Original Article

Prevalence of metabolic syndrome in the family members of women with polycystic ovary syndrome from North India

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is the most complex and common endocrine disorder of women in reproductive years. In addition to irregular menstrual cycles, chronic anovulation and hyperandrogenism, it has many metabolic manifestations such as obesity, hyperlipidemia, hyperinsulinemia, insulin resistance, dysglycemia, increased risk of cardiovascular disease or possibly endometrial cancer. Familial clustering of PCOS in consistence with the genetic susceptibility has been described. **Materials and Methods:** The present study assessed the clinical, biochemical and hormonal parameters including prevalence of metabolic syndrome by two different criteria in the first- degree relatives of patients with PCOS. **Results:** The average age of 37 index patients was 23 ± 3.6 years, with the mean age of menarche as 13.3 ± 1.2 years. The mean age and age of menarche in mothers (n = 22) was 48.8 ± 5.1 and 13 ± 1.3 years, respectively, whereas as it was 23.5 ± 4.7 and 13.3 ± 1.2 years in sisters (n = 22), respectively. Metabolic syndrome (MS) defined by International Diabetes Federation (IDF) criteria was present in 10 index patients, 1 brother, 4 sisters, 17 mothers and 15 fathers while as by Adult Treatment Panel III (ATP III) it was in 8 index patients, 5 sisters, 16 mothers and 11 fathers. **Conclusion:** The presence of MS or related metabolic derangements is high in the family members of women with PCOS.

Key words: Adult treatment panel iii, international diabetes federation, insulin resistance, metabolic syndrome, polycystic ovary syndrome

Introduction

Polycystic ovary syndrome (PCOS) is the most complex and common endocrine disorder affecting women in their reproductive years and is characterized by irregular menstrual cycles, chronic anovulation and hyperandrogenism.[1] The specific population based studies in India shows a 3-10% prevalence of this disorder in women of reproductive age associated with increased chances for the development of metabolic syndrome (MS).[2-5] Although many metabolic disorders manifest in women with PCOS, the degree of expression is highly variable between individuals.[6] Among the metabolic disorders, obesity, hyperlipidemia, hyperinsulinemia, insulin resistance (IR) and impaired beta cell insulin secretion, type-2 diabetes are common in addition to increased risk of cardiovascular disease or possibly endometrial cancer.[7] IR and hyperinsulinemia seem to play important roles in the pathogenesis of PCOS.[8-10] However, some studies have suggested possible role of autoimmune phenomenon in the etiopathogenesis of PCOS.[11] Familial clustering of PCOS in consistence with the genetic susceptibility has been noted and well-documented in literature.[12,13] These studies have demonstrated that significant number of female relatives are affected with this condition and have increased insulin

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levels and increased risk of glucose intolerance.[14] There is also an increased risk of glucose intolerance, IR and MS in the male first-degree relatives.[15-19] The present study assessed the clinical, biochemical and hormonal parameters with estimation of MS prevalence in North Indian women with PCOS and their first-degree relatives.

Materials and Methods

The study was conducted in the departments of Endocrinology Sher-i-Kashmir Institute of Medical Sciences and department of Clinical Biochemistry, University of Kashmir, Srinagar from January 2009 to May 2010. All women presenting with complaints of oligomenorhhoea, infertility, hyperandrogenism were informed about the study. The women who qualified diagnosis of PCOS according to National Institute of Health/National Institute of Child Health and human Development (NIH/NICHHD), 1990 criteria were asked to sign an informed consent. Women with non-classical congenital adrenal hyperplasia, Cushing syndrome, thyroid dysfunction, hyperprolactinemia and androgen-producing tumors were excluded. Hundred girls with PCOS were initially enrolled in the study. Among them a total of 37 index women with PCOS along with their family members agreed to participate in the study. Of these available and living 22 mothers, 23 fathers, 22 sisters and 19 brothers agreed to participate in the study. The study was approved by Institute ethical Committee.

Study protocol

All women between 15 and 40 years age and attending the Endocrine clinic were interviewed in-detail regarding menstrual pattern, fertility duration and extent of hair growth, weight gain, acne etc., A detailed pedigree was drawn for each woman to note family history of hirsutism, infertility, menstrual disorders (except in men), diabetes mellitus, coronary artery disease, obesity in at least three generations. Anthropometric assessment including detailed height, weight, body mass index (BMI), waist/hip ratio with, blood pressure measurement and detailed systemic examination of all subjects was taken. In females, hirsutism assessment was done using modified Ferriman-Gallwey score by counting nine specific body areas by a single observer. Acne vulgaris was assessed in all subjects and acne grade III and above was taken as clinical feature of hyperandrogenemia along with the extent of androgenic alopecia. Oral glucose tolerance test (OGTT) was performed between 08.00-10.00 hour after three days, 300g carbohydrate diet and an overnight fast of 10-11 hours. A 75g oral glucose load was administered and blood samples were collected at 0, 60, 120 minutes for glucose and insulin determination. The basal blood samples were taken for lipid profile, liver and kidney functions and normal analysis including 17-hydroxy-progestrone (17-OHP), T_4, TSH, PRL and cortisol dynamics (morning, evening or overnight dexamethasone suppression if needed), in all subjects. In women, the samples for LH, FSH and testosterone were collected on 3rd-7th day of spontaneous or medroxy-progestrone induced (in amenorrhea patients) menstrual cycle. The ultrasonography (USG) was done by a single observer to record typical features of PCOS and rule out any adrenal or ovarian mass lesion.

Assays

Blood samples for hormones were centrifuged and serum stored at -20°C until analyzed. Hormonal assay were done by radioimmunoassay (RIA) (FT3, FT4, Cortisol, 17-OHP and T) and immunoradiometric assay (IRMA) (TSH, LH, FSH and PRL) using commercial kits in duplicate and according to supplier protocol (Shinjin, Korea for TSH; Immunotech France for T, 17-OHP, cortisol, PRL, LH and FSH). Serum insulin was measured by Electrochemiluminiscence (Cobas e411, Roche Diagnosed Limited Charles Avenue, Burgess Hill, West Sussex). Plasma glucose (mg/dl) was measured by glucose oxidase peroxidase method on Hitachi 912, Japan intra and inter-assay variations were within the limits by manufacturer.

Defining metabolic syndrome

The confirmed cases of PCOS as well as all the first-degree relatives enrolled for the study were subjected to Adult Treatment Panel III (ATP III) criteria for qualifying syndrome X; which may be defined as having at least three of the following:

1. Waist circumference ≥ 102 cm or 40 inches (male), ≥88 cm or 36 inches (female).
2. Triglycerides (TG) ≥1.7mmol/L (150mg/dl)
3. HDL-C < 40 mg/dl (male), <50 mg/dl (female)
4. Blood pressure ≥ 130/85 mmHg
5. Fasting plasma glucose ≥ 110 mg/dl (6.1mmol/L).

MS defined by ATP III was also compared with International Diabetes Federation (IDF) criteria.[20] MS by IDF may be defined as Central obesity {defined as waist circumference ≥94 cm (male), ≥80 cm or (female)} and any two of the following:

1. TG > 150 mg/dl (1.7mmol/L)
2. HDL-C < 40 mg/dl (male), <50mg/dl (female)
3. Blood pressure ≥ 130/85 mmHg
4. Fasting plasma glucose > 100 mg/dl (5.6mmol/L).

Statistical analysis

The data was described as mean ± SD and percentage. Intergroup comparison of pedigree was done by student's *t*-test, Mann Whitney U-test and F-test (ANOVA). $P < 0.05$

was considered significant. Analysis of data was done by SPS 11.5, Minitab 14.0 and Microsoft Excel.

Results

The average age of index patients (n = 37) was 23 ± 3.6 years (13-28), with the mean age of menarche at 13.3 ± 1.2 years (11-16). Among the 22 mothers, mean age and mean age of menarche was 48.8 ± 5.1 years (40-59) and 13 ± 1.3 years (11-15) as was in, 22 sisters 23.5 ± 4.7 years (15-35) and 13.3 ± 1.2 years (11-15), respectively. Mean age of 23 fathers was 55.2 ± 5.6 years (48-70), while mean age of 19 brothers was 23.4 ± 5.2 years (11-32). Thirty four (91.9%) of index patients, 20 (90.91%) sisters and 7 (43.8%) mothers had irregular cycles. Ovarian morphological criteria suggestive of PCOS are seen in 28 (87.5%) index PCOS women, 10 (62.5%) sisters and 2 (9.09%) mothers. Hirsutism score (>9) as calculated by modified Ferriman-Gallwey score was present in 34 (91.9%) index patient, 21 (95.5%) sisters and 19 (86.4%) mothers [Table 1]. Androgenic pattern of alopecia was noted in 13 (35.1%) index patient, 8 (36.4%) sisters and 13 (59.1%) mothers. Premature balding on clinical assessment or by self-reporting was present in 14 (73.7%) brothers and 17 (73.9%) fathers. Acanthosis nigricans of varying grades was seen only in 2 (5.4%) index patients, 2 (9.1%) sisters, 9 (40.9%) mothers and one (4.3%) father. About 15/37 (40.5%) index patients and 7/22 (31.8%) sisters, had moderate grade acne. Severe grade acne was present in 9 (24.3%) index patients and 2 (9.1%) sisters. While one (5.3%) brother and one (4.5%) mother had only moderate grade acne.

Taking BMI cutoff of 23 kg/m^2, according to WHO criteria for Asians, 25 (67.5%) of index patients, 14 (73.6%) brothers, 17 (77.2%) sisters, 21 (95.4%) mothers and 19 (82.6%) fathers were obese. Details of the clinical parameters are given in Table 1.

Impaired fasting glucose (IFG > 100mg/dl) was present in 9 (36%) index patients, 3 (12%) sisters, 3 (12%) mothers, 5 (20%) fathers and 4 (16%) fathers. Three (10%) index patients, 8 (26.6%) sisters, 6 (20%) mothers, 7 (23.3%) fathers, 6 (20%) brothers had impaired glucose tolerance (IGT). Nine mothers, 2 fathers and 2 sisters were diagnosed with type-2 diabetes during the study. Comparison of biochemical features and IR indices is given in Table 2. The serum fasting insulin was elevated in 13 (35.14%) index patients, 16 (27.27%) mothers, 11 (50%) sisters and 9 (47.37%) brothers with a cutoff of >10 μIU/ml, insulin values were not available in fathers group. IR by HOMA (>2)[21] was present in 72.4% index patients, 30% brothers, 72.2% sisters, 100% mothers and 2% cousin sisters.

Serum testosterone of >80 ng/ml (defined as hyperandrogenism in women) was present in 15 (40.54%)

Table 1: Comparative description of clinical parameters of index-PCOS women and their family members

Parameter	Index PCOS women (*n*=37)	Sister (*n*=22)	Mother (*n*=22)	Father (*n*=23)	Brother (*n*=19)
No. of cycles/ year	6.7±2.5	8.0±2.9	9.6±3.5	_	_
Hirsutism duration (years)	3.7±1.9	3.5±1.6	9.6±5.6	_	_
FG Score	13.3±4.7	12.5±3.6	11.0±3.7	_	_
Height (cms)	156.4±5.1	156.3±4.9	153.8±3.0	164.8±5.4	165.6±7.7
Body weight (kgs)	61.9±9.0	63.2±9.9	70.9±10.7	69.0±5.7	67.5±7.2
Waist Circumference (cm)	81.9±12.1	83.3±9.9	98.3±8.7	94.0±5.2	88.0±7.4
Hip circumference (cm)	90.5±7.5	92.0±7.3	94.3±6.1	93.0±4.9	89.6±8.3
W/H	0.9±0.1	0.9±0.1	1.0±0.1	1.0±0.1	1.0±0.1
BMI (kgs/m2)	25.4±3.9	25.9±4.2	30.0±4.5	25.5±2.2	24.8±3.4
SBP (mmHg)	120.1±9.5	118.5±8.1	131.0±8.9	128.6±9.4	117.6±6.6
DBP (mmHg)	79.2±6.0	78.5±6.7	84.8±6.8	83.6±6.6	79.4±2.4

BMI: Body mass index, PCOS: Polycystic ovary syndrome

Table 2: Comparative description of fasting and post-OGTT glucose and insulin sensitivity parameters of index-PCOS women and their family members

Parameter	Index PCOS women (*n*=37)	Sister (*n*=22)	Mother (*n*=22)	Father (*n*=23)	Brother (*n*=19)
BG Fasting (mg/dl)	93.4±17.3	99.5±19.1	132.5±51.9	99.7±25.4	89.9±11.7
BG post OGTT-1hr (mg/dl)	128.6±42.1	133.3±33.7	47.7±38.0	122.7±32.5	122.6±27.8
BG post OGTT -2hr (mg/dl)	118.4±29.9	125.1±31.2	196.5±80.2	144.9±38.0	118.8±32.0
Fastinginsulin (μU/ml)	17.3±15.9	11.6±4.5	14.7±7.6	-	13.5±17.1
Insulin post OGTT-1hr (μU/ml)	69.5±64.6	60.8±39.6	45.6±7.0	-	46.4±31.4
Insulin post OGTT-2hr (μU/ml)	57.7±37.9	62.8±50.3	6.4±1.7	-	26.3±22.9
Belfiore index	0.005±0.002	0.005±0.002	0.004±0.001		0.008±0.006
HOMA	4.2±4.6	2.7±1.3	3.9±0.9		3.1±4.4
QUICKI	0.32±0.3	0.33±0.02	0.32±0.01		0.35±0.04
Ranynaud index	3.5±1.8	4.09±1.9	3.1±1.6		5.7±3.7

OGTT: Oral glucose tolerance test

Table 3: Comparative description of hormonal parameters of index-PCOS women and their family members

Parameter	Index PCOS women (*n*=37)	Sister (*n*=22)	Mother (*n*=22)	Father (*n*=23)	Brother (*n*=19)
Serum LH (IU/L)	4.7±3.8 (1.0-14.7)	6.2±3.9 (2.7-15.9)	6.3±8.4 (0.7-22.8)	-	4.3±4.1 (0.5-13.9)
Serum FSH (IU/L)	5.1±1.8 (1.0-8.0)	5.7±2.0 (1.4-10.2)	6.5±6.1 (0.7-17.9)	-	6.4±8.4 (2.0-31.2)
LH/FSH	1.0±0.7 (0.2-2.6)	1.2±0.7 (0.5-2.5)	0.9±0.3 (0.3-1.3)	-	1.0±0.8 (0.2-3.0)
Serum total testosterone (ng/ml)	82.5±100.9 (26.9-309.4)	66.6±31.4 (34.7-153.1)	78.9±23.7 (55.3-125.0)	-	495.9±181.0 (123.8-835.2)
Serum Prolactin (ng/ml)	12.9±4.9 (3.32-31.7)	9.2±3.1 (4.61-31.7)	11.7±45.9 (3.32-32.6)	-	-
Serum total T4 (µg/dl)	12.9±3.0 (4.7-16.8)	13.83±2.2 (4.91-17.0)	14.71±5.2 (4.2-19.0)	16.01±4.0 (5.3-18.14)	14.83±5.21 (3.8-15.32)
Serum TSH (µIU/ml)	7.7±0.68 (5.01-11.13)	6.92±1.28 (4.0-9.0)	3.32±1.77 (0.03-9.0)	6.32±2.02 (3.14-9.0)	5.82±1.28 (4.0-9.0)

PCOS: Polycystic ovary syndrome

index patients, 9 (40.9%) sisters and 2 (9.09%) mothers. The average testosterone was 82.5 ± 100.9 ng/ml (26.9-309.4) in index patients, 66.6 ± 31.4 ng/ml (34.7-153.1) in sisters, 78.9 ± 23.7 ng/ml (55.3-125) in mothers, and 495.9 ± 181 ng/ml (123.8-835.2) in brothers. Elevated LH/FSH (>2) was found in 19 (51.35%) index patients with mean 1.0 ± 0.7 (0.2-2.6), 6 (27.3%) sisters with mean 1.2 ± 0.7 (0.5-2.5) and 5 (22.7%) mothers with mean 0.9 ± 0.3 (0.3-1.3) Table 3.

MS according to IDF criteria was present in 10 (27%) index patients, 1 (6%) brothers, 4 (19%) sisters, 17 (85%) mothers and 15 (65%) fathers. Using ATP III criteria MS was present in 8 (22%) index patients, 5 (25%) sisters, 16 (80%) mothers, 11 (56%) fathers and no MS was found in brothers [Figure 1].

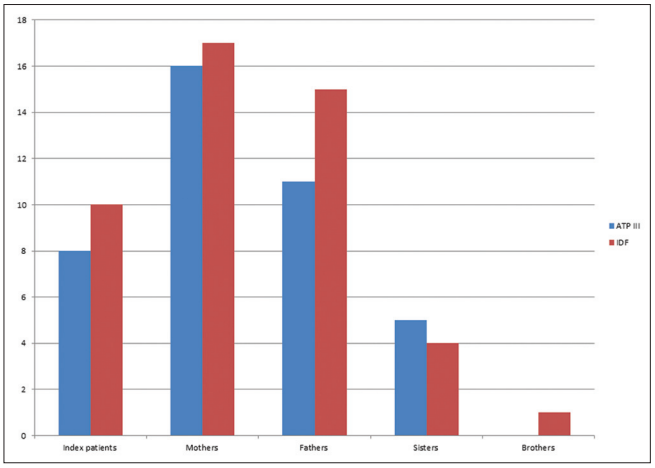

Figure 1: Bar diagram showing prevalence of metabolic syndrome in subjects by ATP III and IDF definitions

Individual parameters of MS revealed that serum TG (≥150 mg/dl) was present in 18 (48%) index cases, 10 (45%) sisters, 16 (76%) mothers, 15 (65%) fathers and 8 (42%) brothers. HDL (men > 40 mg/dl, women > 50 mg/dl) was present in 1 mother and 2 fathers.

Systolic blood pressure (>85 mmHg) was present in 8 (22%) index patients, 3 (15%) sisters, 10 (47%) mothers and 10 (45%) fathers. Diastolic blood pressure (>130 mmHg) was present in 4 (11%) index patients, 3 (15%) sisters, 10 (47%) mothers and 10 (45%) fathers.

Discussion

Although many metabolic disorders manifest in women with PCOS, the degree of expression is highly variable between individuals. MS and PCOS have a significant overlap in the various clinical and metabolic derangements, so much so that some experts have referred PCOS alternatively as syndrome XX.[22] The plethora of data shows that the phenotypic characteristics of women in the PCOS subgroups may be falling in a wide spectrum paralleling the components of MS, thereby hinting at some commonality between the two disorders. Familial aggregation of PCOS suggesting a genetic etiology has been studied and their links suggested.[23] IR and hyperinsulinemia are thought to play central role in the pathogenesis of PCOS and may be a heritable trait.

In the present study, we observed that the first-degree relatives of women with PCOS had higher presence of MS indicating this group as a high risk category for the disorder as had been earlier suggested by Bhattacharya SM and Jha A, 2011.[4] This observation lends support to the concept that the PCOS subjects and their family members are definitely at the higher risk of MS as reported earlier by Sam S *et al.* 2006, Andrea D *et al.*, 2009.[24,25] Our data strongly suggests that MS in the family members is closely related to MS in index patients. We noted that

the maximum subjects (PCOS women as well as family members) had dyslipidemia in the form of low HDL and high triglycerides. Similar observations were made by Apridonidze *et al.*, however, increased levels of LDL cholesterol along with MS in affected sisters of women with PCOS was reported by Sam S *et al.*[26,27] Das M *et al.* showed family history of type-2 diabetes can be used as an early marker for the prediction of MS in the family members in Indian population.[28] Study by Tadon N *et al.* on urban Indian adolescent also showed an increased prevalence of MS.[29]

There has been considerable interest in identifying a possible heritable component that may contribute to the PCOS phenotype. Studies evaluating phenotypes in PCOS families demonstrated that hyperandrogenemia is a common finding in female first-degree relatives of women with PCOS. Kahsar-Miller *et al.,* reported that the rates of PCOS prevalence in mothers and sisters of women with PCOS as 24% and 32%, respectively.[30] Legro *et al.* showed that 22% of reproductive aged sisters of women with PCOS fulfilled diagnostic criteria of PCOS, whereas 24% had increased testosterone and DHEAS valves with regular menstrual cycles.[13] Our study is consistent with other studies that first-degree relatives of patients with PCOS in different populations may have increased androgen levels.[19,31] The males in our study had hyperandrogenism in the form of premature balding and on assessment by self-reporting were present in 73.7% brothers and 73.9% fathers, thus confirming that premature male pattern baldness can be the male phenotype.

In our data, the serum fasting insulin was elevated in index patients and their family members. Insulin sensitivity indices and fasting insulin levels were comparable between the groups indicating higher presence of insulin resistance in the families which may be a heritable trait and therefore needs further studies at molecular genetics level. Our findings confirm the results of the preliminary study by Norman *et al.* which suggested that hyperinsulinemia may be an important marker in family members of PCOS patients.[15] Collila S *et al.,* found a heritable component of β-cell dysfunction in the families of women with PCOS, which is likely to be a significant factor for the predisposition of metabolic syndrome in these families.[32] The findings from Indian MS studies coupled with our observation may suggest a polygenetic occurrence of this syndrome.[33] Although, this is the first Indian study to evaluate familial occurrence of PCOS components, less family size and failure of all family members of the 37 PCOS patients to participate is a limitation. A similar study conducted by Natasha I *et al.,* 2006 included 35 mothers and 19 fathers of 36 PCOS girls to find the relation between PCOS and parental MS.[34] Selection bias due to phenotypic and metabolic differences between PCOS women and their family members, who did and did not participate, could not be ruled out in the present study. However, this study points to the fact that first-degree relatives of women with PCOS may form a subset of the population with increased prevalence of glucose intolerance and MS.

We conclude that the MS or its individual components are very high among Indian women with PCOS and their family members. The study clearly demonstrates that ATP III criteria underestimate the presence of MS when compared with IDF criteria. Earlier observations by Indian authors on non-PCOS subjects agree to the fact that IDF criteria rather than ATP III may suite well in Indian adolescents as well as adults.[33,35] Further large scale, controled family studies are warranted to delineate the risk of glucose intolerance and other metabolic complications as well as to propose screening and preventive strategies among family members with PCOS.

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