82%) No: 766 (84.18%)	Yes: 64 (13.14%) No: 423 (86.86%)
Prevalence of PCOS among women with endometrial cancer between June 2010-2015	(139/910) = 15.27%	(61/487) = 12.53%

illustrates the relatively younger age at diagnosis of endometrial cancer in women with a history of PCOS.

Baseline characteristics of endometrial cancer patients who were also PCOS showed that majority of them were nulligravid (n=49, 80.33%, p-value 0.00) and nulliparous (n=50, 81.97%, p-value 0.00). Almost half of them (44.26%) reached only the primary level of education which could be relevant from the socioeconomic standpoint.

There was a direct correlation seen between body mass index and the occurrence of endometrial cancer in women with PCOS, with the highest seen among obese Type II women (n=33, 62.30%, p-value 0.00). In contrast, such correlation is not evident among endometrial cancer patients without PCOS, with the highest count seen in patients with normal BMI (n=98, 23.00%, p-value 0.00). This suggests that obesity may be an important parameter to look at for increased risk of endometrial cancer particularly in patients with PCOS than in the general population. Similarly, significant number of endometrial cancer patients with PCOS also showed presence of abnormal blood glucose at the time of diagnosis (n=48, 78.69%, p-value 0.00).

The estrogen-dependent Type 1 cancer was more prevalent than the non-estrogen dependent Type 2 endometrial cancer in patients with concomitant PCOS (n=48, 78.69%, p-value 0.01). However, similar finding was demonstrated in patients without PCOS and could suggest that Type 1 endometrial cancer is the more common type of endometrial cancer in the general population, regardless of PCOS status.

PCOS patients were observed to be diagnosed with endometrial cancer at the early stage of the disease (stage I) with a prevalence of 62.30% (n=38) but this was not statistically significant (p value = 0.22). The highest number of non-PCOS patients was similarly observed to be at Stage I on diagnosis of endometrial cancer (n=236, 55.40%, p-value 0.22) but also showed no statistical significance. The presence of metabolic features of obesity and diabetes mellitus in PCOS also demonstrated no statistical significance in terms of early diagnosis of endometrial cancer (Table 3).

Discussion

Several studies including a meta-analysis on endometrial cancer have shown increased risk of developing endometrial cancer in women with PCOS compared to those without the disease.[10] In our study, it accounts for about a significant 12.53% prevalence among the target population. However, only a few epidemiological studies have investigated on the association of PCOS and the development of endometrial cancer particularly in the young premenopausal age group.[7,8,11,17] The present study demonstrates a significant prevalence of PCOS (34.43%) among diagnosed endometrial cancer patients in the 30-39 age group. Furthermore, patients diagnosed with endometrial cancer at an earlier age < 29 years old showed higher prevalence of PCOS characteristics at 9.84% compared to those without PCOS at 2.35% (p-value = 0.00). This supports the hypothesis that

Table 3. Comparison of outcomes among patients with endometrial cancer.

	Stage I (n=274)	Stage II (n=98)	Stage III (n=83)	Stage IV (n=32)	p-value
PCOS with NO Obesity	243 (88.69%)	87 (88.78%)	79 (95.18%)	28 (87.50%)	0.35
PCOS with Obesity	31 (11.31%)	11 (11.22%)	4 (4.82%)	4 (12.50%)	
PCOS with NO DM	247 (90.15%)	88 (89.80%)	78 (93.98%)	26 (81.25%)	0.24
PCOS with DM 27 (9.85%)	10 (10.20%)	5 (6.02%)	6 (18.75%)		
PCOS with NO Obesity and DM	250 (91.24%)	89 (90.82%)	79 (95.18%)	28 (87.50%)	0.53
PCOS with Obesity and DM	24 (8.76%)	9 (9.18%)	4 (4.82%)	4 (12.50%)	

PCOS predisposes to endometrial cancer in young premenopausal women with which intervention for endometrial cancer is crucial especially for those still desirous of pregnancy.

A high percentage of nulligravid endometrial cancer patients (80.33%, p-value = 0.00) in this study were also noted to have PCOS. It is not known, however, if this pool of patients had a history of primary infertility. Brinton et al found a 3.1-fold increased risk of endometrial cancer associated with chronic anovulation[7], while Jitti, et al. corroborated in their own investigation the likelihood of younger patients with endometrial cancer to have a history of chronic anovulation, nulliparity, and PCOS.[6]

Literatures including a recent systematic review[8] showed a three-folds risk of endometrial cancer with obesity. A study done by Xin Li, et al. showed that PCOS and obesity are associated with the development of endometrial cancer.[1] This is consistent with our own study which showed an increasing trend of risk for endometrial cancer with increasing body mass index in patients with PCOS with the highest risk seen in patients who are obese Type II. This trend, however, was not seen in endometrial cancer patients without PCOS.

This study also corroborated studies of Hanprasertpong J, et al. and Nan Mu, et al. that Diabetes Mellitus, a metabolic feature of PCOS, is strongly associated with endometrial cancer through the direct and indirect neoplastic mechanisms of hyperinsulinemia.[6,9]

A comparison of outcomes in terms of cancer stage was done to determine the aggressiveness of endometrial cancer based on the presence of PCOS with and without its associated metabolic features, but all comparisons resulted in no statistical significance.

Conclusion

In summary, we observed an increased prevalence of PCOS in endometrial cancer patients who are at the premenopausal age group (30-39 years old). Furthermore, these set of patients are observed to be more likely nulligravid, nulliparous, obese, with a history of abnormal blood glucose. The histological type of endometrial cancer which is more prevalent in PCOS patients is the well-differentiated type with a good tumor prognosis. Therefore, early screening and detection for endometrial cancer would benefit this high-risk group. Advice on lifestyle modification would address the associated modifiable risk factors for endometrial cancer in women with PCOS.

Recommendation

A high number of initial subjects were excluded from the study although the overall prevalence percentage of the eligible patients for analysis did not significantly differ from the prevalence of PCOS in the total population of endometrial cancer patients. On internal analysis, the excluded group such as those who have undergone previous surgery and/or have incomplete data may have added statistical significance in some of the outcome measures, if they were included. The study included only the PCOS phenotype as defined by ultrasound characteristics and presence of oligo and/or amenorrhea. Other phenotypes as defined by presence of hyperandrogenism were not included in the study because such data cannot be extracted from the charts. Only patients with preoperative ultrasound were evaluated for the polycystic ovarian morphology and this could have underestimated the true number of the target population.

This study observed only an association of PCOS with endometrial cancer especially in the premenopausal women but did not demonstrate a direct causality of PCOS with the development of endometrial cancer in that age group. It is suggested that a well-designed prospective cohort study should be done to establish causality.

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