

# Frequency of insulin resistance in Egyptian women with polycystic ovary syndrome

## Abstract

**Objectives:** To evaluate the prevalence of insulin resistance in polycystic ovary syndrome (PCOS) women and to compare the findings (clinical and laboratory) of PCOS in insulin resistance (IR) to non-IR PCOS women.

**Patients and methods:** Fifty PCOS women included in this cross sectional comparative study. Studied women underwent complete physical examination with calculation of BMI, assessment of hirsutism and measurement of blood pressure. Hormonal and lipid profiles of the studied PCOS women also evaluated. Fasting glucose/insulin (G/I) ratio calculated and a ratio <4.5 was predictive of IR in PCOS women above 18 years old. Studied PCOS women divided into two groups according to presence or absence of IR to evaluate the prevalence of IR in PCOS Egyptian women and the findings of PCOS in IR to non-IR PCOS women.

**Results:** IR (G/I ratio <4.5) detected in 46% (23/50) of studied PCOS women. BMI was significantly high in IR compared to non-IR PCOS women (32.6±6.0Kg/m<sup>2</sup> versus 29.5±4.0) and the hirsutism (Ferriman Gallway score >8) was significantly more common in IR compared to non-IR PCOS women (20 (86.95%) versus 5 (18.5%)). There was no significant difference between IR and non-IR PCOS studied women regarding; mean age, blood pressure, age of menarche, menstrual regularity acne and baldness. In addition, there was no significant difference between the IR women and non-IR PCOS studied women regarding; ultrasound ovarian findings, hormonal and lipid profiles.

**Conclusion:** The prevalence of IR in PCOS Egyptian women is about 46%, BMI was significantly high in IR compared to non-IR PCOS women and the hirsutism was significantly more common in IR compared to non-IR PCOS women.

**Keywords:** insulin resistance, Egyptian, PCOS

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**Abbreviations:** PCOS, polycystic ovary syndrome; IR, insulin resistance; TVS, trans-vaginal ultrasound; LH, luteinizing hormone; FSH, follicle stimulating hormone; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; ELISA, enzyme linked immuno-sorbent assay; Mabs, monoclonal antibodies; ITT, insulin tolerance tests

## Introduction

PCOS is a complex disorder affects 5-6% of women during reproductive age.<sup>1</sup> Diagnosis of PCOS based on Rotterdam ESHRE criteria by at least 2 out of 3 of the following criteria: oligo- or anovulation, clinical or biochemical hyperandrogenism and polycystic ovaries on trans-vaginal ultrasound (TVS).<sup>2</sup> Burghen et al.<sup>3</sup> first noted the association between PCOS and hyperinsulinemia. Burghen and colleagues found a significant positive correlation between insulin, androstenedione and testosterone levels among PCOS women.<sup>3</sup>

Subsequent studies confirmed IR as the cause of hyperinsulinemia in PCOS and a close association between disturbance of insulin metabolism and IR in obese and non-obese PCOS women.<sup>4,5</sup> The first step in the action of insulin involves binding to the cell-surface receptor then the receptor undergoes auto-phosphorylation accomplished by activation of receptor tyrosine kinase. The activated receptor then activates insulin receptor substrates (1,2 and 3) that in turn bind to signaling molecules (phosphatidylinositol-3 kinase) and

activate downstream signaling leading to insulin-mediated glucose transport.<sup>6,7</sup>

Reduced insulin sensitivity reported during the luteal phase of normal menstrual cycles.<sup>8</sup> Furthermore, complete suppression of ovarian steroids does not alter insulin sensitivity.<sup>9</sup> It is unlikely that anovulation is the cause of impaired insulin sensitivity and it is more likely that hyperinsulinemia and IR lead to anovulation.<sup>10</sup> Insulin stimulates ovarian androgen secretion; maintain ovarian hyperandrogenism in PCOS through direct effect of insulin on ovarian steroidogenesis or due to effect of insulin on luteinizing hormone (LH) receptors.<sup>11,12</sup> Excess androgens interfere with the follicular maturation with subsequent anovulation and follicular arrest.<sup>13</sup>

Anovulatory women with hyperandrogenism should be evaluated for IR and glucose tolerance.<sup>14</sup> While anovulatory women without hyperandrogenism should be evaluated by measuring the free testosterone and if elevated, IR and glucose tolerance should be assessed.<sup>1</sup> Insulin sensitivity may be assessed by hyperinsulinemic euglycemic clamp technique,<sup>15</sup> insulin values during oral glucose tolerance test,<sup>16</sup> fasting glucose/insulin (G/I) ratio,<sup>17,18</sup> homeostatic model assessment-insulin resistance,<sup>19</sup> infusion of glucose with model assessment or quantitative insulin sensitivity check index.<sup>16,19</sup> Identifying women with IR and those who are likely to develop IR offers the hope that some or all components of PCOS can be prevented.<sup>20</sup> This study designed to evaluate the prevalence of IR in PCOS Egyptian women

and to compare the findings (clinical and laboratory) of PCOS in IR to non-IR PCOS women.

## Patients and methods

Fifty PCOS women included in this cross sectional comparative study after informed consent and approval of the study by local institute ethical committee of Ain Shams University Maternity Hospital, Cairo, Egypt. Diagnosis of PCOS based on Rotterdam ESHRE criteria by at least 2 out of 3 of the following criteria: oligo-or an-ovulation, clinical or biochemical hyperandrogenism and polycystic ovaries on transvaginal ultrasound (TVS).<sup>2</sup> Women with endocrinal disorders (thyroid dysfunction, Cushing syndrome, hyperprolactinemia and adult-onset congenital adrenal hyperplasia), androgen-secreting tumors (ovarian or adrenal) and women received oral contraceptives pills, corticosteroids, anti-androgens, androgen containing medications, insulin sensitizing agents or ovulation inducing medications during last 6months excluded from the study.

Studied women underwent complete physical examination with calculation of BMI, assessment of hirsutism by modified Ferriman Gallway score (score $\geq$ 8 diagnosed as hirsutism) and blood pressure (3 readings taken after at least 20minutes of complete physical and mental rest). Hormonal profile (follicle stimulating hormone (FSH), luteinizing hormone and prolactin) and lipid profile (total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and triglyceride (TG)) of the studied PCOS women also evaluated. Two fasting blood samples taken from studied women; first blood sample taken on fluorinated tube for detection of fasting glucose and the second blood sample centrifuged to obtain serum which was stored at -20°C for insulin hormone assay measured using enzyme linked immuno-sorbent assay (ELISA). Fasting glucose/insulin (G/I) ratio calculated and a ratio $<$ 4.5 was predictive of IR in PCOS women above 18years old.<sup>21</sup> Insulin hormone assessed by ELISA technique using NS-ELISA kits (Biosource Europe SA Rue, Nivelles, Belgium).

The INS-ELISA is a solid phase Enzyme Amplified Sensitivity Immunoassay performed on microtiter-plates. The assay uses monoclonal antibodies (Mabs) directed against distinct epitopes of insulin. Calibrators and samples react with the capture monoclonal antibody (Mab 1) coated on microtiter well and with a monoclonal

antibody (Mab 2) labelled with horseradish peroxidase (HRP) after an incubation period allowing the formation of a sandwich; coated Mab 1-human insulin-Mab 2-HRP. The microtiter-plate washed to remove unbound enzyme labelled antibody. Bound enzyme-labelled antibody measured through a chromogenic reaction. Chromogenic solution added and microtiter-plate then read at the appropriate wavelength. Studied PCOS women divided into two groups according to presence or absence of IR to evaluate the prevalence of IR in Egyptian PCOS women and to compare the findings (clinical and laboratory) of PCOS in IR to non-IR PCOS women.

## Sample size and statistical analysis

Using data from previous study<sup>17</sup> and G Power software version 3.17 (Heinrich Heine Universität; Düsseldorf, Germany) for sample size calculation, a sample size of 50 women needed to produce significant difference. Data were collected and statistically analyzed using SPSS (Statistical Package for Social Sciences); computer software version 18 (Chicago, IL, USA). Mean and SD (standard deviation) used to represent numerical variables, while, number (n) and percentage (%) used to represent categorical variables. Chi-Square( $\chi^2$ ) test used for analysis of qualitative data and Student t test used for analysis quantitative data. P value $<$ 0.05 was considered significant.

## Results

IR (G/I ratio $<$ 4.5) detected in 46% (23/50) of studied PCOS Egyptian women. Studied PCOS women classified into 2 groups according to IR into; IR group and non-IR group. BMI was significantly high in IR PCOS women compared to non-IR PCOS women (32.6 $\pm$ 6.0Kg/m<sup>2</sup> versus 29.5 $\pm$ 4.0) and the hirsutism (Ferriman Gallway score $>$ 8) was significantly more common in IR PCOS Women compared to non-IR PCOS women (20(86.95%) versus 5 (18.5%)) (Table 1).

There was no significant difference between IR and non-IR PCOS studied women regarding; mean age, mean blood pressure, age of menarche, menstrual regularity acne and baldness (Table 1).

There was no significant difference between the IR women and non-IR PCOS studied women regarding; ultrasound ovarian findings, hormonal and lipid profiles (Table 2).

**Table 1** Comparison between IR and non-IR PCOS studied women regarding; demographic data, menstrual regularity, acne, baldness and hirsutism

Variables	IR PCOS women number =23	Non-IR PCOS women number =27	P value, significance, test used	
Age(Years)	27.4 $\pm$ 6.9	26.3 $\pm$ 5.0	0.13, NS,(95% CI; -2.4, 1.1, 4.6), t test	
Body mass index(BMI) Kg/m <sup>2</sup>	32.6 $\pm$ 6.0	29.5 $\pm$ 4.0	0.02, S,(95% CI; 0.22, 3.1, 5.9), t test	
Blood pressure(mmHg)	Systolic	118 $\pm$ 11	117 $\pm$ 12	0.6, NS,(95% CI; -5.37, 1, 7.37), t test
	Diastolic	75 $\pm$ 9	76 $\pm$ 7.6	0.2, NS,(95% CI; -5.6, -1, 3.6), t test
Age at menarche	12.9 $\pm$ 0.8	13.8 $\pm$ 1	0.8, NS(95% CI; -1.39, -0.9, -0.4), t test	

Table Continued..

Variables		IR PCOS women number =23	Non-IR PCOS women number =27	P value, significance, test used
Menstrual regularity	Regular	9(39.1%)	9(39.1%)	0.7, NS, Chi-Square( $\chi^2$ )
	Oligomenorrhea	12(52.2%)	17(63%)	0.6, NS, Chi-Square( $\chi^2$ )
	Amenorrhea	2(8.7%)	0(0%)	0.6, NS, Chi-Square( $\chi^2$ )
	Menorrhagia	0(0%)	1(3.7%)	0.2, NS, Chi-Square( $\chi^2$ )
Acne		17(73.9%)	21(77.8%)	0.3, NS, Chi-Square( $\chi^2$ )
Baldness		11(47.8%)	13(48.1%)	0.8, NS, Chi-Square( $\chi^2$ )
Ferriman Gallway score >8(hirsutism)		20(86.95%)	5(18.5%)	0.02, S, Chi-Square( $\chi^2$ )

CI, confidence interval; NS, non-significant; S, significant

**Table 2** Comparison between IR and non-IR PCOS studied women regarding; ultrasound findings, hormonal and lipid profiles

Variables		IR PCOS women number =23	Non-IR PCOS women number =27	P Value, significance, test used
Ultrasound Findings	Right Ovarian Volume(Cm <sup>3</sup> )	10.4±2.2	10.6±1.8	0.16, NS,(95% CI; -1.3, -0.2, 0.9)*
	Left Ovarian Volume(Cm <sup>3</sup> )	10.9±1.9	11.3±2.0	0.5, NS,(95% CI; -1.5, -0.4, 0.6)*
	Polycystic Appearance of the Ovaries	21(91.3%)	26(96.3%)	1(>0.05), NS, X <sup>2</sup>
Hormonal Profile	FSH(mIU/l)	5.5±1.6	5.3±2.5	0.9, NS,(95%CI; -0.9, 0.2, 1.35)*
	LH(mIU/l)	9.97±2.9	9.6±3.0	0.5, NS,(95% CI; -1.3, 0.37, 2.0)*
	LH/ FSH	1.9±0.6	1.7±0.7	0.7, NS,(95%CI; -0.16, 0.2, 0.6)*
	Prolactin(ng/ml)	7.8±7.0	8±6.5	0.3, NS(95%CI; -3.9, -0.2, 3.57)*
Lipid profile	Total Cholesterol (mg/dl)	183±25	185±35	0.9, NS(95%CI; -18.7, -2, 14.7)*
	LDL(mg/dl)	97±26	103±37	0.9, NS(95%CI; -23.5, -6, 11.5)*
	HDL(mg/dl)	55.6±7.0	64±24	1, NS(95%CI; --17.9, -8.4, 1.09)*
	TG(mg/dl)	160±42	134±53	0.8, NS(95%CI; -0.35, 26, 52.35)*

\*: t test used for statistical analysis; CI, confidence interval; FSH, follicle stimulating hormones; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LH, luteinizing hormone; NS, non-significant; TG, triglyceride; X<sup>2</sup>, chi-square test used for statistical analysis

## Discussion

Insulin resistance is a prominent feature of PCOS and PCOS is associated with increased risk of impaired glucose tolerance and type 2 diabetes.<sup>15</sup> Women with PCOS are profoundly insulin resistant and the resultant hyperinsulinemia exacerbates the reproductive abnormalities of the syndrome.<sup>5,17</sup> Several methods are available to the clinical investigator for the measurement of IR, yet there is no universally accepted and clinically useful definition.<sup>15</sup> While hyperinsulinaemic glucose clamp considered the 'gold standard' for measurement of IR.<sup>15</sup> Bonora et al.,<sup>22</sup> concluded that the 15-min ITT (insulin tolerance tests) is suitable as a simple and rapid estimation of in vivo insulin action when glucose clamp studies are not feasible, as in large studies.<sup>22</sup>

Wallace et al.<sup>16</sup> & Legro et al.,<sup>17</sup> concluded that the G/I ratio may be useful as a screening test for IR in obese PCOS women.<sup>16,17</sup> Two-hundred and fifty-four PCOS women prospectively evaluated in Legro et al.,<sup>17</sup> study to determine the prevalence of glucose intolerance in

PCOS women.<sup>5</sup> Legro et al.,<sup>17</sup> concluded that PCOS women are at significantly increased risk for IGT and type 2 diabetes mellitus at all weights and at a young age and they concluded that PCOS may be a more important risk factor for IGT than ethnicity or race in young women.<sup>5</sup> Pasquali, et al.,<sup>4</sup> concluded that the IR is present in PCOS women and it is mainly due to the presence of obesity, but other factors may be considered as a cause such as excess androgen of adrenal source.<sup>4</sup>

In this study, IR assessed in 50 PCOS women with classic features of PCOS (according to Rotterdam ESHRE/ASRM criteria),<sup>2</sup> using fasting glucose and insulin ratio to evaluate the prevalence of IR in PCOS women and to compare the findings (clinical and laboratory) of PCOS in IR to non-IR PCOS women. The IR was prevalent in 46% (23/50) of studied PCOS Egyptian women. Karla et al, found Insulin resistance in 76.9% of PCOS women (50/65) in prospective study.<sup>23</sup> Elevated free testosterone, high normal or moderately elevated total testosterone and hyperinsulinemia is a typical finding in PCOS women.<sup>24</sup> The most common manifestation of excess androgen in

PCOS women is hirsutism which is reported in up to 70% of PCOS women.<sup>25</sup> Androgen excess is also associated with acne, which is frequently seen in PCOS women.<sup>26,27</sup>

In this study, the hirsutism (Ferriman Gallway score >8) was significantly more common in IR compared to non-IR PCOS women in (20(86.95%) versus 5(18.5%)). Landay et al.,<sup>28</sup> also, found that insulin appears to have a direct effect on the severity of hirsutism in PCOS women and appears to have a synergistic interaction with total testosterone.<sup>28</sup> Kissebah et al.,<sup>29</sup> concluded that body fat distribution and the accompanying metabolic abnormalities in PCOS women could exacerbated by variability in the androgenic/estrogenic balance.<sup>29</sup> BMI was significantly high in IR compared to non-IR PCOS studied women (32.6±6.0Kg/m<sup>2</sup> versus 29.5±4.0). Pasquali et al.,<sup>30</sup> & Dunaif et al.,<sup>31</sup> found obese PCOS women are usually more insulin resistant than non-obese PCOS women.<sup>30,31</sup> Dunaif, et al.,<sup>31</sup> concluded that;

- i. PCO women have significant insulin resistance that is independent of obesity.
- ii. PCOS and obesity have a synergistic deleterious effect on glucose tolerance.
- iii. hyperinsulinemia in PCOS is not the result of decreased insulin clearance and
- iv. PCO is associated with a unique disorder of insulin action.<sup>32</sup>

Although, Sikka, et al.,<sup>33</sup> found, a positive significant correlation between ovarian size and hyperinsulinemia and positive correlation between number of follicles per ovary and IR.<sup>33</sup> There was no significant difference regarding the ovarian size and number of ovarian follicles between the IR and non-IR PCOS studied women. In this study and in Moran et al study there was no significant difference between IR and non-IR PCOS women regarding hormonal profile (FSH, LH and FSH/LH ratio).<sup>34</sup> Although, in this study there was no significant difference between IR and non-IR PCOS women regarding lipid profile, Kalra et al.,<sup>23</sup> found significantly high triglycerides, total cholesterol and lower HDL in IR PCOS women compared to insulin-sensitive PCOS women.<sup>23</sup>

This study concluded that the prevalence of IR in PCOS Egyptian women is about 46%, BMI was significantly high in IR compared to non-IR PCOS women and the hirsutism was significantly more common in IR compared to non-IR PCOS women. G/I ratio is a useful screening test for IR in PCOS and it is useful parameter for selecting PCOS women most likely to respond to insulin sensitizers.

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None.

## Conflict of interest

The author declares no conflict of interest.

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