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 to compare the findings (clinical and laboratory) 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 ± 6.0 Kg/m^2 versus 29.5 ± 4.0) and the hirsutism (Ferriman Galloway 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

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 [1]. 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) [2]. Burghen, et al. [3] 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 [3].

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 [4,5]. 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 (1,2and3) that in turn bind to signaling molecules (phosphatidylinositol-3 kinase) and activate downstream signaling leading to insulin-mediated glucose transport [6,7].

Reduced insulin sensitivity reported during the luteal phase of normal menstrual cycles [8]. Furthermore, complete suppression of ovarian steroids does not alter insulin sensitivity [9]. It is unlikely that anovulation is the cause of impaired insulin sensitivity and it is more likely that hyperinsulinemia and IR lead to anovulation [10]. 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 [11,12]. Excess androgens interfere with the follicular maturation with subsequent anovulation and follicular arrest [13].

Anovulatory women with hyperandrogenism should evaluated for IR and glucose tolerance [14]. While anovulatory women without hyperandrogenism should evaluated by measuring the free testosterone and if elevated, IR and glucose tolerance should assessed [1]. Insulin sensitivity may be assessed by hyperinsulinemic euglycemic clamp technique [15], insulin values during oral glucose tolerance test [16], fasting glucose/insulin (G/I) ratio [17,18], homeostatic model assessment-insulin resistance, infusion of glucose with model assessment or quantitave insulin sensitivity check index [16,19]. 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 [20]. 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 anovulation, clinical or biochemical hyperandrogenism and polycystic ovaries on trans-vaginal ultrasound (TVS) [2]. Women with endocrine disorders (thyroid dysfunction, Cushingo 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 6 months excluded from the study.

Studied women underwent complete physical examination with calculation of BMI, assessment of hirsutism by modified Ferriman Gallway score (score ≥ 8 diagnosed as hirsutism) and blood pressure (3 readings taken after at least 20 minutes 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 18 years old [21]. 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 monodonal 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 [17] 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(x²) 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 ± 6.0 Kg/m² versus 29.5 ± 4.0) and the hirsutism (Ferriman Gallway score >8) was significantly more common in IR PCOS than non-IR PCOS (32.6 ± 6.0 Kg/m² versus 29.5 ± 4.0) and the hirsutism (Ferriman Gallway score >8) was significantly more common in IR PCOS compared to non-IR PCOS (20 (86.95%) versus 5 (18.5%)) (Table 1).

### 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 ± 6.9                 | 26.3 ± 5.0                     | 0.13, NS, (95% CI: -2.4, 1.1, 4.6), t test |
| Blood pressure (mmHg)    |                            |                                |                                  |
| Systolic                 | 118 ± 11                   | 117 ± 12                       | 0.6, NS, (95% CI: -5.37, 7.37), t test |
| Diastolic                | 75 ± 9                     | 76 ± 7.6                       | 0.2, NS, (95% CI: -5.6, -1.36), t test |
| Age at menarche          | 12.9 ± 0.8                 | 13.8 ± 1                       | 0.8, NS (95% CI: -1.39, -0.9, -0.4), t test |
| Menstrual regularity     |                            |                                |                                  |
| Regular                  | 9 (39.1%)                  | 9 (39.1%)                      | 0.7, NS, Chi-Square (x²)          |
| Oligomenorhea            | 12 (52.2%)                 | 17 (63%)                       | 0.6, NS, Chi-Square (x²)         |
| Amenorrhea               | 2 (8.7%)                   | 0 (0%)                         | 0.6, NS, Chi-Square (x²)         |
| Menorrhagia              | 0 (0%)                     | 1 (3.7%)                       | 0.2, NS, Chi-Square (x²)         |
| Acne                     | 17 (73.9%)                 | 21 (77.8%)                     | 0.3, NS, Chi-Square (x²)         |
| Baldness                 | 11 (47.8%)                 | 13 (48.1%)                     | 0.8, NS, Chi-Square (x²)         |
| Ferriman Gallway score >8| 20 (86.95%)                | 5 (18.5%)                      | 0.02, S, Chi-Square (x²)         |

CI: Confidence Interval; NS: Non-Significant; S: Significant

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

**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 (Cm³) | 10.4 ± 2.2               | 10.6 ± 1.8                  | 0.16, NS, (95% CI; -1.3, -0.2, 0.9)* |
| Left Ovarian Volume (Cm³) | 10.9 ± 1.9               | 11.3 ± 2.0                  | 0.5NS, (95% CI; -1.5, -0.4, 0.6)* |
| Polycystic Appearance of the Ovaries | 21 (91.3%)   | 26 (96.3%)                  | 1 (>0.05), NS, X²               |
| Hormonal Profile         |                          |                             |                                 |
| FSH (mIU/l)              | 5.5 ± 1.6                | 5.3 ± 2.5                   | 0.9NS, (95% CI; -0.9, 0.2, 1.35)* |
| LH (mIU/l)               | 9.97 ± 2.9               | 9.6 ± 3.0                   | 0.5NS, (95% CI; -1.3, 0.37, 2.0)* |
| LH/FSH                   | 1.9 ± 0.6                | 1.7 ± 0.7                   | 0.7NS, (95% CI; -0.16, 0.2, 0.6)* |
| Pro lactin (ng/ml)       | 7.8 ± 7.0                | 8 ± 6.5                     | 0.3NS, (95% CI; -3.9, -0.2, 3.57)* |
| Lipid profile            |                          |                             |                                 |
| Total Cholesterol (mg/dl) | 183 ± 25                 | 185 ± 35                    | 0.9NS, (95% CI; -18.7, -2, 14.7)* |
| LDL (mg/dl)              | 97 ± 26                  | 103 ± 37                    | 0.9NS, (95% CI; -23.5, -6, 11.5)* |
| HDL (mg/dl)              | 55.6 ± 7.0               | 64 ± 24                     | 1NS, (95% CI; -17.9, -8.4, 1.09)* |
| TG (mg/dl)               | 160 ± 42                 | 134 ± 53                    | 0.8NS, (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; X²: 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 [15]. Women with PCOS are profoundly insulin resistant and the resultant hyperinsulinemia exacerbates the reproductive abnormalities of the syndrome [5,17]. Several methods are available to the clinical investigator for the measurement of IR, yet there is no universally accepted and clinically useful definition [15]. While hyperinsulinaemic glucose clamp considered the ‘gold standard’ for measurement of IR [15]. Bonora, et al. [22] 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 [22].

Wallace, et al [16] & Legro, et al. [17] concluded that the G/I ratio may be used as a screening test for IR in obese PCOS women [16,17]. Two-hundred and fifty-four PCOS women prospectively evaluated in Legro, et al. [17] study to determine the prevalence of glucose intolerance in PCOS women [5]. Legro, et al. [17] 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 [5]. Pasquali, et al. [4] concluded that the IR is present in PCOS women and it is mainly due to the presence of obesity, but other factors may considered as a cause such as excess androgen of adrenal source [4].

In this study, IR assessed in 50 PCOS women with classic features of PCOS (according to Rotterdam ESHRE/ASRM criteria) [2], 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 [23]. Elevated free testosterone, high normal or moderately elevated total testosterone and hyperinsulinemia is a typical finding in PCOS women [24]. The most common manifestation of excess androgen in PCOS women is hirsutism which is reported in up to 70% of PCOS women [25]. Androgen excess is also associated with acne, which is frequently seen in PCOS women [26,27].

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. [28], 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 [28]. Kissebah, et al. [29] concluded that body fat distribution and the accompanying metabolic abnormalities in PCOS women could exacerbated by variability in the androgenic/estrogenic balance [29]. BMI was significantly high in IR compared to non-IR PCOS studied women (32.6 ± 6.0 Kg/m2 versus 29.5 ± 4.0). Pasquali, et al. [30] & Duniaif, et al. [31] found obese PCOS women are usually more insulin resistant than non-obese PCOS women [30,31]. Duniaif, et al. [31] concluded that;

a. PCO women have significant insulin resistance that is independent of obesity.

b. PCOS and obesity have a synergistic deleterious effect on glucose tolerance.
c. hyperinsulinemia in PCOS is not the result of decreased insulin dearance and

d. PCO is associated with a unique disorder of insulin action [32].

Although, Sikka, et al. [33] found, a positive significant correlation between ovarian size and hyperinsulinemia and positive correlation between number of follicles per ovary and IR [33]. 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) [34]. Although, in this study there was no significant difference between IR and non-IR PCOS women regarding lipid profile, Kalra, et al. [23] found significantly high triglycerides, total cholesterol and lower HDL in IR PCOS women compared to insulin-sensitive PCOS women [23].

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 women and for selection of PCOS responders to insulin sensitizers.

References

1. Ibrahim A Abdelazim, Walid Farok Eskawah (2015) Metabolic syndrome among infertile women with polycystic ovary syndrome. Asian Pacific Journal of Reproduction 4(1): 44-48.

2. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group (2004) Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 19(1): 41-47.

3. Burghen GA, Givens JR and Kitabrihi AE (1980) Correlation of hyperandrogenism with hyperinsulinism in polycystic ovarian disease. J Clin Endocrinol Metab 50(1): 113-116.

4. Pasquale R, Casimirri F, Venturoli S, Paradisi R, Mattioli L, et al. (1985) Insulin resistance in patients with polycystic ovaries: its relationship to body weight and androgen levels. Acta Endocrinol (Copenh) 104(1): 110-116.

5. Legro RS, Kunselman AR, Dodson WC, Dunia A (1999) Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. J Clin Endocrinol Metab 84(1): 165-169.

6. White MF, Kahn CR (1994) The insulin signaling system. J Biol Chem 269(1): 1-4.

7. White MF (1996) The IRS-signalling system: a network of docking proteins that mediate insulin action. Mol Cell Biochem 182(1-2): 3-11.

8. Valdes GT, Elkind-Hirsch KE (1991) Intravenous glucose tolerance test derived insulin sensitivity changes during the menstrual cycle. J Clin Endocrinol Metab 72(3): 642-646.

9. Dale PO, Janbo-T, Djoseland O, Jervell J, Abyholm T (1992) Persistence of hyperinsulinemia in PCOS after ovarian suppression by gonadotropin releasing hormone agonist. Acta Endocrinol (Copenh) 126(2): 132-136.

10. Kiddey DS, Hamilton-Fairley D, Bush A, Short F, Anyaoku V, et al. (1992) Improvement in endocrine and ovarian function during dietary treatment of obese women with polycystic ovary syndrome. Clin Endocrinol (Oxf) 36(1): 105-111.

11. Caro JF, Rosenfield RD (1988) Insulin like growth factor 1 & insulin potential LH induced androgen synthesis by rat ovarian theca-interstitial cells. Endocrinology 133: 73-739.

12. Gilling-Smith C, Willis DS, Beard RW, Franks S (1994) Hypersecretion of androstenedione by isolated thecal cells from polycystic ovaries. J Clin Endocrinol Metab 79(4): 1158-1165.

13. Hiller SG, Tetsuka M (1997) Role of androgens in follicle maturation and atresia. Baillieres Clin Obstet Gynaecol 11(2): 249-260.

14. Ferrannini E (1998) Insulin resistance versus insulin deficiency in non-insulin dependent diabetes mellitus: Problems and prospects. Endocrinol Rev 19(4): 477-490.

15. Yildiz B0, Gedik O (2004) Assessment of glucose intolerance and insulin sensitivity in PCOS. Repr Bio Med Online 8(6): 649-656.

16. Wallace TM, Mathews DR (2002) The assessment of insulin resistance in man. Diabetic Medicine 19(7): 527-534.

17. Legro RS, Finegood D, Dunia A (1996) A fasting glucose to insulin ratio is a useful measure of insulin sensitivity in women with polycystic ovary syndrome. J Clin Endocrinol Metab 83(8): 2694-2698.

18. Marques-Vidal P, Mazoyer E, Bongard V, Gourdy P, Ruidavets JB, et al. (2002) Prevalence of insulin resistance syndrome in south-western France and its relationship with inflammatory and haematostatic markers. Diabetes Care 25(8): 1371-1377.

19. Misra A, Vikram NK (2003) Insulin resistance syndrome (Metabolic syndrome) and Asian Indians. Current Science 2003; 83(12): 1483-1496.

20. Miriam E Silen, Alexandra M Manibo, Donald J McMahon, Lenore S Levine, Allison R Murphy, et al. (2001) Comparison of simple measures of insulin sensitivity in young girls with premature adrenarche: the fasting glucose to insulin ratio may be a simple and useful measure. J Clin Endocrinol Metab 86(6): 2863-2868.

21. Bergman R, Finegood D, Ader M (1985) Assessment of insulin sensitivity in vivo. Endocr Rev 6(1): 45-86.

22. Bonora E, Moghetti P, Zancanaro C, Cigolini M, Querena M, et al. (1989) Estimates of in vivo insulin action in man comparison of insulin tolerance tests with euglycemic and hyperglycemic glucose clamp studies. J Clin Endocrinol Metab 68(2): 374-378.

23. Kalra A, Nair S, Rai L (2006) Association of obesity and insulin resistance with dyslipidemia in Indian women with polycystic ovarian syndrome. Indian J Med Sci 60(11): 447-453.

24. Tsikhorozidou T, Overton C, Conway GS (2004) The pathophysiology of polycystic ovary syndrome. Clin Endocrinol (Oxf) 60(1): 1-17.

25. Hill KM (2003) Update: The pathogenesis and treatment of PCOS. Nurse Pract 28(7 Pt 1): 8-17.

26. Hunter MH, Carek PJ (2003) Evaluation and treatment of women with hirsutism, Am Fam Physician 67(12): 2565-2572.

27. Legro RS (2003) Diagnostic criteria in polycystic ovary syndrome, Semin Reprod Med 21(3): 267-275.

28. Landay M, Huang A, Aziz R (2009) Degree of hyperinsulinemia, independent of androgen levels, is an important determinant of the severity of hirsutism in PCOS. Fertil Steril 92(2): 643-647.
29. Kissebah AH, Peiris AN (1989) Biology of regional body fat distribution: relationship to non-insulin-dependent diabetes mellitus. Diabetes Metab Rev 5(2): 83-109.

30. Pasquali R and Cairmirri F (1993) The impact of obesity on hyperandrogenism and polycystic ovary syndrome in premenopausal women. Clin Endocrinol (Oxf) 39(1): 1-16.

31. Dunai A (1997) Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. Endocr Rev 18(6): 774-800.

32. Dunai A, Segal KR, Futterweit W, Duhrrjansky A (1989) Profound peripheral insulin resistance, independent of obesity, in PCOS. Diabetes 38(9): 1165-1174.

33. Sikka P, Gainder S, Dhaliwal IK, Bagga R, Saly R, et al. (2007) Ultrasonography of the ovaries and its correlation with clinical and endocrine parameters in infertile women with PCOS. Int J Fertil Womens Med 52(1): 41-47.

34. Moran C, Garcia-Heranandez E, Barahona E, Gonzalez S, Bermudez JA (2003) Relationship between insulin resistance and gonadotropin dissociation in obese and non obese women with polycystic ovary syndrome. Fertil Steril 80(6): 1466-1472.