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The association between polycystic ovarian disease and fibrocystic breast disease

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Abstract
Background: Polycystic ovary syndrome (PCOS) is a multifaceted endocrine disorder that affects approximately 5-10% of women of reproductive age, manifesting in a spectrum of symptoms including hyperandrogenism, menstrual irregularities, and infertility due to chronic anovulation. Notably characterized by insulin resistance and elevated serum luteinizing hormone (LH) levels, PCOS poses an increased risk for type 2 diabetes and cardiovascular diseases. Aim of the study: to investigate the association between polycystic ovary syndrome and fibrocystic breast disease.
Method: Between June 2010 and June 2011, a study at Al-Kadhymia Teaching Hospital examined 100 women, divided into 50 with Polycystic Ovary Syndrome (PCOS) and 50 controls, to explore the correlation between PCOS and clinical manifestations like menstrual irregularities and breast pathology. Using the 2003 Rotterdam consensus criteria for diagnosis, the study included detailed clinical assessments, transvaginal ultrasound, and hormone level measurements. Adhering to ethical standards, it aimed to deepen the understanding of PCOS's impact on women's health.
Results: In a study involving 100 women divided into PCOS and control groups, significant findings included a higher mean BMI in the PCOS group compared to controls and varied endocrine parameters across PCOS phenotypes. Fibrocystic breast disease was notably more prevalent in the PCOS group, with a statistically significant difference and a relative risk of 4.929, indicating a potential link between PCOS and specific benign breast pathologies.
Conclusion: The study revealed a significant correlation between PCOS and fibrocystic breast disease, with non-classic PCOS phenotypes (O + P, H + P, O + H + P) occurring more frequently than the classic phenotype (O + H). Notably, the non-hyperandrogenic phenotype (O + P) presented with the lowest endocrine parameters, suggesting a distinct subtype within PCOS as per the Rotterdam criteria.

Keywords: Association, polycystic ovarian disease, fibrocystic breast disease

Introduction

Polycystic ovary syndrome (PCOS) is a multifaceted endocrine disorder that affects approximately 5-10% of women of reproductive age, manifesting in a spectrum of symptoms including hyperandrogenism, menstrual irregularities, and infertility due to chronic anovulation. Notably characterized by insulin resistance and elevated serum luteinizing hormone (LH) levels, PCOS poses an increased risk for type 2 diabetes and cardiovascular diseases [1]. A critical aspect of its etiology involves the interplay between hyperestrogenism and anovulation, which also implicates a heightened surveillance for benign breast disease (BBD) and breast cancer among affected women due to the mammary gland's sensitivity to hormonal imbalances [2]. Defined at the 2003 Rotterdam consensus as requiring two of the following three criteria for diagnosis - oligo - or anovulation, clinical or biochemical signs of hyperandrogenism, and polycystic ovaries on ultrasound - PCOS's prevalence is underscored by its manifestation in 20-33% of women when solely based on ultrasound criteria. The syndrome is rooted in disordered folliculogenesis, reflecting a primary ovarian disorder with contributions from abnormal endocrine interactions, particularly between elevated LH and insulin levels [3]. This hormonal milieu fosters an environment ripe for the development of PCOS's hallmark features, including insulin resistance, a state exacerbated by obesity, and hyperandrogenism, which contributes to the syndrome's clinical manifestations such as hirsutism and acne [4]. The long-term health implications of PCOS extend beyond reproductive health, encompassing increased risks for metabolic syndrome, type 2 diabetes, cardiovascular complications, and specific types of cancer,

including endometrial, breast, and ovarian cancers [5].

The management of PCOS is symptom-oriented, targeting lifestyle modifications, medical therapy, and, in some cases, surgical interventions to ameliorate its manifestations. Strategies such as weight loss and exercise are emphasized for their beneficial effects on insulin sensitivity and ovulatory function, alongside pharmacological interventions like metformin and oral contraceptives to manage hyperandrogenism and menstrual irregularities [6]. Concomitantly, benign breast disease (BBD), encompassing a heterogeneous group of lesions, emerges as a concern for women with PCOS due to the shared hormonal disturbances. BBD's classification spans from non-proliferative lesions to proliferative lesions with or without atypia, with implications for breast cancer risk stratification. The management of fibrocystic changes, the most frequent manifestation of BBD, focuses on symptomatic relief and monitoring, underscoring the interconnectedness of hormonal regulation in the management of PCOS and related breast conditions [7]. In essence, PCOS embodies a complex interplay between ovarian dysfunction, metabolic derangements, and hormonal imbalances, necessitating a comprehensive approach to management that addresses both the immediate symptomatic concerns and the long-term health risks associated with the syndrome, including its implications for breast health [8]. Aim of the study: to investigate the association between polycystic ovary syndrome and fibrocystic breast disease.

Method

Between June 2010 and June 2011, a study was conducted at the Al-Kadhymia Teaching Hospital involving 100 women aged between 17 and 36 years, who were not on oral contraceptives. This cohort was divided into two groups: 50 women diagnosed with Polycystic Ovary Syndrome (PCOS) and 50 controls without PCOS, identified through clinical and ultrasound examinations. The study aimed to explore the correlation between PCOS and various clinical manifestations, including menstrual irregularities, hyperandrogenism, and breast pathology, under the criteria established by the 2003 Rotterdam consensus. Women in the PCOS group were identified from infertility and outpatient clinics, presenting with symptoms such as menstrual disturbances or hyperandrogenism, and were confirmed to have polycystic ovaries on ultrasound. This group was further divided based on the Rotterdam consensus criteria into four subgroups: (I) oligo- or amenorrhea and hyperandrogenism with polycystic ovaries, (II) oligo- or amenorrhea and hyperandrogenism without polycystic ovaries, (III) hyperandrogenism and polycystic ovaries with regular menstrual cycles, and (IV) oligo- or amenorrhea with polycystic ovaries but no hyperandrogenism. The control group comprised healthy volunteers or women whose infertility was attributed to factors unrelated to PCOS, ensuring they exhibited normal ovarian morphology and lacked PCOS-related symptoms according to the Rotterdam criteria. Both groups were meticulously screened to exclude any influence of medication that could alter the clinical and endocrine presentation. Clinical assessments included detailed personal medical and menstrual cycle histories, body mass index (BMI) calculations, waist-to-hip ratio measurements, and a thorough physical examination. Transvaginal ultrasound examinations were performed to identify polycystic ovaries, while laboratory tests measured hormone levels to aid in the diagnosis of PCOS and rule out other menstrual disorders. Hyperandrogenism was defined by elevated serum testosterone levels, and hirsutism was assessed using the modified Ferriman-Gallwey score.

Both groups underwent breast ultrasound examinations to detect fibrocystic breast disease, characterized by cystic lesions with specific sonographic features. The study adhered to ethical guidelines, with approval from the Iraqi committee for medical specialization and informed consent obtained from all participants. Statistical analysis, conducted using SPSS software, compared mean age, BMI, and other categorical data between the groups, employing student's t-tests, chi-square, or Fisher's tests where appropriate, to identify significant associations between PCOS and breast pathology, with a p-value of less than 0.05 indicating statistical significance. This comprehensive approach aimed to elucidate the relationship between PCOS and its clinical manifestations, contributing valuable insights into the management and understanding of this complex condition.

Results

During the study period, a total of 100 women were included in this study aged between 17 and 36 years old were divided into two groups. The study group consisted of 50 women (with PCOS) mean age 26.30±5.24 years and the control group consisted of 50 women (non-pcos) mean age26.58±5. 85years.There was no significant difference in age distribution between the groups (p=o.802).

The mean BMI of the study group was28.09±5.95Kg/m^2 and the BMI of the control group was25.15±5.14Kg/m^2 and the p value=0.010 as shown in table 1.

Table 1: Demographical Characteristics

	Study group PCOS patients (n = 50)	Control group Non-PCOS Patients (n = 50)	*P*
Mean age (years)	26.30±5.24	26.58±5.85	0.802
Body mass index (kg/m^2)	28.09±5.95	25.15±5.14	0.010

The study group was divided into 4 groups. Of the 50 patients with PCOS, 26 (52%) fulfilled the criteria for O + P, 14 (28%) for O + H + P, 6 (12%) for H + P, and 4 (8%) for O + H. Of the 50 PCOS patients, 18 (36%) met both the diagnosis criteria of NIH 1990 and ESHRE/ASRM 2003 (O + H + P and O + H), and the composition of the two new phenotypes created by the ESHRE/ASRM 2003 consensus was 32(64%) (O + P and H + P). Subjects in each subset differed slightly in age. BMI and WHR were increased in women with O + H and O + H + P compared with those with H + P, O + P, and controls.

The endocrine parameters (gonadotrophins and androgens) in the four phenotypes and the control group are also depicted. LH and the LH/FSH ratio were higher in cases with O + H + P, O + H and O + P compared with that in H + P group and controls, and were higher in cases with O + H + P and O + H than those with O + P. However, FSH levels have not significant difference among groups. Testosterone levels were highest in women with O + H + P and O + H, intermediate in women with H + P, and lowest in those with O + P and controls. As in table 2.

Table 2: Comparison of demographics and clinical endocrine features in women with polycystic ovary syndrome (PCOS) and control subjects

Variable	O+H+P	O+H	H+P	O+ P	Control
N (%)	14(28%)	4 (8%)	6 (12%)	26 (52%)	50 (100%)
Mean age(years)	27.9	26.5	25.7	25.1	26.58
Mean BMI (Kg/m^2)	30.02	29.36	25.06	27.92	25.15
Mean WHR	0.85	0.83	0.8	0.79	0.82
Mean Total test. ng/dl	88	87	79	38	32
Mean LH mIU/ml	9.1	8.7	6.5	7.3	6
Mean FSH mIU/ml	6.2	6.1	6.1	6.2	6.2
Mean LH/FSH	1.46	1.42	1.06	1.17	0.96

Fibrocystic breast disease was found in 15 of 50 PCOS patients (30%) and was found in 4 of 50 non PCOS patients (8%). On breast sonographic examination. The difference between the groups was statistically significant (p=0.005).

Relative risk (95% CIs) was 4.929 (1.503-16.175). Overall sonographic benign breast pathologies were higher in the PCOS group (p=0.023) and that is shown in table 3.

Table 3: Association between breast pathology and PCOS

Breast sonography	Study group PCOS patients (n = 50)	Control group Non-PCOS Patients (n = 50)	*P*	Relative risk (95 % CIs)
Fibrocystic breast	15 (30 %)	4 (8%)	0.005	4.929 (1.503-16.175)
Fibroadenoma	3 (6 %)	8 (16 %)	0.110	0.335 (0.083-1.346)
Lipoma	2 (4 %)	2 (4 %)	1.000	1.000 (0.135-7.392)
Calcification	1 (2 %)	1 (2 %)	1.000	1.000 (0.061-16.444)
Other sonographic benign breast pathology	18 (36 %)	8 (16 %)	0.023	2.953 (1.141-7.646)

The incidence of fibrocystic breast disease in different phenotypes groups of PCOS. The incidence of fibrocystic breast disease was higher in the (O+H+P) phenotype group of PCOS than other groups and was found that one of (O+P) phenotype group had fibrocystic breast disease and p-value was statistically significant in (O+H+P) and in (O+P). As in table 4.

Table 4: Phenotypes groups of PCOS

		Phenotypes groups of PCOS				
		O+H+P	O+H	H+P	O+P	Total
Fibrocystic breast disease	Yes	8(16%)	3(6%)	2(4%)	2(4%)	15(30%)
	No	6(12%)	1(2%)	4(8%)	24(48%)	35(70%)
	Total	14(28%)	4(8%)	6(12%)	26(52%)	50(100%)
P-value		0.011	0.061	1.000	<0.001	

Discussion

Fibrocystic changes (FCCs) are the most common benign breast disorder, predominantly affecting women between 20 and 50 years of age [9]. The balance between estrogen and progesterone is crucial for normal breast function in child-bearing women, with disruptions potentially leading to FCCs. The hypothesis of an "inadequate luteal phase," suggesting decreased progesterone secretion and resulting in unopposed estrogen activity, has been posited as a pathogenic factor in BBD, receiving support from Hale GE et al. [10]. Besides these primary hormones, prolactin, growth factors, insulin, and thyroid hormone significantly contribute to the development of fibrocystic breasts, with the breast's own hormonal production influencing neighboring cells and potentially intensifying the effects of estrogen and progesterone. Despite FCCs being observed in 7% of the general population and being associated with an increased breast cancer risk, no direct correlation has been established between PCOS and an elevated risk of breast cancer [11]. However, the role of insulin-like growth factor 1 (IGF-1) and its binding proteins in breast carcinogenesis suggests a complex interplay of hormonal factors in breast tissue changes [12]. Brkić M et al. and Panaritis et al. have respectively highlighted unopposed hyperestrogenism and changes in the diameter of the main terminal lactiferous ducts as factors associated with BBD and PCOS [13, 14].

In exploring the relationship between PCOS and FCCs, our study, adhering to the Rotterdam criteria, found no significant age difference between PCOS patients and controls. The composition of PCOS phenotypes, indicating a prevalence of the oligomenorrhea or amenorrhea with polycystic ovaries and hyperandrogenism phenotype. Notably, BMI and serum testosterone concentrations were higher in patients with these phenotypes, suggesting a hormonal imbalance in PCOS that could influence the development of FCCs [15].

Fibrocystic breast disease was detected in 30% of PCOS patients compared to 8% of non-PCOS patients, with a notably higher incidence in the oligomenorrhea, hyperandrogenism, and polycystic ovaries (O+H+P) group. This significant association between PCOS and FCCs, underscored by a relative risk of 4.929, suggests that PCOS may be a risk factor for developing FCCs. This finding is corroborated with study found a significant association between PCO and FCCs, although their study's small sample size warrants cautious interpretation [16]. Contrasting findings have emerged from other studies, such as that by A. Soran and E.O. Talbott, which did not observe a significant difference in BBD incidence between PCOS and non-PCOS women over a 12-year follow-up [16]. Furthermore, Hartmann's study highlighted that histologic features, biopsy age, and family history are crucial determinants of breast cancer risk post-BBD diagnosis, indicating that FCCs alone do not significantly elevate cancer risk without a strong familial predisposition [17]. Earlier research by Pierpoint et al. did not demonstrate an increased breast cancer mortality or morbidity risk in women with PCOS, suggesting that while PCOS may predispose women to FCCs, it does not necessarily heighten

breast cancer risk [18, 19]. This is supported by Atiomo WU and Moini A et al, who found no significant increase in breast cancer risk among women with PCOS [20, 21].

Conclusion

PCOS was significantly linked to fibrocystic breast disease in this research. PCOS non-classic phenotypes (O + P, H + P, and O + H + P) were more common than classic.

One of the Rotterdam criteria' new phenotypes, the non-hyperandrogenic PCOS phenotype (O + P), may have the lowest endocrine parameters.

Conflict of Interest

Not available.

Financial Support

Not available.

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