Familial associations between polycystic ovarian syndrome and common diseases

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Abstract

Purpose The goal of this study was focused on two subjects. First, to determine possible association between PCOS and family history of breast cancer, ovarian cancer, endometrial cancer, heart attack, thrombosis, diabetes and cardiovascular disease (CVD). Second, to evaluate maternal and paternal transmission in PCOS patients with positive family history of a disease.

Methods A cross-sectional study was conducted in 549 infertile women (273 with PCOS and 276 controls) in Arash hospital of Tehran, Iran, between 2007 and 2008 by using questionnaire.

Results In this analysis, there were significantly increased number of women with the positive family history of diabetes among PCOS group (28.21% vs. 19.20%, $p=0.01$). Meanwhile, four women in PCOS group had self history of diabetes while no one in the control group reported diabetes. A statistically significant positive family history of breast cancer was found among the control group (4.35% vs. 1.30%, $p=0.02$). Endometrial cancer and

diabetes were observed in mother or mother's side of the family but heart attack and thrombosis manifested in father or father's side of the family more. There were no statistically significant differences in a positive individual or family history of ovarian cancer, endometrial cancer, heart attack, thrombosis and CVD between the two groups. **Conclusion** In the present study, women and their relatives with PCOS had an increased prevalence of diabetes and it is more common in mother's side of the family.

Keywords Polycystic ovarian syndrome (PCOS) · Family history · Diabetes · Breast Cancer · Endometrial Cancer · Heart attack · Thrombosis · Cardiovascular disease (CVD)

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age with clinical symptoms of anovulatory infertility and/or hyperandrogenism. This syndrome is present in 5% to 8% of women of reproductive age and also associated with insulin resistance and obesity. Insulin resistance has potential long-term health consequences and this fact has led to suggest that women with PCOS may be at increased risk of cardiovascular disease later in their lives, especially if disturbances of lipid and carbohydrate metabolism persist after the menopause [1, 2]. The etiology of this syndrome remains unclear but there are strong evidences for a major genetic component in the etiology of PCOS. Cases of PCOS cluster in families revealed heritability of both hyperandrogenaemia and hyperinsulinaemia in affected siblings [3, 4]. It has been suggested that PCOS may be a thrombophilic state, although the differences were not statistically significant in a comparison study of women

Capsule In the present study, women and their relatives with PCOS had an increased prevalence of diabetes and it is more common in mother's side of the family.

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with PCOS and positive family history of thrombosis with the control group [5, 6].

Several lines of evidence suggest that women with PCOS may also be at an increased risk of having a personal history of ovarian cancer and breast cancer [7, 1] particularly as these women are hyperandrogenic and infertile, which are risk factors for breast and ovarian cancers, respectively. One investigation by Atiomo et al. showed a positive association between PCOS and family history of breast cancer and heart disease [8]. Another study by Hunter et al, conducted to measure the prevalence of heart disease, stroke, diabetes and associated risk factors among fathers and brothers of women with PCOS, revealed that the brothers of these women may be at an increase risk of CVD [9].

The objectives of our study were: first, to determine the possible association between PCOS and a family history of breast cancer, ovarian cancer, endometrial cancer, heart attack, thrombosis, diabetes and cardiovascular disease (CVD); and second, to search for the familial inheritance of disease in PCOS patients.

Materials and methods

This was a cross-sectional study conducted in a university referral-based fertility and endocrine clinic and hospital (Arash Hospital, Iran) between January 2007 and January 2008.

In the period of our study, 588 women with infertility were referred to our hospital. After considering exclusion criteria (uncompleted questionnaire, hyperprolactinemia, thyroid dysfunction, hypothalamic amenorrhea and Cushing's syndrome by hormonal assay), 549 infertile women were included in our study. Women who had a history of 2 years of infertility were enrolled for the study.

In order to make the diagnosis of PCOS, it needs to fulfill only two out of three following criteria according to the Rotterdam consensus [10]:

1. Irregular menstruation
2. Clinical and /or biochemical signs of hyperandrogenism
3. Polycystic ovaries (presence of 12 or more follicles in each ovary measuring 2–9 mm in diameter, and /or increased ovarian volume >10 ml).

All patients in this study had polycystic ovaries as important criteria. The Modified Ferriman-Gallwey score was used to score hirsutism. Questionnaires were completed in clinic by nursing staff to avoid forgetfulness; the answers were checked again by a specialist. To get a correct family history, all diseases were fully explained. To be unbiased, our study was performed to find any linkage between fertility

problem and common health problems not specifically related to PCOS.

After a pilot study in 100 PCOS patients and the same number in the control group, 26% of women with PCOS gave a positive family history of diabetes compared with 16% in the control group. According to the Epi Info site (www.cdc.gov/epiinfo/), to have a study of 80% power to detect such a difference in the prevalence of a positive family history of diabetes between two groups (tested and control) at a 5% significant level, 263 women are required in each group. Student's t-test was used to compare continuous variables and Chi-square test as appropriate to test the differences between categorical variables. A two-tailed *p*-value of less than 0.05 was considered as significant. Statistical analysis was performed with JMP software (Version 4; SAS institute, USA). The ethics institutional review board of Tehran University of Medical Sciences approved the study and informed consent was obtained from all participants.

Results

As shown in Table 1, patients with PCOS were younger than the control group (27.94 ± 4.16 versus 31.10 ± 5.77 , $p < 0.0001$). BMI and age of menarche were not significantly different between two groups. Waist/hip ratio was significantly higher in PCOS (0.85 ± 0.08) group than the control (0.82 ± 0.07) by *p* value < 0.0001 . Meanwhile, menstrual pattern and hyperandrogenism signs were presented in total for both groups and the difference was statistically significant between the two groups ($p < 0.05$).

According to Table 2, the proportion of women with positive family history of breast cancer was significantly greater in the control group compared with women with PCOS (4.35% vs. 1.30%, $p = 0.02$). There was also a significantly increased number of women with positive family history of diabetes in PCOS group (28.21% vs. 19.20%, $p = 0.01$). Meanwhile, four women in PCOS group had self history of diabetes and no one in the control group reported diabetes. There were no statistically significant differences of a positive individual or family history of ovarian cancer, endometrial cancer, heart attack, thrombosis and CVD. In Table 3, PCOS patients with positive family history were compared from the viewpoint of paternal and maternal inheritance. Based on this table, 100% of cases with positive history of endometrial cancer were located in mother's side of the family. Maternal history of diabetes was stronger than paternal history of diabetes among PCOS populations (80.82% vs 43.84%, $p < 0.05$). However, paternal history of heart attack (75.86% vs 35.71%, $p < 0.05$) and thrombosis (76.92% vs 30.77%, $p < 0.05$) were stronger than maternal history of these diseases. Among

Table 1 Total characteristics of study population

	Total Group (<i>n</i> =549)	PCOS (<i>n</i> =273)	Control (<i>n</i> =276)	<i>P</i> value
Age (yr)	29.53±5.28	27.94±4.16	31.10±5.77	<0.0001
BMI (kg/m²)	26.73±16.40	27.91±22.81	25.56±4.35	NS
Age of Menarche	13.39±1.62	13.42±1.61	13.35±1.63	NS
Waist/Hip ratio	0.84±0.08	0.85±0.08	0.82±0.07	<0.0001
Menstrual pattern				
Irregular	249 (45.36%)	212 (77.66%)	37 (13.41%)	<0.0001
Regular	300 (54.64%)	61 (22.34%)	239 (86.59%)	
Hyperandrogenism				
Acne	103 (18.76%)	70 (25.64%)	33 (11.96%)	<0.05
Alopecia	87 (15.85%)	67 (24.54%)	20 (7.25%)	
Hirsutism	238 (43.35%)	172 (63%)	66(23.91%)	

NS not significant, PCOS polycystic ovarian syndrome, BMI body mass index

Values are mean ± SD and Number (percent). *P* value refers to t-test and χ^2 -test when appropriate. Comparison was conducted between PCOS and control group.

PCOS women with positive family history of diabetes, two brothers and two sisters were affected; however, among patients with positive history of heart attack, one brother was affected; and among positive family history of thrombosis, one sister was affected. We take these patients as someone who had positive family history of disease in Table 2 but to compare paternal and maternal history, these cases are excluded from analysis section because of

Table 2 Prevalence of a personal or family history of breast cancer, ovarian cancer, endometrial cancer, heart attack, deep vein thrombosis, diabetes, cardiovascular attack

Variable	PCOS <i>n</i> =273	Control <i>n</i> =276	P-value
Number with a family history of breast cancer (%)	3 (1.30)	12 (4.35)	0.02
Number with a family history of ovarian cancer (%)	1 (0.43)	0 (0)	NS
Number with a family history of endometrial cancer (%)	3 (1.30)	3 (1.09)	NS
Number with a family history of heart attack (%)	29 (10.62)	24 (8.70)	NS
Number with a family history of thrombosis (%)	13 (5.65)	8 (2.90)	NS
Number with a family history of diabetes (%)	77 (28.21)	53 (19.20)	0.01
Number with a family history of CVD (%)	19 (8.26)	22 (7.97)	NS
Number with a history of diabetes (%)	4(1.74)	0 (0)	0.04

NS not significant.

Table 3 Comparison of the disease in PCOS positive family history from the viewpoint of paternal and maternal inheritance

	PCOS		<i>P</i> value
	Paternal	Maternal	
Breast cancer (<i>n</i> =3)	2 (66.67)	1(33.34)	NS
Ovarian cancer (<i>n</i> =1)	0 (0)	1(100)	NS
Endometrial cancer (<i>n</i> =3)	0 (0)	3 (100)	S
Heart attack (<i>n</i> =29)	22 (75.86)	10 (35.71)	S
Thrombosis (<i>n</i> =13)	10 (76.92)	4 (30.77)	S
Diabetes (<i>n</i> =73)	32 (43.84)	59 (80.82)	S
CVD (<i>n</i> =19)	8 (42.10)	11 (57.89)	NS

CVD cardiovascular disease, NS not significant, S Significant (*P*<0.05).

uncertainty regarding the disease inheritance from maternal or paternal side.

Discussion

In present study, the frequency of diabetes was significantly higher in women with PCOS and their relatives. Meanwhile, the risk of thrombosis and heart attack was higher in father's side of the family of PCOS patients. The result of our study about diabetes was supported by the study of Norman et al [11], which was conducted in the families of five patients with PCOS and reported that increased insulin levels were common among the first-degree relatives. Collina et al [12] noted that there was a heritable component of B-cell dysfunction in the families of women with PCOS. In our study, the rate of diabetes in maternal family was higher than in paternal family. Whether maternal or paternal inheritance is more significant in diabetes has been a matter of controversy and differs in various populations and races [13]. In a study which was conducted in Fars center referrals on south Iranian population, maternal history of diabetes was stronger than paternal history of diabetes among both type I and type II diabetes populations [14].

PCOS itself has been accepted as a major risk factor for development of type II diabetes. Diabetes screening in these patients is recommended according to the current American Diabetes Association guidelines [15]. Based on the results of our study, screening test should be recommended particularly in maternal family of PCOS patients. Meanwhile, the number of people with diabetes in the world is estimated to double between 2000 and 2030, based solely upon demographic changes [16]. Therefore, early diagnosis and prevention of diabetes complications, especially in the high risk group, are economically important for governments.

Some evidence suggests that women with PCOS may also be at an increased risk of having a personal history of ovarian and breast cancer [7, 1] and high levels of hormones, particularly estrogens, are casually associated with increased breast cancer risk [17, 18]. However, in our study, there was not any case of ovarian or breast cancer either in PCOS patients or in total infertile population. This contradiction may be due to several factors:

First, it is probable that estrogens act as promoters rather than being directly causal. Even as promoters, lifetime exposure to estrogens is not necessary. The cause is most probably a lifestyle factor, changes wherein can rapidly alter risk [19]. It has been suggested that a high body mass index (BMI) can be associated with irregular or long menstrual cycles or with PCOS. It has been suggested that anovulation, which is associated with such characteristics and with decreased estradiol and progesterone levels, may explain the lower risk of breast cancer in these women [20]. However Michels' study revealed that BMI during earlier periods of adult life was more consistently associated with breast cancer than BMI during adulthood [20].

Another factor is that breast cancer risk rises throughout life in almost all population and the rate at which the risk rises decreases significantly around age 50 years [21]. However, in this study, patients belong to young population and the mean age of total population is less than 30 (29.53 ± 5.28). Therefore, the rate of cancer is estimated to be lower in this group. As we know, the incidence of breast cancer is different among populations. Several investigations detected some ethnic differences in mammographic densities as indicators of breast cancer risk [22, 23]. Based on Table 2, PCOS group had three cases of breast cancer among the relatives and the control group had 12 cases of breast cancer among the relatives. Therefore, the result of our study revealed that breast cancer in the relatives of infertile population (without PCOS) was significantly higher than PCOS patients. Our results are inconsistent with the results of Atiomo and Hunter studies [8, 9]. These disparities may be due to the small sample size of tested group in the Atiomo study, genetic in origin or intrauterine and environmental factors.

The strength of our study was a good sample size. However, our study had some limitations: First, we did not have any information about hormonal levels, insulin resistance and environmental factors in patients and their relatives. Second, our data showed no possible explanation of association between PCOS and other disease.

In conclusion, this study showed a positive association between PCOS and diabetes not only in PCOS patients but also in their maternal families. This study could be a preliminary investigation. Therefore, to confirm the

genetic association, further study with more data will be required.

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