Correlation of Polycystic Ovary Syndrome and Recurrent Miscarriage

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ABSTRACT

Background: Numerous studies have investigated the association between polycystic ovary syndrome (PCOS) and recurrent miscarriage (RM). Increased rates of PCOS have been reported for women with RM. However, the actual prevalence is controversially discussed by the scientific community and remains unclear, since a wide range of rates from 8–82% can be found in the literature. **Objective:** To assess the relation between polycystic ovary syndrome and recurrent miscarriage and to evaluate the prevalence of polycystic ovarian syndrome within the recurrent miscarriage population. **Patients and method:** It is a cross sectional conducted at the infertility clinic in the outpatient department of University Hospital from March 2019 to March 2020. Patient sample was 47 participant. Hormonal profile FSH، LH, TSH, TSH, assessment of glycemic status and insulin resistance and ultrasonography for diagnosis of polycystic ovaries were done to every patients. **Result:** There was high statistically significant relation between the PCO and total number of follicles, number of follicles ≥ 18 mm and endometrial thickness. There was high statistically significant relation between the PCO and testosterone hormones and statistically significant relation between the PCO and FSH and LH. There was no statistically significant relation between the PCO and insulin resistance. **Conclusion:** In this study we concluded that the prevalence of PCOS seems slightly increased in women with recurrent miscarriage, PCOS on the other hand showed a rather high prevalence compared to the general population.

Keywords: Polycystic Ovary Syndrome, Recurrent Miscarriage.

INTRODUCTION

According to the World Health Organization (WHO), recurrent miscarriage (RM) is defined as three or more consecutive pregnancy losses before the 20th gestation week [(1)]. It is estimated that five percent of all couples trying to conceive are affected by two consecutive miscarriages and that one percent is affected by three or more [(2)].

In 50% of the cases of RM, the underlying cause remains unknown. Potential pathologies leading to RM include genetic abnormalities, infection, immune dysfunction, endocrine disorders, antiphospholipid syndrome, thrombophilic disorders, uterine pathologies, and cervical weakness [(3)]. Polycystic ovarian syndrome (PCOS) is a clinically and biochemically heterogeneous disorder. It is the most common endocrinopathy in reproductive aged women affecting 4%–12% [(4)]. Numerous studies have investigated the association between PCOS and RM. Increased rates of PCOS have been reported for women with RM [(5)]. However, the actual prevalence is controversially discussed by the scientific community and remains unclear, since a wide range of rates from 8–82% can be found in the literature [(5)]. Certain features of PCOS are associated with an increased risk of RM, including hyperandrogenism, insulin resistance, hyperinsulinemia, obesity, elevated level of plasminogen-activator inhibitor (PAI)-1, and hyperhomocysteinemia [(6)].

Therefore, pathophysiological connections can be assumed and it is unclear whether PCOS would cause RM directly or whether the association is due to certain factors that are linked to both conditions. These uncertainties underline the need for further investigation. The aim of this study was to assess the relation between polycystic ovary syndrome and recurrent miscarriage and to evaluate the prevalence of polycystic ovarian syndrome within the recurrent miscarriage population.

PATIENT AND METHODS

It is a cross sectional conducted at the infertility clinic in the outpatient department of University Hospital from March 2019 to March 2020. Patient sample was 47 participants.

Inclusion criteria: Women with history of recurrent pregnancy loss 3 or more, women age 20-40 years old, patients diagnosed according to Rotterdam criteria (two of three)1= oligoovulation and or anovulation, 2= hyperandrogenism=excess androgen activity, 3= polycystic ovaries (>12 cysts، 2-9 mm in one or two ovaries and ovarian volume >10 ml=), and women with normal ultrasonographic measurement of the uterus.

Exclusion Criteria: Pregnant women, women with diabetes mellitus (DM), hypertensive patients, patients with liver or cardiac or renal diseases, women with uterine anatomical anomalies, and patients with positive tests for antiphospholipid syndrome (APS) (lupus anti-coagulant and anticardiolipin antibodies).

All participants in this research were subjected to:
Full history taking.

Examination: General examination blood pressure, pulse, temperature pallor, jaundice, weight, height, hirsutism, examination of thyroid gland, breast, chest, heart. Examination of abdomen and pelvis for inspection of hair distribution and palpation of pelvi abdominal masses.

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Investigations:
Hormonal profile FSH, LH, TSH and TSH.
Assessment of glycemic status and insulin resistance.
Ultrasonography for diagnosis of polycystic ovaries and to exclude abnormality of uterus and cervix and detect size, position and outlines of uterus and cervix.

Ethical consent:
An approval of the study was obtained from Zagazig University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of the operation. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis:
The collected data were coded, processed and analyzed using the SPSS (Statistical Package for the Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Data were tested for normal distribution using the Shapiro Wilk test. Qualitative data were represented as frequencies and relative percentages. Chi square test (χ^2) was used to calculate difference between two or more groups of qualitative variables. Quantitative data were expressed as mean ± SD (Standard deviation), median, and interquartile range (IQR). Independent samples t-test or Mann-Whitney test was used to compare between two independent groups of normally- or abnormally-distributed variables respectively. P value < 0.05 was considered significant.

RESULT
Table 1 shows the demographic data of the studied cases.

Table (1): Demographic data of the studied cases (n = 47)

	No.	%
Age (years)		
<30	26	55.3
≥ 30	41	44.7
Minimum – Maximum	26.0 – 35.0	
Mean ± SD	29.83 ± 2.66	
Median (IQR)	29.0 (28.0 – 32.0)	
Parity		
Mean ± SD	4.91 ± 0.80	
Median (IQR)	5.0 (4.0 – 6.0)	
History of recurrent abortion		
Mean ± SD	3.94 ± 0.92	
Median (IQR)	4.0 (3.0 – 4.50)	
BMI (kg/m^2)	**No.**	**%**
Normal (18.5 – 24.9)	26	27.7
Overweight (25 – 29.9)	48	51.1
Obese (30 – 34.9)	20	21.3
Mean ± SD	27.52 ± 2.99	
Median (IQR)	27.50 (24.30 – 29.60)	

IQR: Interquartile range, SD: Standard deviation

The mean number of different follicles and the mean endometrial thickness are shown in table 2.

Table (2): Ultrasound results of the studied cases (n = 47)

Total number of follicles	
Mean ± SD	6.40 ± 1.39
Median (IQR)	7.0 (5.0 – 7.0)
Number of follicles 14-18 mm	
Mean ± SD	3.64 ± 0.82
Median (IQR)	4.0 (3.0 – 4.0)
Number of follicles ≥ 18 mm	
Mean ± SD	2.77 ± 1.07
Median (IQR)	3.0 (2.0 – 4.0)
Endometrial thickness (mm)	
Mean ± SD	10.73 ± 1.12
Median (IQR)	11.0 (10.0 – 12.0)

IQR: Interquartile range, SD: Standard deviation
The hormonal profile of the studies cases is shown in table 3.

Table (3): Descriptive analysis of the studied cases according to hormonal profile (n = 47)

Hormonal profile	Mean ± SD	Median (IQR)
FSH (IU/mL)	5.72 ± 1.09	5.70 (3.65 – 5.30)
LH (IU/L)	6.12 ± 1.36	5.70 (3.20 – 4.95)
LH/FSH ratio	1.19 ± 0.04	1.10 (0.60 – 0.80)
TSH (mIU/mL)	2.10 ± 0.1	2.24 (1.23 – 1.94)
Testosterone hormones (ng/dl)	0.35 ± 0.07	0.32 (0.23 – 0.32)

IQR: Interquartile range, SD: Standard deviation

The data of the studied cases according to insulin resistance are shown in table 4.

Table (4): Descriptive analysis of the studied cases according to insulin resistance (n = 47)

Insulin Resistance	Mean ± SD	Median (IQR)
FBG (mg/dL)	86.06 ± 9.53	86.0 (76.50 – 94.0)
Fasting serum insulin levels	4.38 ± 1.17	4.20 (3.60 – 5.55)
Homa-IR	0.94 ± 0.31	0.90 (0.70 – 1.15)

IQR: Interquartile range, SD: Standard deviation

Table 5 shows that there was high statistically significant relation between the PCO and total number of follicles, number of follicles ≥ 18 mm and endometrial thickness.

Table (5): Relation between PCO and Ultrasound (n = 47)

Examinations	PCO		p
	No (n = 76)	Yes (n = 18)	
Total number of follicles			
Mean ± SD	6.87 ± 1.04	4.44 ± 0.88	<0.001*
Number of follicles 14-18 mm			
Mean ± SD	3.74 ± 0.79	3.22 ± 0.83	0.090
Number of follicles ≥ 18 mm			
Mean ± SD	3.13 ± 0.81	1.22 ± 0.44	<0.001*
Endometrial thickness (mm)			
Mean ± SD	11.08 ± 0.88	9.22 ± 0.67	<0.001*

SD: Standard deviation, *: Statistically significant

Table 6 shows that there was statistically significant relation between the PCO and Hb.

Table (6): Relation between PCO and CBC (n = 47)

CBC	PCO		p
	No (n = 76)	Yes (n = 18)	
Hb (g/dl)			
Mean ± SD	12.10 ± 0.68	11.53 ± 0.42	0.005
Median	12.15	11.70	
WBCs (×10³/µl)			
Mean ± SD	6.81 ± 1.21	6.30 ± 1.28	0.265
Median	6.80	6.30	
PLTs (×10³/µl)			
Mean ± SD	221.84 ± 41.16	219.56 ± 41.12	0.882
Median	222.50	229.0	

SD: Standard deviation

Table 7 shows that there was high statistically significant relation between the PCO and testosterone hormones and statistically significant relation between the PCO and FSH and LH.

Table (7): Relation between PCO and hormonal profile (n = 47)

Hormonal profile	PCO		p
	No (n = 76)	Yes (n = 18)	
FSH (IU/mL)			
Mean ± SD	5.41 ± 1.94	7.04 ± 1.27	0.028*
Median	5.40	7.30	
LH (IU/L)			
Mean ± SD	5.31 ± 1.76	9.58 ± 2.61	0.002*
Median	5.35	8.20	
LH/FSH ratio			
Mean ± SD	1.10 ± 0.07	1.54 ± 0.06	0.081
Median	1.05	1.50	
TSH (mIU/mL)			
Mean ± SD	2.07 ± 0.02	2.20 ± 0.55	0.700
Median	2.06	2.24	
Testosterone hormones (ng/dl)			
Mean ± SD	0.29 ± 0.01	0.63 ± 0.01	<0.001*
Median	0.28	0.62	

SD: Standard deviation, *: Statistically significant

Table 8 shows that there was no statistically significant relation between the PCO and insulin resistance.

Table (8): Relation between PCO and insulin resistance (n = 47)

Insulin Resistance	PCO		p
	No (n = 76)	Yes (n = 18)	
FBG (mg/dL)			
Mean ± SD	85.08 ± 9.97	90.22 ± 6.20	0.065
Median	83.50	89.0	
Fasting serum insulin levels			
Mean ± SD	4.34 ± 1.24	4.51 ± 0.92	0.661
Median	4.15	4.40	
Homa-IR			
Mean ± SD	0.92 ± 0.2	1.01 ± 0.22	0.357
Median	0.85	1.0	

SD: Standard deviation

DISCUSSION

In recent years, numerous studies have investigated the association between PCOS and RM. Increased rates of PCOS have been reported for women with RM. However, the actual prevalence is controversially discussed by the scientific community and remains unclear [7].

In this study we found that the prevalence of PCO was 18 (19.1%) with RM. **Mayrhofer *et al.*** [4] found that PCOS was found in 43 (9.5%) of all women. **Rai *et al.*** [8] found that the prevalence of polycystic ovarian morphology amongst women with recurrent miscarriage was 40.7% (895/2199).

In this study we found that among the studied cases there were 52 (55.3%) less than 30 years and 42 (447%) more than 30 years with mean age 29.83 (±2.66 SD) and range (26-35) years, the mean parity was 4.91 (±2.66 SD) with range (4-6) and the mean history of recurrent abortion was 3.94 (±0.92 SD) with range (3-6). **Sanad *et al.*** [9] found that among patients with PCO**,** mean of age 28.2 ± 4.8 with median (20–37) and mean of parity 2.5 ± 2 with median (1–7).

Rai *et al.* [8] found that in study on 233 women with PCO (median age 32 years; range 19–44) and a history of recurrent miscarriage (median 3; 3–14). **Mayrhofer *et al.*** [4] found that negative results for the selected risk factors for recurrent miscarriage were present in 283 (62.6%). Mean age of the sample population was 33.8 ± 6.1 years, Primary RM was observed in 318 (70.4%) cases, secondary RM appeared in 134 (29.6%) cases. The majority of patients had three previous miscarriages (322, 71.2%); while 78 (17.3%) had four and 52 (70.4%) had five or more previous miscarriages.

In the study in our hands, we found that the mean number of follicles was 6.4 (±1.39 SD) and range (3-9), the mean number of follicles 14-18 mm was 3.64 (±0.82 SD) with range (2-5), the mean number of follicles ≥ 18 mm was 2.77 (±1.07 SD) with range (1-4) and the mean endometrial thickness was 10.73 (±1.12 SD) with range (8-12). **Rai *et al.*** [8] found that among PCO patients, the ovarian volume was enlarged (>9 ml), and there were ≥10 cysts of 2–8 mm in diameter in one plane and there was increased density of the stroma, which was subjectively quantified.

In this study we demonstrated that the mean FSH was 5.72 (±2.09 SD) with range (2.1-9.3), the mean LH was 6.12 (±3.36 SD) with range (1.2-15.3), the mean LH/FSH ratio was 1.19 (±0.74 SD) with range (0.2-3.7), the mean TSH ratio was 2.1 (±1 SD) with range (0.52-3.72) and the mean testosterone hormones was 0.35 (±0.17 SD) with range (0.13-0.76).

Mayrhofer *et al.* [4] found that the mean FSH was 5.3 ± 2.1, the mean LH was 8.8. ± 4.1, the mean LH/FSH ratio was 1.9 ± 1.1 and mean testosterone hormones was 0.61 ± 0.12. **Ashaq *et al.*** [10] found that mean luteinizing hormone (LH) level was 7.18 (1.06 - 75.4), mean of follicle-stimulating hormone (FSH) level was 6.54 (0.75 - 16.2), the mean thyroid-stimulating hormone (TSH) level in the cases 2.57 (0.86 - 6.25) and the mean testosterone level in the cases was 6.22 (023 - 58.9).

In this study we found that the mean FBG was 86.06 (±9.53 SD) with range (71-102), the mean fasting serum insulin level was 4.38 (±1.17 SD) with range (2.3-6.3) and the mean Homa-IR was 0.94 (±0.31 SD) with range (0.5-1.5). **Chakraborty *et al.*** [11] found that FBG was 89.23 (±7.53 SD), the mean fasting serum insulin levels was 14.39 (±5.79 SD) and the mean Homa-IR was 2.39 (±0.91 SD).

In this study we illustrated that among the studied cases there were 26 (27.7%) normal weight, 24 (51.1%) overweight and 10 (21.3%) obese with mean BMI 27.52 (±2.99 SD) and range (23-33.6). **Mayrhofer *et al.*** [4] found that mean of BMI was 24.9 ± 5.0 kg/m^2 for patients with PCOS. **Ashaq *et al.*** [10] found that mean of BMI was 31.4 kg/m^2 (16.8 - 47.1) among cases group. **Hussein *et al.*** [12] illustrated that among PCO cases, the mean of BMI was 30.9 ± 5.84 kg/m^2.

In this study we found that there was statistically significant relation between the PCO and BMI and no statistical relation between PCO and age, parity and history of recurrent abortion.

Mostafa *et al.* [13] found that BMI was significantly high in PCOS women compared to non PCOS women (32.6±6.0 Kg/m^2 versus 29.5±4.0). **Rai *et al.*** [8] found that there was no significant difference in neither the age nor the number of previous miscarriages between the two groups of women. **Hussein *et al.*** [12] illustrated that the mean ages in the PCOS and non-PCOS groups were 29.5 ± 5.45 years versus 32.9 ± 6.95 years, respectively (P = 0.00061). Most women in the PCOS group (30.2%) aged 25 - 29 years, while in the non-PCOS group most (24.3%) aged 35 - 39 years. **Ashaq *et al.*** [10] found that women with PCOS with recurrent abortions were slightly older than the controls, with a mean age of 33.1 years (21 - 50) compared to 31.9 years (21 - 47), but the result was not statistically significant (p-value > 0.05).

Chakraborty *et al.* [11] found that both groups were similar in terms of age and marriage duration. However, BMI has been found to be significantly greater (p value<0.01) in PCOS group.

In the study in our hands, we found that there was high statistically significant relation between the PCO and total number of follicles, number of follicles ≥ 18 mm and endometrial thickness.

Odera *et al.* [14] found that the mean ovary size of the study participants with PCOS was noted to be significantly larger, the right ovary being 17.7 cm^3±8.6 cm^3 and the left ovary being 15.8 cm^3±6.4 cm^3 in women with PCOS compared to a mean right ovarian size of 8.3 cm^3±3.7 cm^3 and left ovarian size of 9.6 cm^3±6.9 cm^3 in those without. **Farquhar *et al.*** [15] found that Women with polycystic ovaries had increased number of follicles compared to women with normal ovary.

In this study we found that there was high statistically significant relation between the PCO and testosterone hormones and statistically significant relation between the PCO and FSH and LH. **Mayrhofer *et al.* (4)** found that women in the PCOS group revealed significantly higher LH, testosterone, and AMH levels ($p < 0.05$). **Hussein *et al.* (12)** reported that the incidence of elevated LH level was significantly higher in PCOS group than in non-PCOS group (17% versus 8.4% respectively, P = 0.000). The incidence of elevated FSH level was not significantly higher in the non-PCOS group than in the PCOS group (15% versus 10.4% respectively = 0.476).

There was no statistically significant difference between the two groups in terms of the LH/FSH ratio and total testosterone level. Progesterone was measured in the mid-luteal phase to confirm ovulation and there was a statistically significant difference between the two groups; 90.7% of the non-PCOS group versus 7.5% of PCOS group showed ovulatory cycles. **Odera *et al.* (14)** found that there was also a statistically significant difference in the total serum testosterone levels in the participants with PCOS compared to those without PCOS. Elevated serum testosterone, as part of hyperandrogenemia, is one of the diagnostic criteria of PCOS according to the Rotterdam 2003 criteria (16).

In this study we demonstrated that there was no statistically significant relation between the PCO and insulin resistance. **Chakraborty *et al.* (11)** found that both fasting and post-prandial (PP) insulin was found to be significantly higher (p value<0.0001) in PCOS population along with HOMA2-IR values (PCOS: 2.39±0.91 vs non-PCOS: 1.51±1.34).

CONCLUSION

In this study we concluded that the prevalence of PCOS seems slightly increased in women with recurrent miscarriage, PCOS on the other hand showed a rather high prevalence compared to the general population.

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