



ASSOCIATION BETWEEN POLYCYSTIC OVARY SYNDROME (PCOS) AND ENDOMETRIAL HYPERPLASIA IN REPRODUCTIVE-AGE WOMEN

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is a prevalent endocrine disorder in women of reproductive age, occurring along with chronic anovulation, obesity, and insulin resistance. These elements lead to extended unopposed estrogen exposure, and with that, a higher risk for hyperplasia of the endometrial lining. Understanding this association is important to inform the implementation of screening and early diagnosis, and to enable the use of preventive interventions in a timely manner.

Objectives: To find the prevalence of endometrial hyperplasia in women of reproductive age with PCOS and examine the relationships of clinical symptoms and metrics, fasting glucose and insulin, and sex steroid hormones to hyperplasia development.

Methodology

This cross-sectional study was conducted at Hira Hospital, Abbottabad from July 2023 to Dec 2023 on women of reproductive age who have been diagnosed with PCOS according to the Rotterdam criteria of having two out of the following three: oligo/anovulation, hyperandrogenism, and polycystic ovarian morphology on ultrasound. Eligible women were subjected to thorough clinical evaluations and clinical records were kept for the following: menstrual history, BMI, waist to hip ratio, and hyperandrogenism. Blood was drawn for laboratories to analyze fasting blood glucose, insulin, profile lipids, LH/FSH ratio, and androgens. Transvaginal ultrasound was done for the measurement of the endometrial thickness. If women had >10 – 11 mm, or abnormal uterine bleeding, they were counseled for an endometrial biopsy. For the remaining women, a survey with structured questions was administered to find out their demographics, and hormonal and metabolic data. The data was analyzed statistically with SPSS version 24.0. The relationship between endometrial hyperplasia and the assorted risk factors was evaluated with the chi square, independent t, and logistic regression to determine $p < 0.05$.

Results: A mean average age of 27.6 ± 5.4 years old, a total of 100 reproductive age women with PCOS were also enrolled. We diagnosed with a histopathological confirmation of endometrial hyperplasia of the remaining 22% of the study cohort. The women with hyperplasia had a higher mean BMI than the women without hyperplasia (31.2 ± 4.1 vs 28.8 ± 4.2 ; $p = 0.01$), supporting the contribution of higher body weight to endometrial health risks. As well, the hyperplasia group had higher mean fasting insulin (22.4 ± 7.1 μ IU/mL vs 17.5 ± 5.8 μ IU/mL; $p = 0.01$), which also demonstrates the degree of insulin resistance associated with the presence of endometrial disease. As per transvaginal ultrasonography there was a higher mean endometrial thickness which was greater than 11 mm ($p = 0.002$) associated with hyperplasia. Increase of oligo menorrhea was also prevalent

with hyperplasia (81.8% vs 51.3%; $p = 0.03$), which illustrates the effect of chronic absence of ovulation with unopposed estrogen. We also did not find correlation between serum hyperplasia and androgens which may suggest that the ovulatory dysfunction and metabolic parameters are the greater contributors ($p = 0.21$). After the diagnosis of endometrial hyperplasia, the women received cyclic progesterone therapy and during follow-up a majority of the study participants had improvement of menstrual regularity, sparing of abnormal uterine bleeding, and improvement of endometrial thickness. Therapy was also noted to be complication free.

Conclusion; Patients with PCOS commonly experience an advanced form of endometrial growth due to an evident exposition of unopposed estrogen, displaying one of its hormonal irregularities. Of these patients, those who have a higher BMI, insulin insensitivity, amenorrhea, and endometrial thickening tend to be more advanced with form os such hyperplasia. Since a good portion of patients with these characteristics may have PCOS, given the various risk factors, it is of utmost importance for these patients to receive early intervention and adequate screening to avert further endometrial growth complications, such as atypical hyperplasia or carcinoma.

Keywords: PCOS; Endometrial Hyperplasia; Insulin Resistance; Oligo menorrea

Introduction

Polycystic ovary syndrome (PCOS) stands as one of the most common endocrine disorders in women of reproductive age; the worldwide prevalence ranges from 6- 21% based upon the characteristics of the population in question and the specific diagnostic criteria employed [1]. The syndrome is characterized by a number of clinical and metabolic disturbances that include hyperandrogenism, chronic anovulation, menstrual irregularity, and the presence of polycystic ovarian morphology as seen on ultrasound [2]. The condition is increasingly being acknowledged as a multisystem disorder with reproductive, metabolic, and psychological ramifications. Obesity, insulin resistance, dyslipidemia, and impaired glucose tolerance, each of which can have serious long-term health consequences, are all common among these women [3]. Perhaps the most clinically important consequence of PCOS is the association with endometrial dysfunction, and more specifically, endometrial hyperplasia. Women suffering from chronic anovulation experience prolonged and unopposed estrogen exposure which, when combined with a lack of adequate progesterone stimulation, leads to an imbalance in the hormonal milieu. This imbalance creates a scenario where abnormal proliferation of glandular tissues can occur due to an alteration in the endometrial proliferation and shedding cycle [4,5]. Ultimately, this can result in atypical hyperplasia, and in more severe instances, an endometrial carcinoma. Endometrial hyperplasia is a common complication of PCOS and occurs two to three times more frequently than in women without PCOS, as outlined in prior studies [6]. Most women with endometrial hyperplasia experience irregular bleeding, which can make diagnosis more problematic, particularly in resource-limited settings. Even more troubling is that a significant portion of women have no symptoms at all. Using endometrial ultrasound measurements of endometrial thickness, transvaginal ultrasound can be an effective screening test to determine which women require further intervention. As a result, ultrasound is a reasonable screening test to determine as to whether an office endometrial biopsy is necessary, which is still considered the most accurate method of ascertaining a diagnosis [7,8]. Although the complication of hyperplasia is common in women with PCOS, the prevalence of hyperplasia is not as widespread in all populations. This discrepancy can be attributed to lifestyle differences, metabolic factors, varying access to and delays in diagnosis and healthcare. In South Asian populations, we see a more severe manifestation of symptoms of PCOS, attributed to higher obesity and insulin resistance levels, combined with a greater lag in diagnosis. Women in this area might be at an increased risk for developing endometrial hyperplasia [9]. These differences between regions help in the designing of appropriate screening systems and management techniques [10]. Early diagnosis of endometrial conditions in PCOS patients and the prevention of risks, along with improved menstrual cycle management, and reproductive outcomes, as well as better regulated fertility treatments, is essential.

Study Objectives

Estimating the prevalence of endometrial hyperplasia in women of reproductive age suffering from PCOS, then analyzing the effect of certain metabolic, hormonal and menstrual variables which might help in assessing the cause of the hyperplasia condition.

Materials and Methods

Study Design & Setting

This cross-sectional study of women diagnosed with Polycystic Ovary Syndrome (PCOS) was completed over 6 months in Hira Hospital, Abbottabad from July 2023 to Dec 2023.

Participants

Participants were women aged 18-40 years who were diagnosed with polycystic ovary syndrome (PCOS) based on the Rotterdam Criteria. All of the participants underwent clinical evaluation, hormonal exams, and transvaginal ultrasounds. For participants with endometrial thickness ≥ 11 mm hyperplasia, a biopsy was performed to offer confirmation. A structured data collection form was used to document all of her demographics, menstrual, and metabolic variables.

Sample Size Calculation:

With a 95% confidence level and 7% margin of error (precision), 20% of hyperplasia was selected as a base prevalence for PCOS patients, and an initial sample size of 98 was determined. To account for data protection principle standards, as well as for possible non-responses of data protection compliance levels and reasonable estimation of non-responses, and as also to enhance the accuracy and reliability of the study, the number of participants was set to an even 100.

Inclusion Criteria

Women Diagnosed with PCOS by The Rotterdam Criteria PCOS Criteria Volume 1, 18-40 Years, and able to Participate For The Necessary Study examinations

Exclusion Criteria

History of Endometrial Carcinoma and Pregnancy, History of Endometrial Carcinoma and Pregnancy, Hormonal therapy within 3 months, and contraindications to performing a biopsy.

Diagnostic and Management Strategy

The measurement of endometrial thickness was done through transvaginal ultrasound. Biopsies were done on women whose endometrial thickness was greater than 10-11 mm, or who had atypical uterine bleeding. Those cases were managed through progesterone therapy, while others were given further treatments depending on the clinical presentation.

Statistical Analysis

I analyzed the data using SPSS version 24. Continuous variables were measured, computed, and reported as the Mean $\pm$ SD, while categorical variables were analyzed using count and percentage and computed as framework frequencies and percentages. Associations were analyzed using the Chi-square test, whereas independent and t-tests. Statistical significance was considered when the $p < 0.05$.

Ethical Approval

The Hira Hospital, Abbottabad Institutional Review Board (IRB) granted the study approvals. All study subjects granted written informed consent. To be in full compliance with the confidentiality obligations of our institution and the data protection regulations, patient data were fully anonymized. This study adhered to the regulations governing ethical study involving human subjects defined and set by the institution and internationally.

Results

100 reproductive-age women diagnosed with PCOS. The mean age for the cohort was 27.6 ± 5.4 years. 22% of the study cohort had hyperplasia confirmed via bioarchival histopathology. The women with hyperplasia had higher mean BMI and fasting insulin than those with hyperplasia ($p = 0.01$) which suggests some endometrial disorders are more advanced etiologically due to the relationship of hyperplasia with body fat and insulin resistance. Oligo menorrhea was even further prevalent in the hyperplasia cohort ($p = 0.03$) demonstrating the consequences of chronic anovulation on the endometrial tissue. Greater endometrial thickening (>11 mm) showed stronger histologic concordance for hyperplasia ($p = 0.002$). The correlations were in a low range with no hyperplasia ($p = 0.21$) with respect to androgens. After the diagnosis, that hyperplasia were initiated on cyclic progesterone therapy and subsequently had improvement of their bleeding manifestations and decrease of endometrial thickness on the follow-up.

Intervention Outcomes

Following institutional protocols, all women histologically diagnosed with endometrial hyperplasia ($n = 22$) began cyclic progesterone therapy. Most patients reported clinical improvement during follow-up. Within three months of commencing therapy, 81.8% (18/22) of patients stopped menstruating, and 77.2% (17/22) had a substantial improvement in abnormal uterine bleeding. After 12 weeks of progesterone therapy, most patients had decreased endometrial thickness and 72.7% (16/22) of patients who had previously had endometrial hyperplasia had endometrial thickness in the normal range. There were no significant adverse effects of progesterone therapy and patients were consistent with follow-up appointments. Of the patients, only two needed additional workup for endometrial hyperplasia, and both were referred for gynecology evaluation. For all patients, the outcome of the intervention was positive, supporting the role of early hormonal therapy in management of patients with endometrial hyperplasia and prevention of progression to atypical hyperplasia.

Table 1. Baseline Demographic and Clinical Characteristics of Participants (N = 100)

Variable	Mean $\pm$ SD / n (%)
Age (years)	27.6 ± 5.4
BMI (kg/m^2)	29.4 ± 4.3
Oligo menorrhea	58 (58%)
Obesity ($\text{BMI} \geq 30$)	42 (42%)
Clinical hyperandrogenism	34 (34%)
Elevated fasting insulin	39 (39%)

Table 1 summarizes the demographic and baseline clinical characteristics of reproductive-age women diagnosed with PCOS included in this study.

Table 2. Hormonal and Metabolic Parameters of Study Participants

Parameter	Mean $\pm$ SD
Fasting glucose ($\text{mg}/\text{ld.}$)	96.3 ± 12.5
Fasting insulin ($\mu\text{IU}/\text{mL}$)	18.6 ± 6.4
LH/FSH ratio	2.1 ± 0.9
Serum androgens (ng/mL)	0.82 ± 0.31
Total cholesterol ($\text{mg}/\text{ld.}$)	182.4 ± 28.1
Triglycerides ($\text{mg}/\text{ld.}$)	154.7 ± 42.3

Table 2 presents the metabolic and hormonal findings of participants, including glycemic profile, gonadotropin ratio, and lipid parameters.

Table 3. Comparison Between Women with and Without Endometrial Hyperplasia

Variable	Hyperplasia Present (n=22)	Hyperplasia Absent (n=78)	p-value
BMI (kg/m ²)	31.2 ± 4.1	28.8 ± 4.2	0.01
Fasting insulin (μIU/mL)	22.4 ± 7.1	17.5 ± 5.8	0.01
Endometrial thickness (mm)	12.8 ± 1.9	8.6 ± 2.3	0.002
Oligo menorrhea (%)	18 (81.8%)	40 (51.3%)	0.03
Elevated androgens (%)	6 (27.2%)	26 (33.3%)	0.21

Table 3 compares metabolic, hormonal, and ultrasound parameters between women diagnosed with endometrial hyperplasia and those without hyperplasia.

Table 4. Outcomes After Progesterone Therapy in Patients with Endometrial Hyperplasia (n = 22)

Outcome	n (%)
Normalization of menstrual cycles	18 (81.8%)
Reduction in abnormal uterine bleeding	17 (77.2%)
Regression of endometrial thickness	16 (72.7%)
Persistent thickened endometrium	2 (9.1%)
Adverse effects reported	0 (0%)

Table 4 summarizes the therapeutic outcomes following cyclic progesterone therapy in women diagnosed with endometrial hyperplasia.

Discussion

This study studied endometrial hyperplasia prevalence in women of reproductive age with polycystic ovary syndrome (PCOS) while also studying clinically significant hyperplasia along with specific hormonal and metabolic characteristics [11]. According to the results, endometrial hyperplasia was found in 22% of women suffering PCOS and the results are significant as they represent, to some degree, the extent of pathology involving the endometrium in the sequenced PCOS-analyzed areas. [12] This also coincides with some of the other studies recently completed, specifically those studies in which the risk, to some degree, of endometrial pathology, more specifically endometrial abnormalities, was found to be higher in women suffering PCOS as a byproduct of prolonged anovulation and the subsequently prolonged estrogen exposure. This study determined, and as such, confirmed endometrial hyperplasia prevalence in women with higher BMI, higher rates of insulin resistance, and higher rates of oligo menorrhea [13]. Higher rates in these three components and their abnormal interactions to some degree confirmed endometrial pathology or in other words, hyperplastic endometrial tissue [14]. Higher obesity rates and higher BMI ratio confirmed those women of hyperplasia with higher to define endometrial dysfunction as significantly higher. Higher previously mentioned BMI confirmed the presence of more adipose tissue which in turn caused a higher ratio of hyperestrogenism to progesterone, defined as estrogen which in the absence of an antagonistic progesterone, would directly lead to more dysfunction in the endometrial tissue [15,16]. Evolving hyperplasia with functional insulin resistance also demonstrates an increased prevalence of endometrial pathology from more insulin resistance, or in other words, hyperinsulinemia, which may indirectly lead to pathologic endometrial tissue by more with the use of an insulin-like growth factor. In addition to more insulin resistant women suffering hyperplasia, they tended to have a higher fasting insulin concentration and therefore confirm some degree of metabolic dysregulation [17,18]. This multiplicity illustrates the need for metabolic screenings in patients with PCOS, especially those with disturbances in their menstrual cycle [19]. In the study, women with endometrial hyperplasia had oligo menorrhea much more frequently. Prolonged chronic anovulation leads to further intervals of endometrial lining that is un-shed due to the release of progesterone and permits further unopposed estrogenic growth of the endometrial lining [20]. This method of prolonged unopposed estrogen promotion of endometrial growth underlines the need for evaluation of menstrual cycle irregularity

in PCOS and its relevance to endometrial equity. In contrast, there was no significant association of the hyperandrogenism levels to the hyperplasia. This means that hyperandrogenism by itself is unlikely the only factor that creates endometrial changes, thus, there are other impacts such as disruption of the metabolism and disruption of the ovulation cycle [21,22]. Endometrial thickness was greater than 11 mm, and was seen in hyperplasia, supporting the need for a transvaginal ultrasound as a first line of a screening tool [23]. However, in the absence of ultrasound to distinguish between old endometrial hyperplasia and new endometrial hyperplasia, it is mandatory that surgical excision biopsy be done to obtain proper histopathologic diagnosis [24]. Finally, the study's use of biopsy is what provided the study with its diagnostic accuracy, and fortified the reliability of the conclusions drawn [25]. Results of this study were positive and encouraging [26]. Women with endometrial hyperplasia diagnosed with this condition were able to improve and respond positively to treatments with hormonal cyclic progestin therapies by showing significant improvement in bleeding pattern, and in the majority of cases, endometrial thickness regression [27]. As endometrial counterbalancing, shedding and stabilization are progesterone functions, progesterone remains pivotal in the management of this condition as it opposes estrogen-induced hyperplasia. This high therapeutic success rate illustrates the efficacy of hormonal intervention as an approach in preventing progression to atypical hyperplasia at an early stage.

Limitations

This investigation was restricted in both scope and geographic representation by being performed in only one center and only having a small sampling size. Population's hormonal and metabolic differences were not fully considered. Ultrasound studies may have minor irregularities. Additionally, a lack of comprehensive follow-up restricted the complete evaluation of potential treatment responsiveness and of the likelihood of progression.

Conclusion

In women with PCOS, endometrial hyperplasia with, or without, atypical hyperplasia is largely caused by obesity, insulin resistance, and chronic anovulation. Due to these factors, unprecedented timely hormonal management and screening by ultrasound is required to avoid future atypical hyperplasia. Within Long Term Care of PCOS and Endometrial Protection, managing the metabolism and regulating the menstrual system are required.

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Authors Contribution

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