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REPRODUCTIVE PHYSIOLOGY AND DISEASE

Paternal history of diabetes mellitus and hypertension affects the prevalence and phenotype of PCOS

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Abstract
Purpose The purpose of the present study is to determine if paternal or maternal history of diabetes mellitus (DM) and hypertension (HT) contributes to the prevalence and phenotype of polycystic ovary syndrome (PCOS).
Methods We performed an epidemiologic study about PCOS from four districts in Beijing, China, between 2008 and 2009. Parental histories of DM and HT were collected, and the basic characteristics and serum indices of 123 PCOS patients and 718 non-PCOS controls were tested.
Results The prevalence of a parental history of DM and HT was significantly higher in PCOS patients than non-PCOS women (17.1 % vs. 9.2 % and 42.3 % vs. 26.0 %, $P<0.05$, respectively). When paternal history was separated from maternal history, only a paternal history of DM and HT reached statistical significance between PCOS and non-PCOS patients (odds ratio (OR)=3.42, 95 % confidence interval (CI)=1.69–6.91; OR=2.50, 95 % CI=1.58–3.93, respectively). A paternal history of both DM and HT was significantly associated with sex hormone-binding globulin, fasting plasma glucose, and fasting insulin levels, the free androgen index, and the homeostatic model assessment-insulin resistance in PCOS patients ($P<0.05$ for all). There was no independent association between maternal history and the clinical or biochemical phenotype of PCOS.
Conclusions PCOS patients with a positive paternal history of both DM and HT have an adverse endocrine and metabolic profile. A paternal history of DM and HT poses a risk to PCOS.

Keywords Polycystic ovary syndrome (PCOS) · Paternal history · Diabetes mellitus · Hypertension · Phenotype

Capsule We define a subset of PCOS patients with a positive paternal history of both DM and HT as a high-risk group with an increased prevalence of endocrine and metabolic disturbances.

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Introduction

Polycystic ovary syndrome (PCOS) is a common reproductive, endocrine, and metabolic disorder characterized by oligoanovulation, hyperandrogenism, insulin resistance, and polycystic morphology of the ovary, which accounts for 5–10 % of women of reproductive age [1, 2]. Since first described by Stein and Leventhal in 1935 [3], PCOS has gained special interest in clinical and basic research; however, we still know little about the pathogenesis of PCOS. An abundance of evidence has confirmed that there is a familial clustering of PCOS [4–6]. Numerous candidate genes have been reported

to be associated with obesity, elevated testosterone levels, and the metabolic disturbance in PCOS patients [7–10].

Insulin resistance (IR) is common in PCOS patients and plays an essential role in the pathophysiology of endocrine and metabolic complications of PCOS patients. It has been suggested that IR contributes to PCOS and an increased risk of metabolic syndrome (MetS), type 2 diabetes mellitus (T2DM), and cardiovascular disease [11]. Furthermore, evidence has shown that a family history of diabetes mellitus (DM) and MetS is significantly higher among women with PCOS and strongly associated with an increased risk of DM and metabolic disorders in women with PCOS [12]. Lerchbaum et al. [13] reported that a positive family history of DM was independently associated with metabolic disorders, while a positive family history of PCOS was independently associated with hyperandrogenism. Kulshreshtha et al. [14] reported that the number of parents with hypertension (HT) and DM is associated with the initial symptoms of PCOS. No additional studies separated a paternal history of DM and HT from a maternal history of DM and HT. The aim of our study was to determine if a paternal or maternal history of DM and HT contributed to the prevalence and phenotype of PCOS.

Materials and methods

We performed an epidemiologic study involving PCOS patients from four districts in Beijing, China, between 2008 and 2009. A total of 1083 women were involved in the study, and 930 women completed the questionnaire. Only reproductive-aged women (21–45 years of age) were enrolled in the final data analysis. Women who took any medications affecting endocrine and metabolic parameters were ruled out (Fig. 1). The study was approved by the Ethics Committee of Peking University Third Hospital, and written informed consent was obtained from all participants.

A detailed history was obtained from all participants, and a complete physical examination was performed, including age, height, weight, waist and hip circumferences, blood pressure, menstrual cycle characteristics, pelvic ultrasonography, and serum indices. Parental histories were collected through questionnaires. The questions were arranged as follows: parental history of DM and/or HT (yes or no; father or mother). In addition, information was collected with respect to histories of gynecologic tumors, infertility, and oligomenorrhea in the mother and a history of premature alopecia in the father. Parental history was considered positive if the father or mother was diagnosed by specialists and on medications; otherwise, the history was recorded as negative. The body mass index (BMI) was calculated as the weight/height^2. Central obesity was calculated as the waist–hip ratio (WHR). Transvaginal ultrasonography

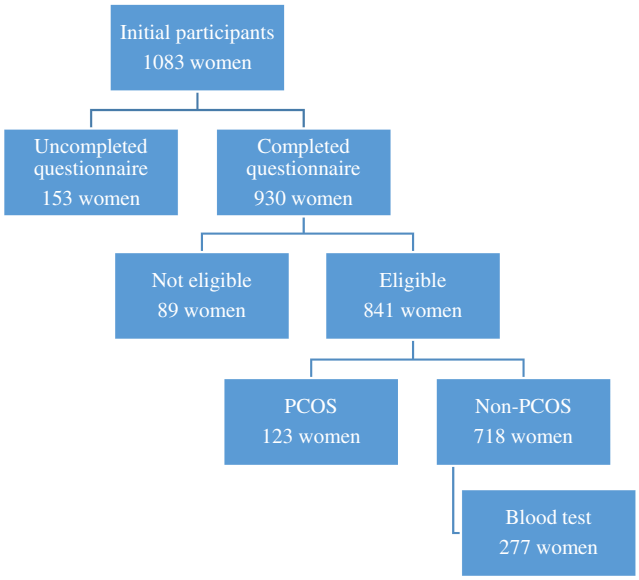

Fig. 1 Flowchart of participants for the study involving the prevalence of PCOS in Beijing

was performed to detect the volumes of the uterus and ovary and the number of antral follicles. Polycystic ovary (PCO) was defined as >12 follicles in each ovary, measuring 2–9 mm in diameter, and/or >10-mL ovarian volume bilaterally [15].

Among the non-PCOS women, 277 were selected based on blood testing as normal controls who had no clinical evidence of hyperandrogenism and were not taking any hormonal medications. Blood samples were collected in the morning after fasting for >8 h. Total testosterone (TT), androstenedione (A), sex hormone-binding globulin (SHBG), and fasting insulin (FI) were tested by chemiluminescence (intra- and inter-assay coefficients of variation <10 %; DPC, USA). Serum total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) levels were determined using a dry-slide enzymatic colorimetric assay. The fasting plasma glucose (FPG) level was tested using the finger stick blood glucose method (Roche ACCU-Chek). IR was determined by the homeostatic model assessment (HOMA-IR=fasting glucose×fasting insulin/22.5). The free androgen index (FAI) was defined as TT×100/SHBG.

The diagnosis of PCOS was based on the 2003 Rotterdam consensus [16], containing at least two of the following three characteristics: (1) oligoovulation or anovulation, (2) clinical and/or biochemical signs of hyperandrogenism, and (3) polycystic ovaries. In addition, other etiologies (congenital adrenal hyperplasia, androgen-secreting tumors, and Cushing's syndrome) were excluded.

Metabolic syndrome was diagnosed according to the NCEP ATP III guidelines [17]. MetS was diagnosed if three or more of the following five findings were present: (1) high

blood pressure ≥130/85 mmHg or anti-hypertensive drugs prescribed, (2) hypertriglyceridemia (TG ≥1.7 mmol/L, (3) low HDL (<1.3 mmol/L), (4) high FPG (≥5.6 mmol/L), and (5) central obesity (waist circumference ≥80 cm for Chinese).

Statistical analysis

All data were recorded and analyzed by SPSS software (version 19; SPSS, Inc., Chicago, IL, USA). Categorical variables were presented as proportions and analyzed by the chi-square test or Fisher's exact test, as appropriate. The normality of continuous variables was analyzed by the Kolmogorov–Smirnov test or analysis of variance (ANOVA). Variables of normal distribution were presented as the mean±standard deviation (SD) and analyzed by an independent sample *t* test or ANOVA. Variables of non-normal distribution were presented as the median (interquartile range) and tested by the Mann–Whitney *U* test or Kruskal–Wallis *H* test. Binary logistic regression and linear regression analyses were used to examine independent predictors. Statistical significance was considered present if the *P* value was <0.05.

Results

There were 841 women eligible for the study (123 PCOS patients and 718 non-PCOS controls). All PCOS and 277 non-PCOS patients underwent blood testing. The demographic data are presented in Table 1. The PCOS group had a younger age, earlier age of menarche, more rapid heart rate, smaller uterine volume, larger ovarian volume, and significantly greater antral follicle count. With respect to blood test results, the PCOS group had higher levels of TT and A and lower levels of SHBG and HDL compared with the control group. With respect to menstrual status, 54.5 and 6.9 % of PCOS patients and controls had cycle disorders, respectively. There was no significant difference in menstrual duration, menstrual volume, and dysmenorrhea.

The prevalence of parental histories is shown in Supplement 1. There was an increased prevalence of parental DM histories in the PCOS group compared to the control group (17.1 vs. 9.2 %, odds ratio (OR)=2.03, 95 % confidence interval (CI)=1.19–3.47, *P*=0.008). The prevalence of parental histories of HT was more frequent in PCOS patients than non-PCOS controls (42.3 vs. 26.0 %, OR=2.08, 95 % CI=1.40–3.09, *P*<0.0001). Additionally, parental histories of gynecologic tumors, oligomenorrhea, and premature alopecia were more common in the PCOS group. Interestingly, when paternal history was separated from maternal history, the only significant difference between PCOS and non-PCOS patients involved paternal DM and HT histories (10.6 vs. 3.3 %, OR=3.42, 95 % CI=1.69–6.91 and 26.8 vs. 12.8 %, OR=2.50, 95 % CI=1.58–3.93, respectively); there was no significant difference in maternal DM and HT histories between the groups (7.3 vs. 6.3 %, OR=1.18, 95 % CI=0.56–2.48 and 18.7 vs. 16.2 %, OR=1.19, 95 % CI=0.73–1.96, respectively; Fig. 2). Moreover, binary logistic regression analyses confirmed that paternal DM and HT histories are independently associated with the prevalence of PCOS adjusted for other family medical histories (OR=2.62, 95 % CI=1.23–5.57 and OR=1.97, 95 % CI=1.20–3.24, respectively).

To determine whether or not a paternal history of DM and HT affects the phenotype of PCOS, we divided PCOS patients into two groups based on a positive versus negative paternal history. As shown in Table 2, the serum level of SHBG was significantly lower in the exposure group than the negative group (38.10 vs. 50.92, *P*=0.004). Therefore, the calculated FAI was significantly higher in PCOS patients with a positive paternal history than the negative paternal history group (4.66 vs. 3.35, *P*=0.022). The BMI, WHR, FPG, lipid parameters, and prevalence of MetS and irregular menstruation were comparable within the groups. When a paternal DM history was separated from a paternal HT history, a lower SHBG level was noted in the positive paternal DM and positive paternal HT history groups. In addition, a higher FAI was shown in the positive paternal DM history group than the negative paternal DM history group (Supplement 2 and 3, respectively). When dividing PCOS patients based on a positive versus negative maternal history, only a lower A level was noted in the exposure group; the other indices did not differ significantly between the groups (Table 3). Linear regression analysis showed that SHBG and FAI were significantly related to paternal DM and HT histories after correcting for age, BMI, and other family history (Table 4).

We conducted further analyses that divided PCOS patients into three groups based on the number of paternal diagnosed diseases. Patients were assigned to group 0 if there was no paternal history of DM or HT, group 1 if there was a paternal history of DM or HT, or group 2 if there was a paternal history of both DM and HT. An increasing trend of FPG, FI, FAI, and HOMA-IR was demonstrated in group 2 (Table 5); a decrease of SHBG was observed in group 2. Endocrine and metabolic homeostasis was decreased with the increase in the number of affected paternal diseases. While we also divided PCOS patients based on the number of affected maternal diseases, no significant difference was observed between groups except a lower A level in group 1 compared to group 0 (Table 6).

Discussion

In the current study, we investigated all of the reproductive-aged women from four districts in Beijing. The PCOS patients

Table 1 The baseline characteristics of PCOS and non-PCOS patients

	PCOS (n=123)	non-PCOS (n=718)	P value
Age (years)	31 (27–35)	37 (31–40)	<0.0001*
Menarche (years)	14 (13–16)	15 (14–16)	0.009*
BMI (kg/m^2)	22 (20–26)	23 (21–26)	0.297
WHR	0.83±0.06	0.82±0.06	0.084
SBP (mmHg)	115 (110–120)	110 (110–120)	0.171
DBP (mmHg)	80 (70–80)	74 (70–80)	0.626
HR (bpm)	78 (75–80)	76 (74–80)	0.044*
Uterine volume (cm^3)	83.03 (68.80–99.84)	97.02 (76.52–121.64)	<0.0001*
Endometrial thickness (mm)	8 (7–10)	9 (7–10)	0.717
L-ovarian volume (cm^3)	10.40 (7.14–13.67)	5.89 (4.02–8.77)	<0.0001*
L-AFC	12 (9–15)	4 (3–6)	<0.0001*
R-ovarian volume (cm^3)	9.54 (7.05–14.03)	6.40 (4.12–9.75)	<0.0001*
R-AFC	12 (8–15)	4 (3–6)	<0.0001*
TT (nmol/L)	1.61 (1.03–2.24)	0.87 (0.69–1.20)	<0.0001*
A (nmol/L)	13.30±4.42	7.28±2.32	<0.0001*
SHBG (nmol/L)	46.39±23.44	59.59±28.37	<0.0001*
FPG (mmol/L)	4.80 (4.50–5.43)	5.00 (4.58–5.51)	0.563
FI (IU/L)	4.86 (2.41–11.35)	3.97 (2.00–7.71)	0.096
TG (mmol/L)	1.08 (0.80–1.90)	1.04 (0.79–1.50)	0.245
TC (nmol/L)	4.37±1.22	4.45±0.90	0.525
HDL (nmol/L)	1.19 (0.96–1.40)	1.28 (1.12–1.48)	0.005*
LDL (nmol/L)	2.12 (1.67–2.54)	2.09 (1.77–2.48)	0.869
FAI	3.62 (2.16–6.46)	1.72 (1.12–2.70)	<0.0001*
HOMA-IR	1.34 (0.62–3.26)	1.17 (0.56–2.18)	0.340
MetS (%)	31.8 (28/88)	24.2 (38/157)	0.197
Menstrual irregularities (%)	54.5 (67/123)	6.9 (49/714)	<0.0001*
Dysmenorrhea (%)	37.4 (46/123)	38.2 (271/710)	0.871

Data are presented as the median (interquartile range), mean±SD, or proportion (%, n/N)

PCOS polycystic ovary syndrome, *BMI* body mass index, *WHR* waist-to-hip ratio, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HR* heart rate, *L-AFC* left antral follicle count, *R-AFC* right antral follicle count, *TT* total testosterone, *A* androstenedione, *SHBG* sex hormone-binding globulin, *FPG* fasting plasma glucose, *FI* fasting insulin, *TG* triglycerides, *TC* total cholesterol, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *FAI* free androgen index, *HOMA-IR* homeostatic model assessment-insulin resistance, *MetS* metabolic syndrome

*Refers to statistical difference

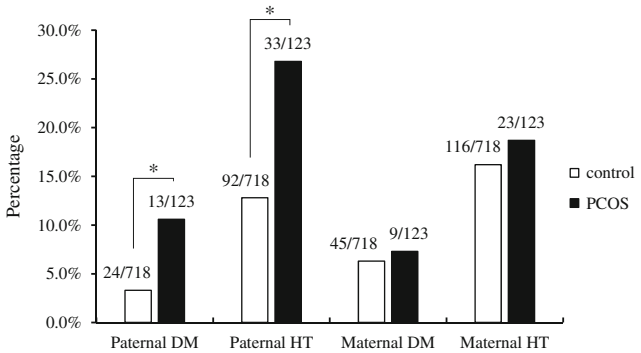

Fig. 2 The prevalence of a parental history of DM and HT in PCOS patients and the controls. Data are presented as n/N and analyzed by chi-square test/Fisher's exact test. *Asterisk* refers to statistic difference; *DM* diabetes mellitus, *HT* hypertension

presented with irregular menstruation, PCO morphology, androgen excess, and an increased prevalence of endocrine and metabolic disorders, features which were consistent with the characteristics of PCOS according to international consensus. The PCOS group is known to be at a higher risk for long-term complications of coronary heart disease (CHD), DM, and MetS. Elevated heart rate is an early marker of myocardial ischemia [18]. An anti-atherogenic lipoprotein, HDL, plays an important role in reverse cholesterol transport from tissues to liver and has been associated with a lower risk of CHD and MetS [19]. Larger ovarian volume and smaller uterine volume were observed in PCOS patients compared to the controls. Eryilmaz et al. [20] showed that the right and left ovarian volumes were significantly greater in PCOS patients than

Table 2 Characteristics of PCOS patients stratified by paternal history of DM and HT

	Positive paternal history (n=41)	Negative paternal history (n=82)	P value
Age (years)	32.10±5.03	30.79±5.30	0.196
Menarche (years)	14.15±1.54	14.44±1.71	0.357
BMI (kg/m^2)	24 (21–27)	22 (20–26)	0.732
WHR	0.83±0.05	0.83±0.06	0.530
TT (nmol/L)	1.83±0.97	1.72±0.85	0.542
A (nmol/L)	13.53±4.99	13.17±4.10	0.674
SHBG (nmol/L)	38.10±19.89	50.92±24.11	0.004*
FPG (mmol/L)	5.10±1.05	4.98±1.02	0.652
FI (IU/L)	4.99 (2.71–7.61)	4.25 (2.28–12.30)	0.917
TG (mmol/L)	1.30 (0.90–2.20)	0.96 (0.71–1.73)	0.061
TC (nmol/L)	4.54±0.99	4.29±1.32	0.286
HDL (nmol/L)	1.21 (1.02–1.53)	1.16 (0.96–1.39)	0.178
LDL (nmol/L)	2.19±0.70	2.18±0.84	0.948
FAI	4.66 (2.91–9.58)	3.35 (1.82–6.20)	0.022*
HOMA-IR	1.31 (0.90–1.50)	1.56 (0.51–4.01)	0.577
MetS (%)	36.4 (12/33)	29.1 (16/55)	0.478
Menstrual irregularities (%)	58.5 (24/41)	52.4 (43/82)	0.522

Data are presented as the median (interquartile range), mean±SD, or proportion (%, n/N)

DM diabetes mellitus, *HT* hypertension, *BMI* body mass index, *WHR* waist-to-hip ratio, *TT* total testosterone, *A* androstenedione, *SHBG* sex hormone-binding globulin, *FPG* fasting plasma glucose, *FI* fasting insulin, *TG* triglycerides, *TC* total cholesterol, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *FAI* free androgen index, *HOMA-IR* homeostatic model assessment-insulin resistance, *MetS* metabolic syndrome

*Refers to statistical difference

Table 3 Characteristics of PCOS patients stratified by maternal history of DM and HT

	Positive maternal history (n=29)	Negative maternal history (n=94)	P value
Age (years)	31.62±5.72	31.10±5.09	0.639
Menarche (years)	13.86±1.62	14.49±1.64	0.074
BMI (kg/m^2)	24 (20–27)	22 (20–25)	0.162
WHR	0.84±0.05	0.83±0.06	0.338
TT (nmol/L)	1.74±0.74	1.76±0.94	0.886
A (nmol/L)	12.03±3.16	13.70±4.69	0.035*
SHBG (nmol/L)	42.88±23.57	47.51±23.43	0.365
FPG (mmol/L)	5.01±0.82	5.02±1.07	0.973
FI (IU/L)	3.26 (2.00–14.95)	5.12 (2.61–10.25)	0.338
TG (mmol/L)	1.25 (0.85–2.16)	1.08 (0.78–1.85)	0.689
TC (nmol/L)	4.42±1.32	4.36±1.19	0.833
HDL (nmol/L)	1.20±0.35	1.24±0.47	0.656
LDL (nmol/L)	2.27±0.92	2.15±0.75	0.476
FAI	4.31 (2.19–9.13)	3.62 (2.01–6.18)	0.412
HOMA-IR	1.28 (0.44–3.74)	1.43 (0.63–3.15)	0.808
MetS (%)	36.4 (8/22)	30.3 (20/66)	0.597
Menstrual irregularities (%)	65.5 (19/29)	51.1 (48/94)	0.172

Data are presented as the median (interquartile range), mean±SD, or proportion (%, n/N)

DM diabetes mellitus, *HT* hypertension, *BMI* body mass index, *WHR* waist-to-hip ratio, *TT* total testosterone, *A* androstenedione, *SHBG* sex hormone-binding globulin, *FPG* fasting plasma glucose, *FI* fasting insulin, *TG* triglycerides, *TC* total cholesterol, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *FAI* free androgen index, *HOMA-IR* homeostatic model assessment-insulin resistance, *MetS* metabolic syndrome

*Refers to statistical difference

Table 4 Linear logistic regression analyses of SHBG and FAI using parental history of DM and HT as explanatory variables adjusting for age, BMI, and other family history

	Paternal DM		Paternal HT		Maternal DM		Maternal HT	
	OR (95 % CI)	*P* value	OR (95 % CI)	*P* value	OR (95 % CI)	*P* value	OR (95 % CI)	*P* value
SHBG	−15.34 (−27.47 to −3.21)	0.014*	−11.75 (−20.68 to −2.81)	0.010*	−5.06 (−19.15–9.04)	0.478	1.70 (−8.14–11.53)	0.733
FAI	5.14 (2.46–7.82)	<0.0001*	2.61 (0.63–4.59)	0.010*	−0.25 (−3.37–2.87)	0.873	0.21 (−1.97–2.38)	0.851

SHBG sex hormone-binding globulin, *FAI* free androgen index, *DM* diabetes mellitus, *HT* hypertension

*Refers to statistical difference

non-PCOS patients. With the use of a 9-MHz transvaginal transducer and Santesoft DICOM Editor Software to analyze ultrasound images, Christ et al. [21] reported that the antral follicle count, rather than the ovarian volume, reflected the severity of reproductive and metabolic disturbance in PCOS patients. Few publications involving uterine volume in PCOS patients exist [22].

Familial clustering of PCOS is well documented [23, 24]. An increased prevalence of DM and HT was observed among the parents of PCOS patients compared to non-PCOS controls in our study. More specifically, a paternal history of DM and HT was associated with the prevalence of PCOS. The morbidity of maternal DM and HT did not reach statistical significance between the groups. It appeared that a paternal history of DM and HT was a risk factor for PCOS. Kulshreshtha et al. [14] obtained the same result; specifically, a paternal history of HT is more common among PCOS patients than controls, while a maternal history of HT did not confer an increased risk for PCOS. Moini et al. [25] reported a significantly increased prevalence of maternal DM in the PCOS group than

Table 5 Characteristics of PCOS patients stratified by the number of fathers diagnosed with diseases

	0 (*n*=82)	1 (*n*=36)	2 (*n*=5)	*P* value
Age (years)	30.79±5.30	32.23±5.19	31.20±4.09	0.399
Menarche (years)	14.44±1.71	14.03±1.48	15.00±1.87	0.308
BMI (kg/m^2)	23.48±4.33	23.47±3.61	22.80±2.77	0.937
WHR	0.83±0.06	0.83±0.05	0.83±0.05	0.820
TT (nmol/L)	1.72±0.85	1.84±1.00	1.72±0.86	0.796
A (nmol/L)	13.17±4.10	13.65±5.17	12.70±3.78	0.829
SHBG (nmol/L)	50.92±24.11	40.37±19.84	21.72±11.45	0.004*†
FPG (mmol/L)	4.98±1.02	4.96±0.83	6.50±2.40	0.041†‡
FI (IU/L)	10.76±14.52	7.04±7.24	27.11±50.83	0.028†‡
TG (mmol/L)	1.32±0.83	1.56±0.88	1.68±1.18	0.298
TC (nmol/L)	4.29±1.32	4.47±0.86	5.01±1.71	0.370
HDL (nmol/L)	1.21±0.49	1.26±0.33	1.39±0.33	0.627
LDL (nmol/L)	2.18±0.84	2.13±0.65	2.61±1.00	0.442
FAI	3.35 (1.82–6.20)	4.58 (2.93–9.21)	6.54 (2.91–27.20)	0.050†‡
HOMA-IR	3.61±4.78	1.95±2.36	7.83±4.05	0.031c‡
MetS (%)	29.1 (16/55)	36.7 (11/30)	33.3 (1/3)	0.772
Menstrual irregularities (%)	52.4 (43/82)	58.3 (21/36)	60.0 (3/5)	0.813

Patients were assigned to group 0 if there was no paternal history of DM or HT, group 1 if there was a paternal history of either DM or HT, or group 2 if there was a paternal history of DM and HT. Data are presented as the median (interquartile range), mean±SD, or proportion (%, *n*/*N*)

BMI body mass index, *WHR* waist-to-hip ratio, *TT* total testosterone, *A* androstenedione, *SHBG* sex hormone-binding globulin, *FPG* fasting plasma glucose, *FI* fasting insulin, *TG* triglycerides, *TC* total cholesterol, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *FAI* free androgen index, *HOMA-IR* homeostatic model assessment-insulin resistance, *MetS* metabolic syndrome

**P*<0.05 for group 0 versus group 1 (SLD and Student–Newman–Keuls test); †*P*<0.05 for group 0 versus group 2 (SLD and Student–Newman–Keuls test); ‡*P*<0.05 for group 1 versus group 2 (SLD and Student–Newman–Keuls test)

Table 6 Characteristics of PCOS patients stratified by the number of mothers diagnosed with diseases

	0 (n=94)	1 (n=26)	2 (n=3)	P value
Age (years)	31.10±5.09	31.15±5.84	35.67±2.08	0.331
Menarche (years)	14.49±1.64	13.92±1.70	13.33±0.58	0.172
BMI (kg/m^2)	22 (20–25)	24 (20–27)	26 (24–27)	0.218
WHR	0.83±0.06	0.84±0.05	0.86±0.06	0.547
TT (nmol/L)	1.76±0.94	1.68±0.75	2.17±0.56	0.668
A (nmol/L)	13.70±4.69	11.69±3.07	14.83±2.92	0.044*
SHBG (nmol/L)	47.51±23.43	44.67±24.29	27.93±6.43	0.337
FPG (mmol/L)	5.02±1.07	5.01±0.86	5.00±1.00	0.999
FI (IU/L)	10.33±16.37	10.59±16.01	7.40±7.19	0.949
TG (mmol/L)	1.40±0.86	1.51±0.91	0.93±0.09	0.536
TC (nmol/L)	4.36±1.19	4.40±1.40	4.56±0.26	0.956
HDL (nmol/L)	1.24±0.47	1.21±0.37	1.09±0.16	0.817
LDL (nmol/L)	2.15±0.75	2.21±0.09	2.77±0.79	0.399
FAI	5.09±5.02	5.62±4.66	8.45±4.44	0.478
HOMA-IR	2.90±4.05	3.14±4.49	3.49±4.01	0.978
MetS (%)	30.3 (20/66)	36.8 (7/19)	33.3 (1/3)	0.863
Menstrual irregularities (%)	51.1 (48/94)	69.2 (18/26)	33.3 (1/3)	0.195

Patients were assigned to group 0 if there was no maternal history of DM or HT, group 1 if there was a maternal history of DM or HT, or group 2 if there was a maternal history of DM and HT. Data are presented as the median (interquartile range), mean±SD, or proportion (%, n/N)

BMI body mass index, *WHR* waist-to-hip ratio, *TT* total testosterone, *A* androstenedione, *SHBG* sex hormone-binding globulin, *FPG* fasting plasma glucose, *FI* fasting insulin, *TG* triglycerides, *TC* total cholesterol, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *FAI* free androgen index, *HOMA-IR* homeostatic model assessment-insulin resistance, *MetS* metabolic syndrome

*P<0.05 for group 0 versus group 1 (SLD and Student–Newman–Keuls test)

the control group, and a maternal history of DM was more predictive than a paternal history of DM. Moreover, mothers of women with PCOS had a higher HOMA-IR, an increased prevalence of MetS, and an elevated risk for CHD [26]. Whether paternal or maternal inheritance underlies PCOS has been a matter of controversy and varies in different populations and races.

Our results indicated that paternal history had a greater influence on PCOS phenotype than maternal history. A paternal history of DM and HT was shown to be independently associated with SHBG and FAI, excluding the impact of additional parental history. In contrast, maternal history was only related to the serum A level and showed no significant association with SHBG, HOMA-IR, and other recorded metabolic parameters. The prevalence of gynecologic tumors, oligomenorrhea, infertility, and premature alopecia was not different between the positive and negative history groups and had no effect on TT, SHBG, FAI, and metabolic parameters (data not shown). Our assessment and questionnaire were not comprehensive, and other confounding factors may not have been considered, such as the age of onset, severity of parental DM and/or HT, and history of CHD and MetS. SHBG was significantly lower in the positive paternal history group. SHBG is a protective factor, and a low level of SHBG might serve as a critical factor during the pathogenesis of PCOS and MetS [27]. Several sources of evidence have shown that decreased SHBG is associated with MetS and IR in women with PCOS [28–32]. Therefore, paternal history aggravates the metabolic disturbance in PCOS patients. These findings might have implications for clinical practice. Those PCOS patients with a positive paternal history of DM and HT might be at high risk for metabolic disorders. Risk stratification of PCOS patients should be done, and early prevention and treatment should be implemented.

Interestingly, our results showed an increased FAI and HOMA-IR in PCOS patients with a positive paternal history of both DM and HT, while this trend was not observed in the positive maternal history group. The third ESHRE/ASRM consensus [33] pointed out that metabolic disorders of PCOS are predictors of DM and MetS, and not all PCOS phenotypes have a similar metabolic risk. To stratify PCOS patients according to metabolic risk was suggested. We could discreetly define this subset of PCOS patients with a positive paternal history of both DM and HT as a high-risk group with an increased prevalence of endocrine and metabolic disturbances.

We separated paternal history from maternal history of PCOS patients, and it showed a different influence on the prevalence and phenotype of PCOS. The limitation of our study was that we collected the family history via questionnaires, but we did not confirm the diagnosis via medical testing. It was possible that the use of questionnaires might impair the reliability of our findings.

In conclusion, the prevalence of a parental history of DM and HT was significantly higher in women with PCOS than non-PCOS controls. A paternal history of DM and HT contributed more risk to PCOS. Not only the prevalence of PCOS, but also the phenotype of PCOS was affected by a paternal history of DM and HT. PCOS patients with a positive paternal history of both DM and HT had a higher FAI and HOMA-IR. We have thus defined PCOS women with a positive paternal history of both DM and HT as a high-risk group with an increased prevalence of endocrine and metabolic disturbances, and a parental history should be collected in clinical practice.

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