

*Original Article***The prevalence of metabolic syndrome and insulin resistance according to the phenotypic subgroups of polycystic ovary syndrome in a representative sample of Iranian females \***

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**Abstract**

**BACKGROUND:** Polycystic ovary syndrome (PCOS) is associated with metabolic abnormalities which are also parts of metabolic syndrome (MetS). It is debated whether all women with PCOS should be screened for MetS and Insulin resistance (IR), since they may vary in terms of PCOS phenotype, ethnicity and age. This large scale study aimed to determine the prevalence of MetS among Iranian women diagnosed with different phenotypic subgroups of PCOS based on the Rotterdam criteria.

**METHODS:** This study was conducted from January 2006 to June 2008 in Isfahan, Iran. The study population comprised females diagnosed with PCOS referred to the infertility clinic. The subjects were divided into for subgroups according to different phenotypes of PCOS based on the Rotterdam criteria. They underwent metabolic screening according to NCEP ATP III guidelines and IR screening based on homeostasis model assessment (HOMA) of insulin resistance.

**RESULTS:** The prevalence of MetS and IR were 24.9% and 24.3%, respectively. A significant difference in the prevalence of MetS was documented between anovulatory women having PCOS with or without hyperandrogenism (23.1% and 13.9%, respectively;  $p = 0.001$ ). Likewise, in PCOS women with hyperandrogenism, the MetS prevalence differed among those with or without polycystic ovary (23.1% and 63.8%, respectively;  $p = 0.001$ ).

**CONCLUSIONS:** The prevalence of MetS and IR varies between the phenotypic subgroups of PCOS. Hyperandrogenemia PCOS phenotypes of Iranian women, in particular those without sonographic polycystic ovary, are highly at risk of MetS and IR.

**KEYWORDS:** Polycystic Ovary Syndrome, Rotterdam Criteria, Metabolic Syndrome, Insulin Resistance.

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Polycystic ovary syndrome (PCOS) is the most common endocrinopathy, present in 15.2% Iranian women of reproductive age based on Rotterdam Criteria.<sup>1</sup>

It is thought that insulin resistance and compensatory hyperinsulinemia are key pathological factors of PCOS.<sup>2-5</sup>

Insulin may act directly and/or indirectly through the pituitary, to stimulate ovarian androgen production.<sup>6,7</sup>

Clinical and biochemical features of these patients may vary well according to race, ethnicity and the diagnostic criteria used.<sup>8</sup>

The most commonly used definition of PCOS includes at least two of the three following criteria: clinical and/or biochemical signs of hyperandrogenism, oligo and/or anovulation and polycystic ovary on ultrasonography, excluding other related diseases such as

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adrenal congenital hyperplasia, Cushing's syndrome and androgen-secreting tumors.<sup>9</sup>

IR also appears to play a pathogenic role in the metabolic syndrome (MetS).<sup>10</sup> The national cholesterol education program adult treatment panel (NCEP ATP III) guidelines define the MetS as having at least three of the following abnormalities: increased waist circumference, high blood pressure, elevated fasting blood glucose, low serum high-density lipoprotein (HDL) cholesterol and hyperglycemia.<sup>11</sup>

Strong evidence exists that women with PCOS have an increased risk for developing type II diabetes mellitus.<sup>12</sup> In addition, some studies found an increased risk for cardiovascular disease among these women.<sup>13</sup> PCOS patients have an eleven fold increase in the prevalence of MetS and even at a young age, the risk is enhanced.<sup>12</sup> However, prevalence varies according to the criteria used to define MetS and different dietary constituents. For instance, higher levels of HDL cholesterol in Americans as compared with those of Italians were linked to proportion of saturated fat in the dietary intake.<sup>14</sup>

Likewise among Italian PCOS women, diabetes and glucose intolerance were less prevalent as compared with PCO patients in the USA.<sup>15</sup>

Identifying women at risk for developing diabetes, hypertension, and cardiovascular disease by using simple diagnostic tools could have a beneficial impact on women's health if prevalence measures could be undertaken.

The first aim of the present study was to assess the prevalence of MetS in Iranian women with different phenotypic subgroups of PCOS according to Rotterdam criteria.<sup>9</sup> The second aim was to define clinical predictive factors in order to determine PCOS women who should or should not be screened for full lipid profile and measures of insulin sensitivity.

## Methods

The present cross-sectional comparative study was conducted from January 2006 to June 2008 in Isfahan, the second largest city in Iran. 539 female participants with PCOS were referred

to the infertility clinic in Shahid Beheshti hospital, affiliated to Isfahan University of Medical Sciences, Isfahan, Iran. We only included the subjects between the age of 18 and 42 years. They were diagnosed retrospectively according to the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine (ESHRE/ASRM) criteria, i.e. presence of at least two of the following conditions: chronic anovulation, hyperandrogenism and polycystic ovaries.<sup>9</sup> Written informed consent was obtained from all participants and the study was approved by the Ethics Committee at Isfahan University of Medical Sciences.

Weight and height were measured by standard protocol and calibrated instruments. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m<sup>2</sup>). Menstrual irregularity was assessed as the presence of chronic amenorrhea or the usual cycle length of less than 21 days or more than 35 days, or more than 4 days variation between cycles. Hirsutism was defined as the presence of excessive body hair, Ferriman-Gallwey score > 8. Biochemical hyperandrogenism was present if the calculated free androgen index  $FAI = [(testosterone/sex \text{ hormone binding globulin (SHBG)} \times 100)]$  was > 4.5.

All participants with menstrual irregularity and/or mFG score of  $\geq 8$  consented to blood test and a vaginal sonography of the ovaries. Serum thyroid stimulating hormone (TSH) (TSH, IRMA, Pooyesh Tashkhis, Tehran, Iran), prolactin (PRL, IRMA, Pooyesh Tashkhis, Tehran, Iran) and 17-hydroxyprogesterone levels were measured.

Polycystic ovaries were identified on ultrasonography (ALOKA 1000, 7.5 MHZ Probe) by either 12 or more follicles with 2-9 mm in diameter or increased ovarian volume (> 10 cm in at least one of the ovaries).<sup>10</sup>

MetS was defined according to NCEP ATP III guidelines. Individuals with at least three of the following criteria were diagnosed with MetS: increased waist circumference (> 88 cm) low serum HDL cholesterol (< 50 mg/dl in women), hypertriglyceridemia (>150

mg/dl), increased blood pressure (systolic blood pressure >130 mmHg or diastolic blood pressure > 85 mmHg) and high fasting blood glucose (> 110 mg/dl). IR was estimated using the homeostatic model assessment (HOMA-IR): (fasting Insulin  $\times$  fasting glucose) / 22.5).<sup>11</sup>

A HOMA-IR value > 3.5 probably reflects severe IR, because the HOMA-IR threshold of 3.8 was based on insulin concentration above the upper limit of normal after a 100gr oral glucose tolerance test as the standard test.<sup>16</sup>

### Statistical Analysis

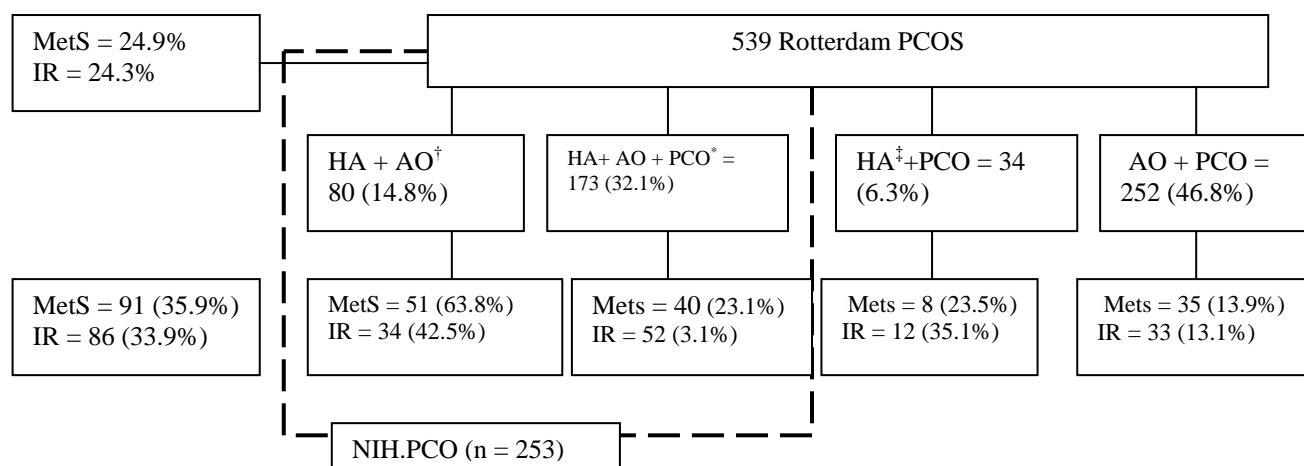
Quantitative variables were expressed as mean  $\pm$  SD and were compared between groups using one-way ANOVA, ANOVA and "Tamhane" post hoc statistical tests. Qualitative variables were expressed as frequencies in percents and were analyzed by  $\chi^2$  test. Binary logistic regression was used for quantifying the effect of predictor variables (age, waist circumference, hip circumference, BMI and phenotypic subgroups of PCOS) of MetS and IR. Data analysis was performed using SPSS15 (SPSS, Inc Chicago, USA).

### Results

Of the 550 women screened 7 women excluded

because of incomplete data and 4 because of other etiologies, which could mimic PCOS. Of the remaining 539 individuals, 173 (32.1%) had hyperandrogenism (HA) + anovulation (AO) + polycystic ovary (PCO), 80 (14.8%) had HA + AO, 252 (46.8%) had PCO+AO and 34 (4.3 %) had HA + PCO.

The mean and standard deviation of clinical and demographical characteristics of participants in the studied groups, i.e. HA + PCO + AO, HA + AO, PCO + AO and PCO + AO are presented in Table 1. The overall prevalence of MetS in women with Rott-PCOS was 24.9%. Of these, 97 cases (18%) met three criteria for MetS, 28 cases (5.2%) met four criteria and 9 cases (1.7%) met all five criteria. All women with MetS had increased waist circumference, 85% had reduced fasting plasma HDL cholesterol concentrations, 50% had high blood pressure, 75% had elevated fasting plasma triglyceride concentration, and 18% had increased fasting plasma glucose concentrations. In PCOS patients with MetS, the BMI was significantly higher than in the PCOS patients without MetS ( $28.02 \pm 5.09$  vs.  $24.63 \pm 4.52$  kg/m<sup>2</sup>, respectively;  $p < 0.05$ ). The prevalence of the MetS varied significantly according to the specific PCOS phenotypes (Figure 1).



**Figure 1.** An overview of the study cohort

\* PCO = Polycystic ovaries

† AO = anovulation

‡HA = clinical or biochemical hyperandrogenism

**Table 1.** Baseline characteristics of different phenotypic subgroups of PCOS

	HA+PCO+AO	HA+HO	PCO+AO	HA+PCO	p
Age (years)	291.6 ± 6.9	30.66 ± 0.15	28.94 ± 6.63	29.53 ± 6.46	0.255
Height (cm)	159.4 ± 5.9	159.5 ± 6.6	159 ± 5.4	158.9 ± 5.6	0.621
Weight(kg)	61.83 ± 11.3	70.4 ± 12.8	59.57 ± 10.4	62.5 ± 7.9	<0.0001
BMI(kg/m <sup>2</sup> )	24.38 ± 4.48	27.72 ± 5.03	23.33 ± 4.24	24.83 ± 3.54	<0.0001
Waist circumference (cm)	79.11 ± 12.3	88.9 ± 13.4	77.22 ± 12.5	53 ± 10.4	<0.0001
Hip(cm)circumference (cm)	105.22 ± 17.94	118.96 ± 23.61	102.22 ± 14.86	103.82 ± 9.72	<0.0001
Fasting glucose(mg/dl)	85.04 ± 12.52	89.59 ± 13.33	84.62 ± 14.93	91.97 ± 25.25	0.005
Fasting Insulin (Iu/L)	15.38 ± 4.06	16.64 ± 4.71	13.38 ± 2.95	15.47 ± 2.84	<0.0001
HOMA-IR	3.27 ± 1.14	3.74 ± 1.38	2.82 ± 0.97	3.60 ± 1.68	<0.0001
HDL cholesterol (mg/dl)	50.85 ± 7.63	49.69 ± 16.78	57.75 ± 9.25	51.03 ± 7.33	<0.0001

Data presented as mean ± SD

AO: anovulation, HA: clinical and /or biochemical hyperandrogenism

PCO: polycystic ovaries, HOMA-IR: homeostatic model assessment of Insulin resistance, HDL: high density lipoprotein, BMI: Body mass index.

Prevalence of MetS in PCOS women was 35.9% according to National Institute of Health (NIH) criteria and 13.9% in the women with only anovulation and PCO in sonography.

Also there was a significant difference in the prevalence of MetS between anovulatory women with PCOS with or without hyperandrogenism (23.1% vs. 13.9%, respectively;  $p < 0.001$ ). Among PCOS women with hyperandrogenism, the MetS prevalence differed for those with or without PCO (23.1% vs. 63.8% respectively;  $p < 0.001$ ).

Due to non-homogeneity of variance, one-way Welch's ANOVA was performed for comparing BMI between phenotypes of PCOS ( $F = 20.78$ ;  $p < 0.01$ ). Tomhane post hoc test was used for pairwise comparisons. In women with HA + AO mean BMI was significantly higher than in those with HA + AO + PCO (27.72 vs. 24.38 Kg/m<sup>2</sup> respectively;  $p < 0.01$ ). Furthermore, mean BMI in women with HA + AO was higher than those with PCO + AO (27.73 vs. 23.33 Kg/m<sup>2</sup> respectively;  $p < 0.01$ ).

The multivariable logistic regression analysis showed that BMI [OR = 1.13 (1.02-1.25 95% CI);  $p < 0.05$ ] and waist circumference [OR = 1.16 (1.1-1.22 95% CI);  $p < 0.01$ ] were associated

with the risk of having MetS. The effect related to phenotypes of PCOS was statistically significant ( $p < 0.01$ ). Among the studied groups HA+AO had the highest positive correlation with the MetS [OR = 49.6 (11.6-210.7 95% CI);  $p < 0.0001$ ]. Furthermore, waist circumference had a significant effect on MetS [OR = 1.16 (1.1-1.22 95% CI);  $p < 0.01$ ].

Insulin resistance (HOMA-IR)  $> 3.8$  was present in 24.3% of all Rott-PCOS women. Its prevalence was 33.9% in the subjects according to NIH criteria and 13.1% in the PCOS women with only anovulation and PCO.

There was a significant difference among four phenotype groups in terms of prevalence of IR ( $\chi^2 = 39$ ;  $p < 0.01$ ), as well as in the prevalence of HOMA-IR between anovulatory women with PCO with or without hyperandrogenism (30.1% vs. 42.5% respectively;  $p < 0.001$ ). Similarly, for PCOS women with hyperandrogenism, the HOMA-IR prevalence differed for those with or without PCO (30.1% vs. 42.5% respectively;  $p < 0.001$ ).

In the logistic regression analysis, the effect of belonging to AO + HA or AO + PCO on having IR was statistically significant [OR = 10.9 (6.9-19.46 95% CI);  $p < 0.01$ ]. The effect of

belonging to AO + HA + PCO phenotype on IR was also significant [OR = 1.89; (1.14-3.1 95% CI);  $p < 0.05$ ]. Furthermore, the effects of age [OR = 1.04 (1.01-1.08 95% CI)] and waist circumference [OR = 1.08 (1.05-1.12 95% CI)] were statistically significant at  $p < 0.05$  and  $p < 0.01$ , respectively.

## Discussion

We studied the prevalence of MetS and IR in different phenotypic subgroups of PCOS based on Rotterdam criteria in Iranian population. The overall prevalence of MetS in these women was 24.9%.

Prevalence of MetS in American and Italian women with PCOS was reported 43-46%<sup>17</sup> and 8.2%<sup>18</sup>, respectively. Several factors affect the prevalence of MetS, including obesity,<sup>19</sup> IR and diabetes<sup>20</sup> and polycystic ovary syndrome.<sup>21</sup> The diagnosis of MetS in the mentioned studies was based on some NCEP ATP III criteria. In the current study, the main difference may be as a result of different body weight, dietary characteristics, lifestyle and genetic factors in different countries. A recent suggestion was made to screen all obese women with PCOS for MetS.<sup>9</sup>

Several studies have reported endocrine and metabolic differences between lean and obese women with PCOS. In addition to alteration in insulin sensitivity that was independent of obesity,<sup>22</sup> these studies have demonstrated more marked hyperandrogenemia, IR, and relative hyperglycemia, and lower sex hormone binding globulin (SHBG) in the obese compared with lean women with PCOS.<sup>23</sup>

In the current study, of the subset of women who were hyperandrogenemic and also diagnosed as having PCOS according to the NIH criteria, 35.9% had MetS. This prevalence is lower than other reports in comparably classified PCOS women in the USA (43-46%),<sup>17, 24</sup> but higher than south Italian population (8%). All women in American studies presented a higher BMI compared with the Italian population.<sup>18</sup>

We found that prevalence of MetS in PCOS women with hyperandrogenism was higher

than in those without hyperandrogenism (35.9% vs. 13.9%), which is supported by some other studies.<sup>16, 25</sup> It is suggested that IR and compensatory hyperinsulinemia are key pathogenic factors in PCOS.<sup>2-5</sup> Insulin may act directly and/or indirectly through the pituitary to stimulate ovarian androgen production.<sup>6, 7</sup> IR also appears to play a pathogenic role in the MetS.<sup>10</sup>

In our study we found that the prevalence of MetS and IR in hyperandrogenic PCOS women with PCO on ultrasound was lower than those without PCO (14.8% vs. 32.1%). In a study in China, it has been showed that PCOS women without PCO had higher cholesterol and low density lipoprotein. Also, significantly higher rate of diabetes mellitus and hypertension were observed in patients' first grade relatives in subjects without PCO than in those with PCO.<sup>25</sup>

In another study in the Netherlands, it has been found that the prevalence of PCO was negatively associated with MetS and IR.<sup>26</sup> Both above findings support our current study.

On the contrary, the American study has proposed that serum insulin levels correlate with increased ovarian size and blood flow.<sup>26</sup> In another study in Germany, testosterone levels and the free androgen index significantly correlated with ovarian volume and the number of ovarian follicles.<sup>27</sup> Considering these controversies, the process mechanism responsible for PCO in sonography in PCOS patients needs to be further investigated.

The current study had some limitations. We used waist circumference of 88cm according to NCEP ATP III criteria for diagnosis of MetS. Ethnic consideration needs to be taken into account when using waist circumference for diagnosis of the MetS syndrome because optimal cut off point for waist circumference varies in different populations.<sup>28</sup>

The other study limitation is using HOMA-IR threshold value for diagnosis of IR resistance that may have underestimated the true prevalence of IR. The gold standard for establishing IR is the euglycemic hyperinsulinemic clamp. However, this elaborate procedure is

not suitable for large scale clinical use and therefore we used the HOMA-IR calculation, which correlates with the euglycemic hyperinsulinemic clamp and is often used as a surrogate marker for IR.<sup>16</sup>

The novelty of our study is including a considerable high sample size and close monitoring by specialists of obstetrics and gynecology. To the best of our knowledge, this is the first study of its kind not only in Iran, but also in the Eastern Mediterranean region.

In conclusion, the prevalence of MetS and IR varies between the different PCOS phenotypes in women with PCOS. The hyperandrogenemic PCOS phenotypes, especially without PCO, are highly related to the presence of MetS and IR in Iranian women with PCOS.

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### Conflict of Interests

Authors have no conflict of interests.

### Authors' Contributions

FM contributed in design and conducting the study as well as writing the manuscript draft; B Kh contributed in design and conducting the study and RK contributed in design of the study as well as writing and editing the manuscript; NK contributed in conducting the study. All authors read and approved the manuscript content.

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