The Prevalence of Insulin Resistance and Its Association With Thyroid-Stimulating Hormone and Obesity in Infertile Women With Different Polycystic Ovary Syndrome Phenotypes

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Abstract- The aim of this study was to investigate the prevalence of insulin resistance (IR) according to the phenotypic subgroups of polycystic ovary syndrome (PCOS) and to determine the associations of TSH levels and body mass index (BMI) with IR in infertile women with PCOS. In this cross-sectional study, we included 400 infertile women with a diagnosis of PCOS according to Rotterdam criteria who were referred to the infertility clinic of amir-al-Momenin University Hospital from April 2018- to January 2020. They were classified into four different phenotypic subgroups according to ESHRE guidelines. The homeostasis model (HOMA-IR) was used to measure IR. The prevalence of insulin resistance was 39.3% in infertile women with PCOS. Among women with PCOS, the commonest phenotype was type I (68%), with type II (18.2%), type III (8.8%), and type IV (5%), respectively. Furthermore, there was no significant difference in the prevalence of IR among different phenotypes of PCOS. Logistic regression analysis showed that the chance of insulin resistance was higher in overweight (OR: 1.76, 95% CI: 1.07, 2.88, P=0.024) and obese PCOS women (OR: 3.25, 95% CI: 1.86, 5.67, P<0.001) compared with those who were normal or underweight. Moreover, the chance of IR was higher in PCOS women with TSH ≥2.5 μIU/ml as compared with those who had TSH <2.5 μIU/ml (OR: 2.00, 95% CI: 1.18, 3.40, P<0.001). Insulin resistance is a prevalent disorder among infertile Iranian women with PCOS BMI, and serum levels of TSH ≥2.5 μIU/ml are independent predictors of IR.

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Keywords: Insulin resistance; Infertility; Obesity; Prevalence; Polycystic ovary syndrome; Thyroid-stimulating hormone

Introduction

Polycystic Ovary Syndrome (PCOS), characterized by hyperandrogenism, chronic anovulation, and polycystic ovarian morphology, is the commonest endocrine disorder that affects about 6-10% of women at reproductive age in the world (1). About 50-70% of these patients are insulin resistant (IR) and suffer from a metabolic syndrome that predisposes them to diabetes mellitus and cardiovascular disease (2). Moreover, many women with PCOS are overweight or obese. Obesity significantly worsens IR and metabolic disorders (3). Clinical and biochemical characteristics of these patients may vary according to race, ethnicity, the diagnostic criteria used (1), and the phenotypic subgroups of PCOS (4). The prevalence of IR in different studies in PCOS has been found between 27%-64% (5-7). Several studies have reported that women with PCOS are more insulin resistant when compared with the population of the same age and body mass index (BMI) (2). The circumstances leading to this phenomenon are not entirely known. Even

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though hyperandrogenaemia may play a part (8), other factors like thyroid function may be responsible as well. Thyroid hormones keep a fine balance of glucose metabolism (9). In hypothyroidism there are higher amounts of insulin because glucose absorption in muscle and adipose tissue is resistant to insulin. Whereas these changes have been established in overt hypothyroidism (9,10), the evidence regarding such an association in subclinical hypothyroidism (SCH) is conflicting (11,12).

Recently a meta-analysis demonstrated that PCOS was strongly associated with an increased risk of SCH (13). In women with PCOS, who often have IR and metabolic syndrome, the additional development of SCH may aggravate IR. Several studies were conducted to determine an association between SCH or TSH levels and IR in PCOS women (14-18) but with controversial results. However, there is no study to evaluate this association in infertile PCOS women. On the other hand, in a large-scale epidemiological survey the National Academy of Clinical Biochemistry indicated that 95% of normal people have a TSH level ≤2.5 μIU/ml and recommended lowering the upper reference limit of TSH to 2.5 μIU/ml contrary to the conventionally used levels of 4-5 μIU/ml (19). As consistent with this opinion some studies revealed that high normal TSH (2.5-4.5 μIU/ml) posed a greater risk of metabolic syndrome (20) or is associated with adverse obstetrical outcomes (21).

Objectives

Considering the contradictory results in this field, the absence of a study about the association of high normal TSH (2.5-4) and IR in the infertile PCOS women and the variation of IR with race, ethnicity and subgroups of phenotype, we decided to do a large study in the urban population of Semnan, a city in the center of Iran, in order to evaluate the prevalence of IR according to the subgroups of PCOS among infertile women and investigate the association of TSH levels (cutoff level of ≥2.5 μIU/ml and BMI with IR in these patients.

Materials and Methods

Patients

In this cross-sectional study we included 400 infertile PCOS women aged 20-36 with a period of infertility more than 1 year without other causes of infertility who referred to infertility clinic of Amir-al-Momenin University Hospital from April 2018 to January 2020. The sample was selected and enrolled to the study from the patients available at the infertility clinic until the pre-determined number was reached with a convenient approach. The sample size was calculated to be 400 using the following formula, $n = \frac{Z^2_{1-\frac{\alpha}{2}}\, p(1-p)}{d^2}$ when set the following parameters to *P*=0.05, d=0.05 and α=0.05.

The study was approved by the Research Council and Ethical Committee of Semnan University of Medical Sciences (Ethical code: IR.SEMUMS.REC.1397.019). Written informed consent and personal medical histories were obtained from each woman by using a validated questionnaire. Patients with thyroid surgery, chronic diseases such as overt hypothyroidism or hyperthyroidism, Cushing's disease, renal, liver, or cardiac dysfunction, a history of ovarian or adrenal neoplasm, hyperprolactinemia, late-onset adrenal hyperplasia, ovarian drilling, and diabetes were removed from the study. Women who had been receiving thyroid hormone or iodine medication, hormonal therapy, including oral contraceptive pills or steroid medications, or any other drugs are known to influence glucose metabolism or blood pressure (BP) within three months of their initial visit were likewise excluded.

It should be noted that the confirmed diagnosis of PCOS was made based on having at least two criteria from the following three Rotterdam criteria: 1- anovulation or oligo-ovulation 2- clinical and/or biochemical hyperandrogenism, 3- polycystic ovaries diagnosed by ultrasound (the presence of 12 or more follicles measuring 2 to 9 mm or an increase in the ovarian volume of more than 10 cm3 in one or both ovaries) and exclusion of other aetiologies. We defined anovulation or oligoovulation as oligomenorrhea (having fewer than eight menstrual cycles per year, or intermenstrual intervals ≥35 days) or amenorrhea (the absence of three to six consecutive menstrual cycles per year). They were also divided into four different phenotypic subgroups according to ESHRE guidelines: type I: hyperandrogenism, anovulation or oligo-ovulation, and polycystic ovaries; type II: hyperandrogenism and anovulation or oligo-ovulation; type III: hyperandrogenism and polycystic ovaries; and type IV: anovulation or oligo-ovulation and polycystic ovaries (22). Weight in kilogram, height in meter, and BP (mm Hg) were measured using standard methods. Hirsutism was calculated by Ferriman-Gallwey (F-G) methods. The score of ≥6 over nine body parts was

considered positive (23). The homeostasis model assessment for insulin resistance (HOMA-IR) was calculated as fasting insulin concentration (μU/mL) multiplied by fasting glucose concentration (mg/dL) divided by 405 (24).

According to Hosseinpanah *et al*., in the Iranian population (25), HOMA-IR ≥2.3 was taken as laboratory evidence of IR. After 10 hours of fasting during the 3rd-5th day of a normal menstrual cycle or menstruation happening after the daily administration of 10mg of medroxyprogesterone for a week, 5 ml of the blood sample was obtained and stored at -80° C for measuring hormonal and biochemical parameters. Leutinizing hormone (LH), follicle-stimulating hormone(FSH), 17-hydroxy progesterone (17-OHP), serum prolactin (PRL), thyroid-stimulating hormone (TSH), total testosterone (TT), dehydroepiandrosternesulfate (DHEA-S), and insulin were assessed by enzyme-linked immunosorbent using commercially available kits (DiaPlus, Inc, Canadian). It should be mentioned that the only measurement of TT may not be a highly sensitive indicator of androgen excess.So biochemical hyperandrogenism was defined by considering the TT >80 ng/dl or DHEA-S>321μg/dl. Because a small number of patients with PCOS may have isolated increase in DHEA-S (22). Blood glucose was estimated by the glucose oxidation method. We also divided the PCOS cases into four groups based on BMI: underweight (BMI< 18.5 kg/m2), normal weight (BMI: 18.5-24.9), overweight (BMI: 25-29.9), and obese (BMI ≥30).

Statistical analysis

In this study, we used the Wald method to estimate the 95.0% confidence interval (CI) for the prevalence of the insulin resistance in participants. Kolmogorov-Smirnov test was used to check the normality of the distribution of numerical variables, which was rejected for all of them. Therefore, in addition to the mean and standard deviation (SD), the median and inter-quartile range (IQR) of each were reported, and we used U Mann-Whitney test to compare them between the two groups of patients with and without insulin resistance. We used frequency distribution tables and chi-square test to describe and analyze the categorical variables. Afterwards the relationship between the serum level of TSH and insulin resistance were assessed by using multiple (full and reduced) logistic regression models, adjusting for significant variables (P<.05). Based on the results of initial marginal statistical tests, we used the backward stepwise (likelihood ratio) method to achieve the reduced model. Statistical analyses were performed with SPSS-18, and all tests were interpreted at a significance level of 5%.

Results

The average age of 400 women under study was 27.20±4.12 years. Oligo-menorrhea was present in 361 (90.25%) patients, hirsutism in 344 (86%), and hyperandrogenemia in 83(20.75%). 167 (41.8%) were overweight, and 97 (24.3%) patients were obese. 157out of the 400 (39.2%) were diagnosed to have IR. We found PCOS phenotype I in 272 patients (68%), phenotype II in 73 patients (18.2%), phenotype III in 35 patients (8.8%), and phenotype IV in 20 patients (5%). There was no significant difference in the prevalence of IR in phenotypes I to IV (40.1%, 35.6%, 34.3%, and 50%, respectively; P=0.612). We compared the basic anthropometric and biochemical characteristics in infertile PCOS women with and without IR. The two groups of with and without IR showed significant differences regarding the BMI (P<0.001), systolic blood pressure (SBP) (P=0.037), diastolic blood pressure (DBP) (P=0.029), total testosterone (P=0.003), free testosterone (P=0.022) and TSH levels (P=0.005). There was no significant difference in age, menstrual irregularity, hirsutism, acne, ovarian volume, and serum concentration of DHEAS, FSH, LH, and prolactin between IR women with non-IR women (Table 1 and 2). Logistic regression analysis indicated the significant effects of BMI and TSH in the emergence of insulin resistance in infertile PCOS women meaning that the chance of insulin resistance was higher in overweight (OR: 1.76, 95% CI: 1.07, 2.88, P=0.024) and obese PCOS women (OR: 3.25, 95% CI: 1.86, 5.67, P<0.001) compared with underweight and normal-weight women; Also, the chance of insulin resistance was higher in PCOS women with TSH ≥2.5 μIU/ml as compared with those who had TSH <2.5 μIU/ml (OR: 2.00, 95% CI: 1.18, 3.40, P<0.001) (Table 3).

Table 1. Comparison of the clinical, hormonal, and metabolic parameters in infertile polycystic ovary syndrome women with and without insulin resistance

Characteristics	Non-Insulin resistance (n=243)				Insulin resistance (n=157)				*P**
	Mean±SD	Median	Q1	Q3	Mean±SD	Median	Q1	Q3	
Age(years)	27.19±4.00	27.0	24.0	30.0	27.21±4.32	27.0	24.0	31.0	.848
BMI(Kg/m2)	25.87±4.56	25.7	22.5	28.0	28.04±4.78	27.0	25.0	31.0	<.001
Systolic blood pressure(mmHg)	112.22±7.48	110.0	105.0	120.0	113.73±7.66	115.0	110.0	120.0	.037
Diastolic blood pressure(mmHg)	74.11±5.92	75.0	70.0	80.0	75.56±6.12	75.0	70.0	80.0	.029
Right ovarian volume(cm3)	10.55±3.44	10.0	8.5	12.0	10.73±3.34	10.5	9.0	12.0	.585
Left ovarian volume(cm3)	10.16±3.38	10.0	8.0	12.0	10.58±3.05	10.0	9.0	12.0	.167
Fasting blood glucose(mg/dL)	90.22±11.16	89.0	84.0	95.0	96.56±14.01	95.0	89.0	100.0	<.001
DHEA-S(µg/ml)	.74±.52	.59	.39	.90	.76±.54	.61	.40	.90	.824
Testosterone(ng/mL)	.68±1.59	.50	.38	.71	.70±.45	.60	.42	.85	.003
Insulin(µlU/mL)	6.91±2.06	6.9	5.5	8.6	14.80±7.23	13.5	10.6	18.4	<.001
LH(mIU/mL)	6.89±4.64	5.9	3.8	8.4	6.53±3.91	6.0	3.5	8.2	.669
FSH(mIU/mL)	5.28±1.91	5.2	4.0	6.4	5.40±2.44	5.4	4.1	6.3	.739
Prolactin (ng/mL)	20.88±14.77	18.0	10.3	27.0	21.06±13.62	18.0	12.0	27.0	.531
TSH(µIU/ml)	2.93±1.91	2.58	1.7	3.6	3.63±2.89	3.0	1.9	4.5	.014
HOMA-IR	1.52±.46	1.57	1.2	1.9	3.66±1.64	3.1	2.6	4.1	<.001

*U Mann-Whitney test, BMI: body mass index, SD: standard deviation, Q1: first quartile, Q3: third quartile

Table 2. Comparison of categorical variables in infertile polycystic ovary syndrome women with and without insulin resistance

Characteristics		Non-Insulin resistant(n=243)		Insulin resistance (n=157)		*P**
		Count	%	Count	%	
Age group	**20-25**	88	36.2	67	42.7	.106
	26-30	103	42.4	50	31.8	
	31-36	52	21.4	40	25.5	
BMI group	**Underweight**	6	2.5	0	.0	<.001**
	Normal	93	38.3	37	23.6	
	Overweight	101	41.6	66	42.0	
	Obese	43	17.7	54	34.4	
Menstrual disorders	**No**	23	9.5	13	8.3	.686†
	Amenorrhea	2	.8	1	.6	
	Oligo-menorrhea	218	89.7	143	91.1	
Hirsutism	**No**	30	12.3	26	16.6	.236
	Yes	213	87.7	131	83.4	
Acne	**No**	227	93.4	144	91.7	.523
	Yes	16	6.6	13	8.3	
TSH status	**Normal(0.3-4.5)**	208	85.6	116	73.9	.004‡
	More than normal	33	13.6	39	24.8	
	Less than normal	2	.8	2	1.3	

*Pearson Chi-Square Tests, ** Underweight and normal weight were added together, † Amenorrhea and oligo-menorrhea were added together, ‡ More than normal and less than normal were added together

Table 3. Results of logistic regression analyses to assess the relationship between the serum level of TSH and insulin resistance adjusting for BMI, blood pressure, and testosterone level in infertile women with polycystic ovary syndrome

Variables		Full model				Reduced model*			
		OR	95.0% CI		*P*	OR	95.0% CI		*P*
			Lower	Upper			Lower	Upper	
BMI	Underweight/normal	1	-	-	-	1	-	-	-
	Overweight	1.76	1.07	2.89	.026	1.76	1.07	2.88	.024
	Obese	2.98	1.69	5.28	<.001	3.25	1.86	5.67	<.001
Systolic blood pressure		1.01	.97	1.04	.502	-	-	-	-
Diastolic blood pressure		1.01	.97	1.06	.379	-	-	-	-
Testosterone		1.04	.89	1.22	.578	-	-	-	-
TSH	<2.5	1	-	-	-	1	-	-	.008
	≥2.5	2.00	1.17	3.40	2.000	2.00	1.18	3.40	.010
Constant		.012	-	-	.012	.16	-	-	<.001

*Backward Stepwise (Likelihood Ratio), OR: odds ratio, CI: confidence interval, BMI: body mass index

Discussion

In the current study, the prevalence of IR among infertile women with PCOS was %39.2. We did not find any significant difference in the prevalence of IR between the different subtypes of PCOS. BMI and serum levels of TSH ≥2.5 µIU/ml were independent predictors of IR in infertile women with PCOS. The prevalence of IR in our study was similar to that recently reported for Brazilian women (39.6%) (23) but different from that of other countries: 27.0% in Vietnam (6), 60.2% in Mexico (7) in infertile PCOS women and 64% in the USA (5) and 24.3% in Iran infertile PCOS women (4). These variations could be explained by differences in the age of studied subjects, geographical region, and environmental factors such as diet, lifestyle, and the selected cut-off point for insulin resistance definition. Our study showed that the commonest PCOS phenotype was type I, which was consistent with the results of two separate studies in Mexico (7) and Brazil (26) and in contrast to that of two other studies in Iran (4) and China (27) in which type IV (non-hyperandrogenic phenotype) was the commonest. This study showed no significant difference in the prevalence of IR between different phenotypes of PCOS, similar to Shroff *et al.*, a study in 2007 (28), and Tavares *et al*., a study in 2019 (26). They also showed that abdominal obesity, irrespective of the PCOS phenotype, played a relevant role in the development of metabolic changes (26,28). However, in two other studies in Iran and Mexico; women with phenotypes that included hyperandrogenism+oligoanovulation with or without polycystic ovary had higher fasting insulin and HOMA-IR than other types (4,7). This difference may be due to the choice of the population under study, lower rates of hyperandrogenemia in this study and obesity as a more important determinant of IR than TT levels. Further studies are needed to validate our findings. The aetiology of IR in women with PCOS, although intensively studied, is not entirely obvious. It is suggested that the increased insulin receptor serine phosphorylation decreases its protein tyrosine kinase activity and is one mechanism for the post-binding defect in insulin action that selectively affects metabolic pathways in classic insulin target tissues and in the ovary (2).

We showed that patients with PCOS in the IR group had significantly higher SBP, DBP, and greater serum concentration of testosterone and TSH levels than the non- IR group. Le *et al.*, in 2017, reported the same results (7). In DeUgarte *et al*., study patients with PCOS with IR were also more androgenized and had a more severe degree of ovulatory dysfunction (5). In this study, the chance of insulin resistance was higher in overweight and obese PCOS women as compared with those who were underweight and normal weight, similar to Reyes-Muñoz *et al*., study (7). In DeUgarte *et al.*, a study in both controls and PCOS patients, IR also increased with rising BMI (5). Visceral obesity, but not subcutaneous type, causes excess lipid accumulation in the liver, which in turn leads to insulin resistance and an increased risk of type 2 diabetes mellitus (T2DM). This event may lead to faulty insulin signaling through cell-autonomous mechanisms or through the production of inflammatory cytokines by macrophages, which interfere with insulin action. Our findings also showed that TSH≥2.5 µIU/ml

was a predictive risk factor for insulin resistance in infertile PCOS women. Thyroid hormones have a big influence on glucose metabolism. In hypothyroidism, possible mechanisms supposed to explain IR include the dysregulation of mitochondrial oxidative metabolism leading to the decline of blood flow in muscle and adipose tissue (9). Although clinical hypothyroidism is associated with insulin resistance, there is controversial information about the association of IR with SCH in PCOS. Our finding confirmed the result of some other studies, such as Mueller *et al*.,'s in 2009 (16). In another study, the same group showed that women with TSH ≥2.5 µIU/ml had significantly higher BMI, IR indexes, and total and free testosterone levels in comparison with women with TSH <2.5 µIU/ml (14).

Salama *et al*., also showed that PCOS women with TSH ≥2.85 µIU/ml had significantly higher waist circumference, BP, FBS, and marker of IR as compared with PCOS women with TSH <2.85 µIU/ml (17). These are in contrast to the findings of Ganie *et al.*, in 2011 (15) and Benetti-Pinto *et al*., in 2017 (18), who did not find any significant correlation between TSH and HOMA-IR in PCOS subjects. This study has a number of advantages including the large number of homogenous infertile PCOS women without overt hypothyroidism and the use of estimates of insulin sensitivity adjusted for common cofounders, such as age, BMI and testosterone level. However, the disadvantages were the cross-sectional design, the lack of healthy women without PCOS as a control group and the evaluation of IR by the HOMA-IR, which is a less sensitive marker for insulin sensitivity than hyperinsulinemic-euglycemic clamp method.

Insulin resistance is a prevalent disorder among infertile Iranian women with PCOS. There is no significant difference in the prevalence of IR between different phenotypes of PCOS. BMI and serum levels of TSH ≥2.5 µIU/ml are independent predictors of IR in infertile women with PCOS. We recommend the correction of the BMI and assessing for the presence of IR in women with TSH levels ≥2.5 µIU/ml prior to attempting pregnancy in these groups of women.

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