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# THE RELATIONSHIP BETWEEN SERUM HOMOCYSTEINE LEVEL AND INSULIN RESISTANCE LEVEL IN WOMEN WITH POLYCYSTIC OVARIAN SYNDROME AND RECURRENT PREGNANCY LOSS

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**Abstract:** Introduction: Women with polycystic ovarian syndrome (PCOS) who experience spontaneous miscarriages may have high levels of homocysteine (Hcy). It has been proposed that this connection might be a significant feature of PCOS.

Aim: To evaluate the association between elevated serum homocysteine level and insulin resistance in PCOS patients who have a history of recurrent miscarriages.

Materials and Methods: This prospective study was performed at Basrah Maternity Hospital between 1st of May 2022 till the 1st of June 2024. 124 women were included in the study. 68 women diagnosed as PCOS with history of 2 or more recurrent miscarriages. PCOS was diagnosed based on Rotterdam criteria. In addition to estimation of homocysteine and Insulin Resistance with serum level of FSH, LH, Testosterone and DHEA in both groups.

Results: The age of women in the sample ranged between 28.9± 4.28 and 29.85 ± 3.69 years; most of the women had BMI between 24.79 ±2.21.and 34.71±3.45. There was no statistical difference in both groups with regard to age and number of Miscarriages but there was significant difference in relation to BMI. Moreover, there was a significant difference in regard to insulin level, insulin resistance and the level of homocysteine in PCOS which were higher than the control group.

Conclusion: Insulin resistance and hyperinsulinaemia in patients with PCOS is associated with elevated plasma homocystiene with regard to BMI which may have important implications in the short term regarding reproductive performance.

**Key words:** Homocysteine, Insulin resistance, Miscarriage, Polycystic ovarian syndrome.

## 1. Introduction

Polycystic ovarian syndrome is linked to various health conditions, such as decrease fertility, metabolic syndrome, increase BMI, impaired glucose tolerance and diabetes mellitus (DM-2), ischemic heart disease risk, depression, obstructive sleep apnea and endometrial cancer. Each of these illnesses has specific screening standards, but clinicians should be proactive in investigating any signs or symptoms in patients with PCOS (1).

Insulin resistance (IR), obesity and hyperandrogenism are considered potential risk factors for reproductive failure in individuals with endocrine and metabolic illnesses associated with the syndrome (2). Approximately one to two-thirds of individuals with PCOS have an atypical level of insulin resistance (3).

Obesity screening is necessary for women and adolescents with PCOS because it heightens the likelihood of hyperandrogenism and metabolic problems.

It has been established that Hhcy is a mediator for increasing hypercoagulable state of pregnancy and the likelihood of developing thrombosis in the maternal-fetal circulatory system and the undesirable adverse outcome of pregnancy (4).

Recent research has emphasized the possible involvement of increased homocysteine levels in the development of PCOS and its related metabolic abnormalities (5). Elevated levels of homocysteine in the blood, known as hyperhomocysteinemia, may worsen insulin resistance, which is a typical characteristic of polycystic ovary syndrome (PCOS). This can further contribute to the metabolic complexity of the illness. It is essential to recognize the connection between homocysteine and insulin resistance (IR) in the setting of PCOS in order to create particular approaches that may effectively reduce the impact of both interrelated disorders (6). Prior studies examined the correlation between increased homocysteine levels and insulin resistance in women with PCOS have shown conflicting findings. Although several studies indicate a substantial association, others have been unable to establish a definite connection. The precise mechanisms by which hyperhomocysteinemia affects insulin sensitivity and reproductive outcomes in PCOS are not well understood. Therefore, further researches are needed for a better understanding and discover potential targets for treatment (7). Therefore, the aim of the study was conducted to assess the link between elevated serum homocysteine level and insulin resistance in women with PCOS with history of recurrent pregnancy loss.

## 2. Patients and Methods

It is a forward-looking study that was held at Basra Maternity Hospital between 1 May 2022 and 1 June2024. The patients were recruited from women who visited the outpatient Obstetrics clinic. Within 3 months of the study, 124 female subjects were contacted for having a history of recurrent miscarriage. Sixty-eight (68) women who had been diagnosed as having PCOS and a history of two or more recurrent miscarriage. PCOS was defined according to the Rotterdam criteria (4) when at least two of the following three criteria were met oligo/amenorrhea, clinical or biochemical hyperandrogenism, and PCOS in genesis by Ultrasound examination.

Exclusion criteria: In PCOS patient, the inclusion was based on the exclusion of other causes of recurrent miscarriages such as women with a history of hyperandrogenism (congenital adrenal hyperplasia, Cushing syndrome and virilizing ovarian/adrenal tumors) or past or current usage of oral contraceptive tablets (in the previous 6 months) and those who were on medications like metformin, antiandrogens, glucocorticoids, or inedible product user like cigarette smokers, coffee intake exceeding 2 cups/day and they were removed from the research. Besides this the women with known to have hypertension, diabetic mellitus and cardiovascular diseases were also excluded. The control group is 56 women, non-PCOS but with history of recurrent miscarriage.

Both groups were atter he time of examination was HEALTH SCIENCE JOURNAL10 diagnosed with uterine anatomical anomalies as documented by USG, chromosomal abnormalities examined by karyotyping of both partners from peripheral blood, TSH, RBS, positivity for tests of APS (lupus anticoagulant and anti-cardiolipin antibodies), screening for TORCH (Toxoplasma gondii, Herpes simplex virus, Cytomegalovirus and Rubella). The study was approved by the Ethical Committee of the Iraqi Board for Medical Specialization. All patients as well as the controls were provided with written informed consent prior to enrolment in the study.

### Hormonal and biochemical measurements

Between day 2 to 4 of the menstrual cycle, both PCOS patients and controls were subjected to blood sampling, after an overnight fast. the following tests were obtaining included serum TSH, PRL, LH, testosterone (total), Androstenedione, Plasma glucose, insulin and Blood samples for homocysteine measurement were collected, were immediately were placed on ice, and were centrifuged at 4°C. Plasma was separated within 30 min. Plasma homocysteine (Hcy) concentration was determined by fluorescence polarization immunoassay (FPIA) using the ABBOTT diagnostic kit (USA). Polarization Immunoassay by IMX analysis (Abbott Diagnostics, Axis-Shield, Norway). 5 to 11 pmol/L from our laboratory was considered as normal reference range. Hyperhomocysteinemia was defined as plasma homocysteine > 11 pmol/l. Homeostatic model assessment of insulin resistance (HOMA-IR) normal value > 2.5, which is calculated by this equation: fasting glucose (mmol /L x fasting insulin (mU/L) / 22.5. The analyses were performed with the help of a computerized statistical package (SPSS for Windows, Version 6.1, SPSS Inc. USA), Fisher's exact test was used to evaluate differences in proportions, and Student's t-test was utilized to assess differences between parametric data sets.

## 3. Results

The demographic and obstetric characteristics of the two groups are shown in Table (1). There are no significant differences between the two groups with respect to age, number of abortions and history of infertility. However, BMI was significantly higher ($p<0.01$) in group PCOS.

**Table 1. Demographic and obstetrical parameters in women with (PCOS) and the control group.**

| Variable | PCOS (N=68) | Non-PCOS (N=56) | P- value |
|---|---|---|---|
| Age (years) | 28.95±4.28 | 29.85±3.69 | 0.12 |
| No. of abortion<br>23 | 51<br>17 | 45<br>11 | 0.1 |
| BMI (kg/m$^2$) | 34.71±3.45 | 24.79±2.21 | <0.01 |
| History of infertility (>2years) | 5 | 7 | 0.1 |

The average serum levels of DHEAS, TSH, and prolactin were similar in the two groups, however. LH /FSH ratio and LH level, T level were significantly higher in PCOS patients compared to control group. Fasting insulin was observed to be raised significantly) in IR women with PCOS. Fasting homocysteine levels were significantly elevated ($p=0.01$) in RPL women with PCOS (Table 2).

**Table 2: Comparison of Biochemical and Hormonal Parameters Between the Two Study Groups**

| Parameter | Group I (Mean ± SD) | Group II (Mean ± SD) | P-value |
|---|---|---|---|
| TSH (µIU/mL) | 2.76 ± 1.46 | 2.49 ± 1.42 | 0.10 |
| Prolactin (ng/mL) | 14.21 ± 3.97 | 13.21 ± 7.79 | 0.10 |
| LH (mIU/mL) | 9.94 ± 5.00 | 4.46 ± 3.00 | 0.01 |
| Fasting Blood Sugar (mg/dL) | 89.23 ± 7.53 | 87.36 ± 7.99 | 0.10 |
| Fasting Insulin (µIU/mL) | 14.39 ± 5.90 | 7.77 ± 1.20 | 0.01 |
| HOMA-IR | 2.49 ± 0.91 | 1.11 ± 1.34 | 0.01 |
| Homocysteine (µmol/L) | 13.14 ± 0.60 | 6.39 ± 2.20 | 0.01 |
| Testosterone (pg/mL) | 2.31 ± 4.00 | 1.46 ± 5.00 | 0.01 |
| DHEA (µg/L) | 341.20 ± 87.00 | 366.72 ± 7.00 | 0.13 |
| LH/FSH Ratio | 1.54 ± 0.70 | 0.87 ± 0.70 | 0.01 |

Table (3) revealed that the PCOS group with high IR as compared with the PCOS group with normal IR level was significant as regards to homocystine level, fasting insulin but the pcoc group with high IR was also statistically significant as compared to the control group as regards the level of homocystine, fasting insulin but against the statistical result revealed that the control group was not significantly different from PCOS group with normal insulin resistance.

**Table 3. Clinical and biochemical data of all patients; polycystic ovary syndrome (PCOS) group and control group in relation to insulin resistance**

| Group | Age | BMI | F Insulin (mIu/l) | Glugose: insulin ratio | HOMA-RI | Homocysteine (micro. Mol) |
|---|---|---|---|---|---|---|
| Total PCOS Reference range | 18-29 | 20-32 | 14-19 | >.33 | 3. 94±1.81 | 12.16-13.7 |
| PCOS-IR :>2.5 (n = 52) | 28.8±4 | 25.4±3 | 22.3+1.2 | 0.2±0.06 | 4.2+23 | 12.4±8.4 |
| PCOS-NIR <2.5 (N:23) | 27.5±3 | 23.9±3 | 11.6+3.2 | 0.43+4.4 | 1.34±2 | 9.6±5.3 |
| P- value: PCOS-IR versus PCOS-NIR | 0.5 | 0.2 | 0.01 | 0.01 | 0.01 | 0.02 |
| Control normal ovary | 28.6 | 24.6 | 10.3 | 0.53+0.17 | 0.24 | 7.41±21 |
| P –value: PCOS-IR versus control | NS | 0.01 | 0.01 | 0.01 | 0.02 | 0.0I |
| P-value: PCOS-NIR versus control | NS | NS | NS | NS | NS | 0.001 |

**BMI = body mass index; IR = insulin-resistant; NIR = non-insulin-resistant; HOMA-IR.**

The 11.0 mmol/l was found to be the 95th percentile for homocysteine in our control population: the normal range is reported to be 5±1 std 11 mmol/l. 63.1% (43/68) of the PCOS patients had Hcy values <11 mmol/L and the controls group was80% (47/56), whereas 25 of the 68 (42%) IR-PCOS patients had an elevated Hcy level (, P = 0.01). There is statistically significant between between the PCOS group in regared to BMI and fasting insulin and IR in comparising to the other groups of normal homo cysteine (Table 4).

**Table 4. Clinical and biochemical data for all patients by using normal homocysteine (Hcy) as a threshold (PCOS :68, normal: 56)**

| Group N: | BMI (kg/m2) | Glucose: insulin ratio | Insulin (mIU/l) | HOMA-IR | Homocysteine (mmol/l) |
|---|---|---|---|---|---|
| Hcy<11, normal ovaries N:47 | 24.5±2.1 | o.5 ±3.1 | 10.5±4 | 1.2±0.2 | 7.16±1.7 |
| Hcy <11.0, PCOS N:43 | 27.1±5.8 | 0.32±2 | 21.4±12 | 1.6±0.2 | 8.36±1.7 |
| Hcy >11. normal ovaries N:9 | 23.1±3.4 | 0.65±3 | 7.45±2.2 | 3.4±0.21 | 13.3±1.7 |
| Hys> 11 PCO N:25 | 28.2±6.5 | 0.24±5.2 | 25.1±10 | 7.3±0.2 | 17.5±10 |
| **P value** | **0.01** | **0.01** | **0.01** | **0.01** | **0.01** |

HOMA IR was strongly positively correlated with insulin levels (r 0.987) and there were moderate positive correlations between HOMA IR and BMI, homocysteine levels. A positive correlation was also found with the FSH/LH ratio) (Table 5).

**Table 5. Correlation of different clinical and laboratory parameters with HOMA index.**

| Parameter | Value |
|---|---|
| Insulin | r 0.987 |
| BMI | r-0.50 |
| Homocysteine | r-0.51 |
| S. FSH/LH ratio | r-0.75 |

## 4. Discussion

RPL occurs in 1–5% of couples seeking pregnancy. Despite multiple investigations for an etiologic agent of RPL, 50% of the cases are considered idiopathic. Metabolic derangements of the syndrome, such as obesity and IR, have been identified as independent risk factors for recurrent pregnancy loss (RPL) (6).

Numerous factors have been invoked for infertility in PCOS. These include oligo-anovulation, abnormal gonadotrophin secretion, increased systemic and/or local ovarian androgen concentrations, and abnormalities in one or more ovarian growth factors and the proteins to which they bind (6).

In the present study, neither the age nor the numbers of abortions had a significant difference in the two groups. The women suffering from PCOS were of 28 years young age (Regard ın young age ı) and no cases with PCOS > 38 was found in the present study. It has been shown that younger women with PCOS are more likely to be exposed to higher miscarriage rates and early reproductive failure, whilst older women with PCOS have an increased risk of diabetes mellitus, hypertension, dyslipidemia, nephropathy and cardiovascular diseases (8,9). But comorbid metabolic conditions including obesity and insulin resistance are more prevalent among women with PCOS, and deterioration in glucose metabolism with increasing severity of phenotypic features (8).

Similarly, in our study some of the Biochemical, hormonal parameters that have been tested among women with (PCOS) such as serum TSH, prolactin levels were not significantly different from those in non-PCOS group. The LH /FSH levels were significantly elevated in PCOS patients as compared to controls in the present study, however recently it has been shown that the LH/FSH ratio is not that useful in the diagnosis of PCOS, in the recent Rotterdam ESHRE/ ASRAM consensus it was recommended that this ratio has minimal value in clinical practice in diagnosis (10).

It was noted in this study that fasting insulin is significantly elevated in PCOS women along with HOMA-IR and these were significantly higher in PCOS women with previous history of RPL as compared to non-PCOS. All these results were in accordance with other studies (1,11), although the OC whereas age and IR (11), and deranged the etiology of PCOS is unknown, in PCOS excess fat mass contributes to the hyperinsulinemic state by both increased insulin secretion and decreased clearance of insulin is modulated by Akt and IR modulate secretion of insulin and serum androgens modulate the clearance of insulin acts as the PMID (11).

Serum homocysteine (Hcy) level was significantly higher in PCOS group compared to control group, this observation was consistent with various previous studies in which they observed a relationship between IR and high homocysteine in PCOS group of woman with RPL with that of the normal controls, although the causality between them remains elusive and there is one theory explain that homocysteine inhibits pro-insulin receptor cleavage and leading to the development of insulin resistance via protein cysteine-homocysteinylation (12, 13). Insulin Resistance was proven in previous study which could elevate Insulin levels has also been proposed as a regulator of Hcy,by inhibiting the hepatic activity of cystathione beta synthase which is involved in the degradation of homocysteine (14).

There was an elevation of fasting insulin and Hcy levels in women with PCOS as compared to the control group in present study, this result is similar to one previous study by Yarali et al. (6), that noted that plasma Hcy which is elevated in patients with PCOS was more correlated to fasting insulin than to glucose increase after glucose loading in PCOS and they found that insulin resistance and Hcy levels were significantly higher in both lean and obese pcop patients, and was linked to IR and not absolutely to body weight. Contradictory to the findings of Sills et al (15), who found no relationship between the diagnosis of PCOS and plasma Hcy despite high insulin levels were greter in polycystic ovaries with recurred miscarriage.

The speculative theory that the risk of an elevated Hcy and recurrent miscarriage relation is due may be for impair the implantation through disruption of endometrial blood flow and vascular integrity, which is related to placental vasculopathies, and has been reported to increase the risk of early pregnancy loss (16,17). Disrupted implantation and higher rates of miscarriage are both more prevalent in PCOS, after accounting for ovulatory dysfunction, raised LH and hyperandrogenism and this could be partially attributable to elevated Hcy levels in these women which could be considered a risk factor for cardiovascular disease, diabetes, hypertension nephropathy, and dyslipidaemia in the future (18). A number of reports indicated that insulin resistance syndrome-related long-term consequences of the `metabolic syndromes' could be exacerbated by increased Hcy. Therefore, PCOS, from a metabolic perspective, may simply be viewed as a manifestation of the IRS, or perhaps as an early 'marker' of the IR.

The interesting point in most of the research who was concluded that at the time of infertility treatment, women with PCOS should be aggressively evaluated for evidence of metabolic derangement, such as increased Hcy and IR levels, and should be treated to correct these metabolic parameters to the extent possible so as to maximize the chance of shortening of treatment interval (reproductive function) and also for improving the chance of conception and for cardiovascular and metabolic function in the long term (18,19). There was no difference in ethnicity in our study population which might have influenced the elevated Hcy when compared with the subjects in the previous European, American studies may be attributed to varied ethnicity in their countries. A study by Wijeyaratne et al. (20) was the first report of an ethnic difference showing the ethnic differences in Hcy levels and consequently, in IR indices of women with PCOS. Recently, some have stressed the significance of ethnic factors in Hcy metabolism (21,22). Even differences between studies performed in the same country could be attributed to ethnicity. The ethnic were not analyzed in our study, but we thought that the diversity of ethnicity in our country would not contribute to the different response in patients in this study.

**5. Conclusions:** Several studies have proved that women with PCOS have significantly higher BMI, fasting insulin and IR levels. Insulin resistance and hyperinsulinaemia in patients with PCOS are associated with increased plasma homocystiene independent of BMI which could have relevant short - term implications for reproductive function. A study with large sample size is suggested to assess the various parameters in relation to IR and homocystiene level in women with PCOS and recurrent miscarriage. The work has been approved ethically by the Iraqi Board for Medical Specialization.

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