Research Article

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Preliminary Pilot Study for the Incidence of Association between PCO and Endometrial Hyperplasia / Endometrial Cancer in KHUH Patient in 2018

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ABSTRACT

Introduction: *PCOS syndrome is a common endocrine disease in females. Previous studies have stated that PCOS is associated with an increased risk of endometrial hyperplasia and cancer. This study aims to investigate the feasibility of using the HOPE system in KHUH for exploring the association between PCOS and Endometrial hyperplasia and cancer.*

Methods: *A retrospective cross-sectional study to find the incidence of association between PCOS and Endometrial cancer cases following up in King Hamad University Hospital (KHUH) and Bahrain Oncology Center (BOC) in 2018.*

Results: *A total of 241 women included in our study. A total of 165 women were diagnosed with PCOS in 2018, and a total of 55 women that underwent endometrial sampling, and 21 women diagnosed with endometrial cancer. No significant relationship between PCOS and EH and EC. High BMI was found significant in all sample groups.*

Conclusion: *Our study showed that there is a link between PCOS and EC but the percentages are very low. A large prospective study with a control group would provide further information regarding the relationship between PCOS and EC.*

Keywords

PCOS, Endometrial hyperplasia, Endometrial cancer, Family history.

Abbreviations

BOC: Bahrain oncology center; KHUH: King Hamad University Hospital; PCOS: Polycystic Ovarian Syndrome; EH: Endometrial hyperplasia; EC: Endometrial cancer; US: Ultrasound.

Introduction

Polycystic ovarian syndrome (PCOS) is a common endocrine disease, with a prevalence of 3.4% in the female population globally [1]. It is an important cause of androgen excess, menstrual irregularity and cardiometabolic dysfunction in women. When fully expressed, women may present with irregular menstrual cycles, hirsutism, obesity, insulin resistance and anovulatory infertility.

Guidelines from the Endocrine Society recommend using the Rotterdam criteria for diagnosis, which mandate the presence of two of the following three findings-hyperandrogenism, ovulatory dysfunction, and polycystic ovaries-plus the exclusion of other diagnoses that could result in hyperandrogenism or ovulatory dysfunction [2].

The first line therapy for women with PCOS and obesity is lifestyle modification in the form of a low-calorie diet combined with moderate exercise activities [3]. Beyond lifestyle charges, multiple pharmacological agents are used to treat PCOS and must be multitargeted to address each patient's phenotype, symptoms, personal goals and expectations.

The prevalence of insulin resistance and insulin secretory defects, menstrual dysfunction, and androgen excess is high in patients with PCOS. The irregular metabolic and hormonal status of women with PCOS may increase their risk of some cancer types and other medical conditions. Therefore, at the evaluation of women with PCOS, it is important to exclude risk factors for endometrial cancer, mood disorders, obstructive sleep apnea, diabetes, and cardiovascular disease [4-7].

Endometrial cancer is one of the commonest gynecological cancers that affects women of all ages [8]. The Incidence and prevalence of this disease is increasing worldwide with one of the highest prevalence rates in North America, Northern and Western Europe.

The most common symptom of endometrial carcinoma is abnormal uterine bleeding, postmenopausal bleeding. Intermenstrual bleeding and irregular menstrual cycle can be symptoms that occur in premenopausal women. Other symptoms are vague and not very specific to endometrial cancer, including abdominal pain, pelvic pain and dysuria. Most guidelines recommend transvaginal US followed by Endometrial biopsy to diagnose Endometrial hyperplasia and endometrial cancer [9-12].

Previous studies have stated that PCOS was associated with an increased risk of Endometrial hyperplasia and endometrial cancer. For instance, a study conducted in 2013 found PCOS patients are at a 2.7-fold increasing risk for developing EH or endometrial cancer [13]. Important risk factors for Endometrial cancer often present in women with PCOS are obesity, null parity, infertility, hypertension, diabetes, chronic anovulation, unopposed estrogen and insulin resistance [14].

The exact strength of the association between PCOS and gynecological cancer is unclear. The first meta-analysis about the association between PCOS and cancer risk has found that women with PCOS were at an increased risk of endometrial cancer, but the risk of ovarian and breast cancer was not significantly increased. However, studies report conflicting findings about whether PCOS increases the risk of gynecological cancer. Reliable estimates of the relationship between PCOS and gynecological cancer are important for public health, which can inform medical workers to improve the diagnosis and treatment strategies. Therefore, we conduct this study to qualify the association between PCOS and endometrial cancer [15].

Material and methods

In our research study regarding incidence of association polycystic ovarian syndrome and endometrial hyperplasia and gynecological malignancies, our objective and aim of study is to determine the basis of PCOs and their association with gynecological malignancies and to analyze the different factors wither genetic, environmental, or biochemical.

The type of study that is suitable for our research purpose is retrospective cohort, and our sample size will composed of patient that have established polycystic ovarian syndrome and endometrial cancer, and patient who underwent endometrial sampling in 2018 with selected variables such as demographic data, family history, medical history, previous PCOs treatment, if they underwent any genetic testing, clinical presentation, ultrasound findings, histopathological findings in patients that underwent total abdominal hysterectomy/bilateral sapling-oophorectomy and endometrial sampling. The sample technique used is convenience sampling.

To Navigate and select our intended sample, patient needed data will be collected from KHUH hope system that already have been consented during consultations. The statistical analysis of the data will be analyzed by using SPSS.

Data Analysis

Data was analyzed using SPSS v 25.0. Descriptive statistics was used to compute the frequencies, percentages, mean and standard deviations. Chi-square test was used to compare significant differences between two groups with categorical data. Mann-Whitney tests were conducted to compute the differences between continuous variables. All the statistical tests were 2-tailed, and a p value of <0.05 was considered significant.

Results

There were 165 females who were diagnosed with PCOS in 2018. The patients with PCOS had a mean age of 27.68 ± 7.64. 73 (44.2%) women were single and only 13 (7.9%) had comorbidities. Majority of the patients had no family history of PCOS or endometrial cancer. Abnormal uterine bleeding was seen in 37 patients (22.4%) and abnormal menstrual pattern was seen in 122 (73.9%) patients.

Hirsutism was seen in 82 patients (49.7%) and acne was seen in 42 (25.5%) PCOS patients. Mean FSH among the PCOS patients

was 6.85 ± 6.58 and mean LH was 6.90 ± 4.88. Forty-one (24.8%) patients had LH: FSH ratio greater than one (Table 1).

Table 1: Patients diagnosed with PCOS in 2018.

	PCOS
Age	27.68 ± 7.64
BMI	33.55 ± 18.72
Marital status	
Single	73 (44.2%)
Married/Divorced	92 (55.8%)
Comorbidities*	
Yes	13 (7.9%)
No	152 (92.1%)
Family Hx of PCOS	
Yes	5 (3.0%)
No	133 (80.6%)
Missing	27 (16.4%)
Family Hx of endometrial cancer	
Yes	-
No	127 (77.0%)
Missing	38 (23.0%)
Abnormal uterine bleeding**	
Yes	37 (22.4%)
No	128 (77.6%)
Abnormal menstrual pattern***	
Yes	122 (73.9%)
No	43 (26.1%)
Hirsutism	
Yes	82 (49.7%)
No	83 (49.7%)
Acne	
Yes	42 (25.5%)
No	84 (50.9%)
Missing	39 (23.6%)
FSH	6.85 ± 6.58
LH	6.90 ± 4.88
LH: FSH ratio	
≤ 1	59 (35.7%)
>1	41 (24.8%)
Missing	65 (39.3%)
Testosterone	37.51 ± 17.00

* Comorbidities: Diabetes mellitus, hypertension, dyslipidemia and metabolic syndrome.

** Abnormal uterine bleeding: Abnormal uterine bleeding such as postmenopausal bleeding and post-coital bleeding.

*** Abnormal menstrual pattern: Menstruation of abnormal quantity, duration, or schedule ex: Amenorrhea, oligomenorrhea, and menometrorrhagia.

There were 55 patients who underwent endometrial sampling in 2018 due to abnormal per vaginal bleeding. Mean age and BMI of those patients was 42.98 ± 13.27 and 32.71 ± 8.81 respectively. All patients included in this group reported comorbidities. Frequency of patients with family history of PCOS and endometrial cancer was minimal in this group. Abnormal uterine bleeding was noted in 26 (47.3%) of the patients and abnormal menstrual pattern was seen in 11 (20.0%) of the patients. Number of patients with hirsutism was 2 (3.6%). Ultrasound data was missing for 76.4% patients and only 2 (3.6%) in this group were reported with PCOS. Histopathology showed that 53 (96.4%) had no evidence of endometrial hyperplasia and 2 (3.6%) patients had simple endometrial hyperplasia with no atypia (Table 2).

Table 2: Patients underwent endometrial sample.

Age	42.98 ± 13.27
BMI	32.71 ± 8.81
Marital status	
Single	3 (5.5%)
Married	52 (94.5%)
Comorbidities*	
Yes	55 (100.0%)
No	0 (0.0%)
Family Hx of PCOS	
Yes	0 (0.0%)
No	55 (100.0%)
Family Hx of endometrial cancer	
Yes	2 (3.6%)
No	53 (96.4%)
Abnormal uterine bleeding**	
Yes	26 (47.3%)
No	29 (52.7%)
Abnormal menstrual pattern***	
Yes	11 (20.0%)
No	44 (80.0%)
Hirsutism	
Yes	2 (3.6%)
No	53 (96.4%)
Acne	
Yes	0 (0.0%)
No	55 (100.0%)
FSH	16.48 ± 11.40
LH	6.05 ± 2.75
Testosterone	17.03 ± 7.99
Histopathology	
No evidence of endometrial hyperplasia is seen. No evidence of malignancy.	53 (96.4%)
Simple endometrial hyperplasia with no atypia	2 (3.6%)
Ultrasound	
No data	42 (76.4%)
No PCOS	11 (20.05)
PCOS	2 (3.6%)

* Comorbidities: Diabetes mellitus, hypertension, dyslipidemia and metabolic syndrome.

** Abnormal uterine bleeding: Abnormal uterine bleeding such as postmenopausal bleeding and post-coital bleeding.

*** Abnormal menstrual pattern: Menstruation of abnormal quantity, duration, or schedule ex: Amenorrhea, oligomenorrhea, and menometrorrhagia.

There were 21 patients who were diagnosed with endometrial cancer in 2018 in KHUH. Mean age and BMI of the patients was 60.28 ± 11.78 and 35.13 ± 10.66 respectively. All patients in this group reported comorbidities. Frequency of patients with family history of PCOS and endometrial cancer was minimal in this group. Abnormal uterine bleeding was noted in 17 (81.0%) of the patients and abnormal menstrual pattern was seen in 1 (9.5%) of the patients with missing information of about 81%. There were no patients with hirsutism. Ultrasound data was missing for 12(57.14%) patients and only 1 (4.76%) in this group were reported with polycystic features in the US. No surgery was done in 4 patients, 10 (47.6%) patients had normal ovaries upon histology after surgery, one had left ovarian cyst, one had benign papillary serous cyst, one had stromal hyperplasia in both ovaries; small serous and follicular cysts was seen in two patients (Table 3).

Table 3: Patients with endometrial cancer.

Age	60.28 ± 11.78
BMI	35.13 ± 10.66
Marital status	
Single	2 (9.5%)
Married	19 (94.5%)
Comorbidities*	
Yes	21 (100.0%)
No	0 (0.0%)
Family Hx of PCOS	
Yes	-
No	15 (71.4%)
Missing	6 (28.6%)
Family Hx of endometrial cancer	
Yes	3 (14.3%)
No	18 (85.7%)
Abnormal uterine bleeding**	
Yes	17 (81.0%)
No	4 (19.0%)
Abnormal menstrual pattern***	
Yes	1 (9.5%)
No	2 (9.5%)
Missing	17 (81.0%)
Hirsutism	
Yes	0 (0%)
No	21 (100.0%)
Acne	
Yes	0 (0.0%)
No	21 (100.0%)
FSH (only 1 record)	5.19
LH (only 1 record)	8.58
Testosterone (only 1 record)	1.06
Histopathology	
No evidence of endometrial hyperplasia is seen. No evidence of malignancy	53 (96.4%)
Simple endometrial hyperplasia with no atypia	2 (3.6%)
Ultrasound	
No data	12 (57.14%)
No PCOS	8 (38.09%)
PCOS	1 (4.76%)
Histopathology endometrial sampling	
· Unknown	12 (57.1%)
· No evidence of endometrial hyperplasia is seen. No evidence of malignancy	1 (4.8%)
· Simple endometrial hyperplasia with no atypia	1 (4.8%)
· Simple endometrial hyperplasia with no atypia	1 (4.8%)
· POORLY DIFFERENTIATED adeno CARCINOMA	4 (19.0%)
· Moderately DIFFERENTIATED adeno CARCINOMA	1 (4.8%)
· Fragments of endometrium show foci of autolysis, necrosis and hemorrhage. Many fragmented glands show stratification, nuclear pleomorphism and clearing. Few mitosis are noted.	1 (4.8%)

* Comorbidities: Diabetes mellitus, hypertension, dyslipidemia and metabolic syndrome.

** Abnormal uterine bleeding: Abnormal uterine bleeding such as postmenopausal bleeding and post-coital bleeding.

*** Abnormal menstrual pattern: Menstruation of abnormal quantity, duration, or schedule ex: Amenorrhea, oligomenorrhea, and menometrorrhagia.

Discussion

A total of 241 women were included in our study. 165 women diagnosed with PCOS in 2018, 55 women that underwent endometrial sampling, and 21 females diagnosed with endometrial cancer.

Several factors have been linked to the predisposition of PCOS including age, BMI, hormonal changes, and family history. Initially, we noted that age played an important role in the manifestation of PCOS patients. Females with PCOS typically had been diagnosed between the ages of 25 and 30.

Our research has demonstrated, along with numerous other studies, that a patient's susceptibility to developing PCOS increases with increasing BMI. Which is something we were expecting because of the direct relationship between obesity and the increased levels of total testosterone and decreased levels of Sex Hormone Binding Globulin which anticipates to hyper-androgens, which contributes to the clinical sign and symptoms of PCOS such as acne, hirsutism, and abnormal uterine bleeding [10]. According to our data, we found that most of the patients had a BMI of 33.55 with a standard deviation of 18.72. Abnormal uterine bleeding was seen in 22.4% of the patients, and abnormal menstrual pattern was seen in 73 9% of the patients. Hirsutism was seen in 49.7% of them, and acne was seen in 25.5% of PCOS patients.

We noted that along with PCOS symptoms, only 13 patients (7.9%) present with non PCOS related signs and symptoms which are classified as comorbidities. These comorbidities are hypertension, diabetes, dyslipidemia, and metabolic syndrome. It triggered our curiosity towards the hidden reasons behind such a phenomenon.

In regard to, preexisting family history of PCOS, we were expecting to find a direct relationship between having a relative with PCOS and being at risk of getting PCOS, however, we were astonished that in our research the opposite had occurred. While previous research showed that the prevalence of PCOS in the first degree relative to the pro-band that was found in nearly 55-60% in several small families [11]. We think that it might be due to several reasons, one of them is the size of the sample. As the bigger the sample, is the more inclusive it is and the more accurate it is.

Speaking of hormonal changes, follicle-stimulating hormone, and luteinizing hormone plays an important role in the appearance of the signs and symptoms of PCOS. In healthy women, usually, the ratio between LH and FSH lies between 1 and 2. In polycystic ovary disease women, this ratio is reversed, and it might reach as high as 2 or 3 [12]. As a result of that raised LH/FSH ratio, ovulation does not occur in polycystic ovary disease patients, and thus patients may suffer from minor symptoms such as abdominal pain to more complex symptoms like infertility.

In addition to that, testosterone levels are also affected in PCOS patients. The abnormally high level of this hormone contributes to the external symptoms like acne and hirsutism, and the internal symptoms like the interference with the physiological function of the ovaries.

Endometrial sampling procedures were most performed on patients with a history of abnormal uterine bleeding and or abnormal menstrual bleeding. As abnormal uterine bleeding was documented in 26 (47.3%) of the patients and abnormal

menstrual pattern was seen in 11 (20.0%) of the patients (table 2). A study conducted in Turkey between 2010 and 2016, stated that endometrial sampling was most performed with the indication of menorrhagia or menometrorrhagia [5]. Routine endometrial sampling is not recommended before hysterectomy for exclusion of endometrial pathology in patients presenting with uterine fibroids; however, it is still widely performed by many physicians [6]. During data collection, 55 patients underwent endometrial sampling in 2018. Mean age of the patients was 42.98 and all of them had comorbidities. 53 patients contributing to 96.4% of the sample size, their endometrial samples finding showed no evidence of endometrial hyperplasia, endometritis, atypia or malignancy. Whereas the remaining 4 patients, their sample findings were endometrial hyperplasia with no atypia. The study conducted in Turkey demonstrated that proliferative secretory endometrium in 63.62% of the patients who had undergone endometrial biopsy due to abnormal uterine bleeding and they found that rate as 63.62%, consistent with the literature [(5)]. Another study conducted in Saudi Arabia stated that the commonest histopathological diagnosis for the 2295 samples from women presenting with abnormal abnormal uterine bleeding was secretory endometrium 571 (24.9%), followed by proliferative endometrium 498 (21.7%).

In our data regarding histopathology of the obtained endometrial sample, most of the patients 53 (96.4%) were found to have no evidence of endometrial hyperplasia and no evidence of malignancy and only 2 patient (3.6%) were documented to have normal endometrial hyperplasia with no atypia seen [1]. A retrospective study published in 2013 discussing endometrial samples as a predictor of endometrial cancer investigated patients with current existing endometrial cancer with previous endometrial samples and how those initial samples were an indicator of impending malignancy [7]. The study showed that endometrial sampling is not a strong predictor if the patient would progress into malignancy and as in our study, the information obtained only shows the cellular makeup of the endometrium and its changes.

Frequency of patients with family history of PCOS and endometrial cancer was minimal in this group. As for hirsutism, only two patients that were documented to have been dealing with hirsutism alongside their other symptoms (3.6%). Ultrasound data was missing for 76.4% patients and only 2 (3.6%) in this group were reported with PCOS. Acne was not documented as a symptom among the selected 55 individuals [6].

There were 21 patients who were diagnosed with endometrial cancer in 2018. There is no evidence that any of these patients has a self or a family history of PCOS. Previous studies illustrate important risk factors for Endometrial cancer often present in women with PCOS. This includes obesity, null parity, infertility, hypertension, diabetes, chronic anovulation, unopposed estrogen and insulin resistance. We investigated those risk factors in our patients with Endometrial cancer and we found that patients with EC have high BMI (35.13 ± 10.66). This can be explained by the fact that androgens are converted into estrogen by aromatase enzymes in the visceral adipocytes, which contributes to ideational increase in estrogen levels. Estrogen-driven proliferation and differentiation might then lead to the development of endometrial hyperplasia and ultimately endometrial cancer.

Supporting this, two studies assessing the associations between PCOS, and risk of endometrial cancer found that this increased endometrial cancer risk related to PCOS was attenuated when additionally adjusted for body mass index, emphasizing obesity as a confounding risk factor for developing endometrial cancer [13]. In another case control study, the role of different reproductive factors and their association with endometrial cancer were investigated in detail. In line with the results of Fernley et al., the association between PCOS and endometrial cancer was abolished after adjustment for BMI. These examples demonstrate that the association between PCOS and endometrial cancer is well explained by the association of both disorders with obesity.

Additionally, Hyperinsulinemia stimulates adrenal and ovarian androgen production, endogenous estrogen production from progesterone, and decreases hepatic sex hormone binding globulin production. Insulin, androgens and estrogens enhance mitotic activity through insulin-like growth factor. These changes together stimulate endometrial proliferation and mutagenic potential, which may increase the risk of EH and EC. All our patients were found to have other comorbidities including Diabetes and hypertension. Therefore, data regarding a possible association between PCOS and endometrial cancer should be evaluated after adjustment with other well known risk factors, which are associated with PCOS.

Hormonal levels were not tested in our patient with Endometrial cancer and no previous records were suggestive for previous history of hormonal imbalance.

Previous studies have stated that PCOS was associated with an increased risk of Endometrial hyperplasia and endometrial cancer. For instance, a study conducted in 2013 found PCOS patients are at a 2.7-fold increasing risk for developing EH or endometrial cancer [13]. Important risk factors for Endometrial cancer often present in women with PCOS are obesity, null parity, infertility, hypertension, diabetes, chronic anovulation, unopposed estrogen and insulin resistance [14].

The hormonal imbalance caused by anovulation in patients with PCOS is associated with unopposed estrogen action. Estrogen-driven proliferation and differentiation might then lead to the development of endometrial hyperplasia and ultimately endometrial cancer [16]. Hyperinsulinemia stimulates adrenal and ovarian androgen production, endogenous estrogen production from progesterone, and decreases hepatic sex hormone binding globulin production. Additionally, androgens are converted into estrogens by aromatase enzymes in the visceral adipocytes. Average progesterone levels are significantly reduced in women with anovulation. Insulin, androgens and estrogens enhance mitotic activity through insulin-like growth factor. These changes together stimulate endometrial proliferation and mutagenic 67, which may increase the risk of EH and EC [14].

The exact strength of the association between PCOS and gynecological cancer is unclear. The first meta-analysis about the association between PCOS and cancer risk has found that women with PCOS were at an increased risk of endometrial cancer but the risk of ovarian and breast cancer was not significantly increased This study did not take BMI into consideration but showed a 3.9 risk of developing EC [15]. However, studies report conflicting findings about whether PCOS increases the risk of gynecological cancer. Reliable estimates of the relationship between PCOS and gynecological cancer are important for public health, which can inform medical workers to improve the diagnosis and treatment strategies. Most of the data for ultrasound was missing 57.14% but we found that one person had PCOS 4.76% which was reported in our study. Women with PCOS have an increased risk of having metabolic syndrome and insulin resistance.

A meta-analysis was done to prove if there is association between PCOS and endometrial cancer which showed that females with PCOS have an increased risk of EC [1]. In conclusion, our study showed that there is a link between PCOS and EC, but the percentages are very low. A key limitation of our study is the sample size and that it was confined to only one year (2018) making it difficult to have enough data to collect. Moreover, conducting a retrospective study by using the HOPE system resources to undertake a study to determine the relationship between PCOS, EH, and EC was not feasible. A large prospective study with a control group would provide further information regarding the relationship between PCOS and EC. Recruiting patients from more than one year could have improved the outcome.

Approval by ethical comity at King Hamad University Hospital.

References

1. Dah Ching Ding, Weishan Chen, Jen-Hung Wang, et al. Association between Polycystic Ovarian Syndrome and Endometrial, Ovarian, and Breast Cancer: A Population-Based Cohort Study in Taiwan. Medicine, U.S. National Library of Medicine. 2018; 97: e12608.
2. Legro A, Arslanian, Ehrmann A, et al. Diagnosis and Treatment of Polycystic Ovary Syndrome: An Endocrine Society Clinical Practice Guideline. The Journal of Clinical Endocrinology & Metabolism. 2013; 98: 4565-4592.
3. Lim, Hutchison, Ryswyk, et al. Lifestyle Changes in Women with Polycystic Ovary Syndrome. Cochrane Database of Systematic Reviews. 2019; 3.
4. Xu, Yalan, Jie Qiao. Association of Insulin Resistance and Elevated Androgen Levels with Polycystic Ovarian Syndrome (PCOS): A Review of Literature. Journal of Healthcare Engineering, edited by Enas Abdulhay. 2022; 2022: 1-13.
5. Zeynep Ozturk Inal, Hasan Ali Inal, Ilknur Kucukosmanoglu, et al. Assessment of Endometrial Sampling and Histopathological Results: Analysis of 4,247 Cases. The Eurasian Journal of Medicine. 2017; 49: 44-47.
6. Layla Abdullah, Nabeel Bondagji. Histopathological Pattern of Endometrial Sampling Performed for Abnormal Uterine Bleeding. Bahrain Medical Bulletin. 2011; 33: 1-6.
7. Zeina Haoula, Maisa Salman, William Atiomo. Evaluating the association between endometrial cancer and polycystic ovary syndrome. Human Reproduction. 2012; 27: 1327-1331.
8. Shuang Zhang, Ting-Ting Gong, Fang-Hua Liu, et al. Global, Regional, and National Burden of Endometrial Cancer, 1990-2017: Results from the Global Burden of Disease Study, 2017. Frontiers in Oncology. 2019; 9: 1440.
9. Setiawan, Yang P, Pike C, et al. Type I and II Endometrial Cancers: Have They Different Risk Factors? Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology. 2013; 31: 2607-2618.
10. Cooper A, Page T, Amory K, et al. The Association of Obesity with Sex Hormone Binding Globulin Is Stronger than the Association with Ageing--Implications for the Interpretation of Total Testosterone Measurements. Clinical Endocrinology. 2015; 83: 828-833.
11. Muhammad Jaseem Kan, Anwar Ullah, Sulman Basit. Genetic Basis of Polycystic Ovary Syndrome (PCOS): Current Perspectives. The Application of Clinical Genetics. 2019; 12: 249-260.
12. Mitrašinović Brulić M, Buljan M, Suljević D. Association of LH/FSH ratio with menstrual cycle regularity and clinical features of patients with polycystic ovary syndrome. Middle East Fertil Soc J. 2021.
13. Daniel A. Dumesic and Rogerio A. Lobo. Cancer Risk and PCOS. Steroids. 2013; 78: 782-785.
14. Nina Sofie Lillegaard Holm, Dorte Glintborg, Marianne Skovsager Andersen, et al. The Prevalence of Endometrial Hyperplasia and Endometrial Cancer in Women with Polycystic Ovary Syndrome or Hyperandrogenism. Acta Obstetricia et Gynecologica Scandinavica. 2012; 91: 1173-1176.
15. John A. Barry, Mallika M. Azizia, Paul J. Hardiman. Risk of Endometrial, Ovarian and Breast Cancer in Women with Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis. Human Reproduction Update. 2014; 20: 748-758.
16. Ignatov Atanas, Olaf Ortmann. Endocrine Risk Factors of Endometrial Cancer: Polycystic Ovary Syndrome, Oral Contraceptives, Infertility, Tamoxifen. Cancers. 2020; 12: 1766.