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Frequency of Insulin Resistance Among Infertile Women with Polycystic Ovary Syndrome at Zagazig University Hospitals

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ABSTRACT
Background: Assessment of Insulin Resistance (IR) as well as glucose intolerance are advised among Polycystic Ovary Syndrome (PCOS) cases.
Objective: To study the rate of IR among infertile women with PCOS at Zagazig University Hospitals.
Subjects and Methods: the study was conducted on 60 infertile women with age from 18 to 35 years old as cross sectional trial, at Clinical Pathology Department and outpatient clinic of Obstetrics and Gynecology Department Zagazig University Hospitals with calculation the frequency of insulin resistant among infertile women with polycystic ovaries.
Results: The prevalence of IR among the studied cases was 60%. body mass index (BMI), waist circumference (WC), and presence of hirsutism differed significantly between both studied groups. Testosterone levels and FBI were significantly higher among IR cases compared to non IR cases.
Conclusion: incidence of insulin resistance is around 60% in PCOS infertile cases. Clinically, the G/I ratio may be beneficial in identifying insulin-resistant PCOS women and choosing those most likely to benefit from therapy interventions that increase insulin sensitivity.
Keywords: Insulin Resistance, Polycystic Ovary Syndrome, Infertility.

INTRODUCTION

Polycystic ovaries, oligo/amenorrhea as well as hyperandrogenism, are the three main phenotypic characteristics of polycystic ovarian syndrome (PCOS), which impacts six to ten percent of women worldwide. Weight problems, insulin resistance (IR), high insulin levels, and type 2 diabetes mellitus are among metabolic conditions that may accompany PCOS (IR prevalence is about 80 % among PCOS) **(1).** Cancers of the breast and uterus are linked to polycystic ovary syndrome (PCOS), as are neurological and psychological impacts on quality of life (such as anxiety and sadness). PCOS has been identified in as much as 20% of infertile women. That study goal was to evaluate the safety, efficacy, and adverse effects of both oral and vaginal contraceptive methods. Using misoprostol 600 mcg for ovum that has been blighted **(2).**

Impairment in insulin's capacity to promote glucose consumption constitutes IR. In response (hyperinsulinemia), pancreatic β-cells produce and secrete more insulin, although glucose tolerance is unaffected. As a result of an insufficient physiological response of peripheral tissues to circulating insulin, IR leads to CVD and T2D. IR is also present in conditions such as poor glucose tolerance, obesity, polycystic ovary syndrome, essential hypertension, and non-alcoholic fatty liver disease **(3).**

IR is a key player in PCOS's etiology and progression. Treatment for polycystic ovary syndrome has traditionally included the use of medications to increase insulin sensitivity **(4).** Women who are anovulatory but do not have hyperandrogenism should have their free testosterone measured, and if it is high, their insulin resistance and glucose tolerance should be checked. Women with IR and those at risk for developing IR should be sought out, since this may lead to the prevention of some, or all of the symptoms associated with polycystic ovary syndrome **(5).** Patients with polycystic ovary syndrome should be evaluated for insulin resistance and glucose intolerance. The hyperinsulinemic euglycemic clamp is the gold standard for evaluating IR, although it is notoriously difficult to perform in clinical settings **(6).**

Rotterdam criteria for PCOS diagnosis call for two of oligo/anovulation, hyperandrogenism, and ultrasound evidence of polycystic ovaries. Twelve or more follicles between 2 and 9 mm in diameter, or an ovarian volume increase of more than 10 cm^3, are among the Rotterdam consensus group's proposed criteria for polycystic ovarian morphology. The presence of many cysts in a single ovary is diagnostic of polycystic ovarian syndrome **(7).**

It was the goal of our study to study the rate of IR among infertile women with PCOS at Zagazig University Hospitals.

SUBJECTS AND METHODS

Sixty infertile women aged from 18 to 35 years old were included in this cross-sectional trial, at Clinical Pathology Department and outpatient clinic of Obstetrics and Gynecology Department Zagazig University hospitals.

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Ethical consent:

Research Ethics Council at Zagazig University approved the study (ZU-IRB #9630) as long as all participants provided informed consent forms. Ethics guidelines for human experimentation were adhered to by the World Medical Association's Helsinki Declaration.

Inclusion Criteria:

1- For infertile women with PCOS aged from 18 to 35 who have ruled out all other possible reasons of infertility, for couples who have been sexually active for a year or more without using contraception, infertility was considered to exist if they have not been successful in conceiving a child naturally. Primary infertility was used when a woman has never conceived, whereas secondary infertility was used when a couple has previously had a successful conception but was at the time of the study unable to have another. These definitions come from the World Health Organization (WHO) **[8].**

2- Possession of at least two of the following three symptoms indicates the presence of PCOS according to the Rotterdam criteria:

- Amenorrhea and oligomenorrhea are common symptoms of oligo-ovulation and anovulation; If woman have had more than 35 days between periods or fewer than eight periods in the past year, you may be suffering from oligomenorrhea. For patients with previously regular periods, amenorrhea is defined as a cessation of menstruation lasting 6 months or longer; for patients with previously irregular cycles, the duration must be 12 months or more **[9]**.
- Hyperandrogenism can be either clinical or biochemical; the former is indicated by a Ferriman-Gallwey (FG) score below 8, while the latter corresponds to a free testosterone concentration of 8 pg/mL or higher **[10].**
- Rotterdam consensus group definition for polycystic ovary morphology: 12 or more follicles measuring 2–9 mm in diameter and/or an enlarged ovarian volume more than 10 cm^3. The presence of many cysts in a single ovary is diagnostic of polycystic ovarian syndrome **[7].**

Exclusion Criteria:

- Women who suffer from thyroid dysfunction, Cushing syndrome, hyperprolactinemia, type 2 diabetes, and androgen-secreting ovarian or adrenal tumours are at an increased risk for developing breast cancer.
- Hormonal contraceptive users, steroid users, anti-androgen users, and insulin-sensitizing drug users in the past three months.
- In the previous six months, women have used drugs to induce ovulation.

The following was done to each patient on admission:

1- Full history was taken:

i- Personal history: name, age, occupation, marital status special habits and address.
ii- Complaint and present history.
iii- Obstetric history: parity, gravidity and mode of previous deliveries or abortions.
iv- Menstrual history: first day of the period (LMP).
v- Past history: of diabetes mellitus (DM), hypertension, cardiac problems, renal troubles, bleeding tendency, blood disease, bronchial asthma, glaucoma, allergy or previous operations (especially previous uterine scare).
vi- Family history.

2- General examination.

3- Vaginal examination.

4- Investigation:

i- Ultrasound was done for confirmation of the diagnosis.
ii- Laboratory tests (most of them were done routinely at admission)

A 10-cc sample of blood was drawn for the assessment of free testosterone levels, plasma glucose and plasma insulin, FSH and LH levels, when the menstrual cycle was between days 2 and 5 (natural or bleeding after progestin withdrawal).

Methods of hormonal assay: The enzymes were determined by (enzyme-linked immunosorbent assay) ELISA technique.

Calculation of Insulin resistance:

Insulin resistance was assessed using both: Fasting insulin levels and fasting glucose levels by the following method.

- Fasting glucose/ insulin (G/I) ratio was calculated, polycystic ovary syndrome (PCOS) women over the age of 18; a ratio less than 4.5 was proven to be a useful screening test for insulin resistance **[11].**

Statistical analysis

In order to analyze the data acquired, Statistical Package for the Social Sciences (SPSS) version 20 was used to execute it on a computer. The quantitative data were presented in the form of the mean, and standard deviation (SD). The qualitative data were presented as frequency and percentage. The student's t-test (T) was used to assess the data while dealing with quantitative independent variables. Pearson Chi-Square was used to assess qualitatively independent data. The significance of a P value of 0.05 or less was determined.

RESULTS

Basal demographic clinical data, and menstrual history of the studied patients are shown in table 1. Oligo-menorrhea was majority with 60.0%.

Table (1): Basal demographic clinical data, and menstrual history among studied group (N=60)

		Studied patients (N=60)
Age *(years)*, Mean± SD		**27.83±2.4**
BMI *(kg/m²)*, Mean± SD		**29.68±2.02**
WC *(cm)*, Mean± SD		**96.22±3.26**
Systolic blood pressure *(mmHg)* Mean± SD		**115.66±9.4**
Diastolic blood pressure *(mmHg)* Mean± SD		**75.41±7.4**
Age of Menarche (years) Mean± SD		**12.55±1.1**
Menstrual regularity	**Regular**	**20 (33.3%)**
	Oligo-menorrhea	**36 (60.0%)**
	Amenorrhea	**4 (6.7%)**

In the studied group of patients hirsutism was found in 53.3% and **primary** infertility was majority with 71.7% (Table 2).

Table (2): Manifestations of androgen excess, and infertility distribution among studied group (N=60)

		Studied patients (N=60)
Androgen excess manifestations	**Acne**	**20 (33.3%)**
	Androgenic alopecia	**8 (13.4%)**
	Hirsutism	**32 (53.3%)**
Infertility type	**Primary**	**43 (71.7%)**
	Secondary	**17 (28.3%)**
Infertility duration (years) Mean± SD	**2.95±0.64**	

In the studied group of patients 60% had IR (Table 3).

Table (3): Fasting glucose/fasting insulin ratio (G/I) and IR distribution among studied group (N=60)

		Studied patients (N=60)
G/I ratio (Mean± SD)		**5.14±1.1**
IR	**Non IR PCOS** (G/I >4.5)	**24 (40%)**
	IR PCOS (G/I <4.5)	**36 (60%)**

No significant difference or association was found except BMI and WC as they were significantly higher among IR group (Table 4).

Table (4): Comparison of basal demographic and clinical data between IR and non IR groups

Variable	Non IR PCOS (n=24)	IR PCOS (n=36)	P
Age *(years)* *Mean ± SD*	**26.92±4.12**	**27.53±5.25**	**0.284**
BMI *(kg/m²)* *Mean ± SD*	**28.95±2.21**	**32.82±1.86**	**0.029 ***
WC *(cm)* *Mean ± SD*	**94.95±3.4**	**101.93±2.90**	**0.011 ***
SBP *(mmHg)* *Mean ± SD*	**114.37±8.63**	**116.52±9.91**	**0.390**
DBP *(mmHg)* *Mean ± SD*	**72.5±6.07**	**74.36±7.69**	**0.118**

*: Significant

There was no significant difference between groups as regard ovarian sonogradpic findings (Table 5),

Table (5): Comparison of ovarian sonographic findings between IR and non IR groups

	Non IR PCOS (n=24)	IR PCOS (n=36)	P
Right Ovarian volume *(cm³)*	**10.5±1.25**	**10.7±1.59**	**0.802**
Left Ovarian volume *(cm³)*	**10.2±0.98**	**10.4±1.55**	**0.699**
Polycystic appearance of the ovaries	**(22) 91.7%**	**(35) 97.2%**	**0.91**

Hirsutism was significantly higher among IR group (Table 6).

Table (6): Manifestations of androgen excess distribution between IR and non IR groups

	Non IR PCOS (n=24)	IR PCOS (n=36)	P
Acne	**5 (20.8%)**	**15 (41.4%)**	**0.193**
Baldness	**1 (4.2%)**	**7 (19.4)**	**0.088**
Hirsutism	**5 (20.8%)**	**27 (75%)**	**<0.001****

**: Highly significant

Free testerone was significantly higher among IR group (Table 7).

Table (7): Hormones levels between IR and non IR groups

	Non IR PCOS (n=24)	IR PCOS (n=36)	P
FSH *(IU/L)* *Mean ± SD*	**5.17±0.64**	**4.87±0.78**	**0.136**
LH *(IU/L)* *Mean ± SD*	**9.03±0.96**	**8.77±1.38**	**0.086**
LH/FSH *Mean ± SD*	**1.84±0.52**	**1.91±0.64**	**0.935**
Free Testerone *(pg/mL)* *Mean ± SD*	**5.91±1.56**	**9.27±2.58**	**0.002***

*: Significant

FBG and FBI were significantly high among IR group while G/I was significantly low (Table 8).

Table (8): Comparison of fasting blood glucose (FBG), fasting blood insulin (FBI) and G/I between IR and non IR groups

	Non IR PCOS (n=24)	IR PCOS (n=36)	P
FBG *(mg/dL)*	**103.50±15.4**	**119.52±8.9**	**<0.001****
FBI *(µU/ml)*	**16.41±3.76**	**27.86±1.86**	**<0.001****
G/I	**6.43±0.81**	**4.28±0.14**	**<0.001****

**: Highly significant

DISCUSSION

Polycystic ovarian syndrome (PCOS) is a diverse disorder that affects 5-10% of reproductive-aged women. Hyperandrogenism and a halt in follicle formation are hallmarks of this condition, which is also related with metabolic traits like insulin resistance and obesity and is the leading cause of anovulatory infertility [(12)]. Pathogenesis and progression of polycystic ovary syndrome (PCOS) are influenced by IR. Treatment for PCOS that includes medication to increase insulin sensitivity is thought to be very helpful. Hyperinsulinemia in polycystic ovary syndrome (PCOS) is caused by IR, studies of PCOS patients, both obese and lean, have revealed a link between insulin metabolism disturbance and IR[(4)]. This study measured insulin resistance in 60 infertile women, aged 18-35, who exhibited typical PCOS symptoms according to the Rotterdam criteria. Both normal-weight and overweight women were included in the analysis, we used a mathematical method based on fasting levels of glucose and insulin from which a ratio was calculated to detect those with insulin resistance.

In this study regarding menstrual history of the studied cases (60), the mean age of menarche was 12.55 (±1.1 SD) years. Regarding menstrual regularity, menstruation was regular in 33.3% (20/60), amenorrhea in 6.7% (4/60) and majority of the cases had oligo-menorrhea 60% (36/60). In the study done by **Al-Jefout *et al.*** [(13)] the average age of menarche was 13 and the following was found on menstrual regularity. According to the findings of this study, 32.7% (52/159) of the participants experienced regular menstruation and 67.3% (107/159) experienced oligo/amenorrhea.

Regarding infertility data of the studied cases (60), the mean infertility duration was 2.95(±0.85 SD) years, with majority of cases 71.7% (43/60) suffered from primary infertility. In the study done by **Smitha *et al.*** [(14)] infertility lasted an average of 2.3625 years, and in a study by **Dhagat *et al.*** [(15)] discovered that 70% (70/100) of the cases analyzed were affected by primary infertility, these findings corroborated those of the present study.

This study showed that the overall prevalence of IR among the studied PCOS cases was 60% (36/60) using the G/I ratio. In the study by **Popovska-Dimova *et al.*** [(16)] of the 62 women diagnosed with PCOS, 36 (58.06%) had fasting G/I ratios <4.5, indicating insulin resistance. These findings agreed with the findings of this investigation. In the study done by **Azargoon *et al.*** [(17)] the percentage of infertile women with PCOS who also had IR was 39.3 percent, and this result was also similar to the study of **Jamil *et al.*** [(18)] in their research of 263 women with PCOS, 42.6% had IR. These results were lower than our study results. But in the prospective study of **Kalra *et al.*** [(19)] Insulin resistance was detected in 76.9% (50/65) of PCOS women. When put next to the percentage we found, this is a far larger difference. It's possible that dietary and lifestyle factors, as well as the influence of ethnicity on disease phenotype, play a role in these variations. Hyperinsulinemia and insulin resistance are common in PCOS-affected obese women, especially those who also have the abdominal obesity phenotype [(20)].

In this study we found significant difference between the two studied groups regarding BMI and WC as follows, the mean BMI among all study participants was 29.68 kg/m² and it was higher among IR cases (32.82±1.86) compared to non-IR cases (28.95±2.21), the mean WC among all study participants was 96.22 cm and it was higher among IR cases (101.93±2.90) compared to non IR cases (94.95±3.4). In the study of **Al-Jefout *et al.*** [(13)] they looked at 159 PCOS women and found that both BMI and waist circumference were considerably greater in IR cases than in non-IR instances, which is in line with our research.

In this study the finding of ovarian volume and polycystic ovary morphology on transvaginal ultrasound was not statistically different between the IR and the non-IR PCOS groups. In the study of **Mostafa *et al.*** [(21)] women with PCOS who had IR or didn't have IR showed no discernible difference in ovarian size or follicle count. Unlike **Sikka *et al.*** [(22)] who discovered a positive association between the number of follicles on each ovary and insulin resistance, and a substantial positive relationship between ovarian size and hyperinsulinemia. In this study regarding androgen excess manifestations, 53.3% (32/60) had hirsutism and 33.3% (20/60) had acne. Among women with PCOS, hirsutism was more

prevalent in the IR group than in the non-IR group (75%) vs (20.8%). This is in accordance with the study done by **Landay *et al.* (23)** who discovered a synergistic interaction between insulin and total testosterone, resulting in a reduction in the severity of hirsutism in PCOS. However, when it came to acne and baldness, we did not notice a significant difference between the IR and non-IR groups.

In this study we found no statistically significant difference between IR and non IR groups as regards FSH, LH and FSH/LH ratio but on the other hand free testosterone levels were significantly higher among IR cases compared to non IR cases. The same results were in a study done by **Moran *et al.* (24)**. Fndings imply that PCOS-related IR and gonadotropins may be determined by separate hereditary diseases.

CONCLUSION

Incidence of insulin resistance is around 60% in PCOS infertile cases. G/I ratio may be useful as a screening test for insulin resistance in PCOS women and this may be a clinically useful parameter for selecting PCOS women most likely to respond to therapeutic intervention that improve insulin sensitivity. There was decreased insulin sensitivity and increased insulin resistance among infertile women with PCOS. BMI, WC, FBG, FBI, and free testosterone were significantly high in IR compared to non-IR PCOS women.

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