Abstract

Objective: To study the clinical, metabolic, hormonal parameters, and differential response to clomiphene among the obese and non-obese PCOS (polycystic ovarian syndrome).

Design: Prospective observational study.

Setting: Infertility OPD, a government hospital.

Sample Size: About 164 women with PCOS-related infertility.

Study Groups: Obese PCOS group (body mass index (BMI) ≥23 kg/m²) and non-obese PCOS group (BMI <23 kg/m²).

Results: Of the total 164 PCOS women, 124 (75.61%) were in the obese group with BMI ≥23 kg/m² and 40 (24.39%) were in the non-obese PCOS group. The prevalence of menstrual irregularity, hypertension, insulin resistance (IR), metabolic syndrome, endometrial hyperplasia, and clomiphene resistance in the PCOS women were 82.34%, 3.66%, 59.76%, 24.39%, 7.93%, and 53.7%, respectively. The Ferriman–Gallwey score, menstrual irregularity, IR (fasting insulin and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR)), metabolic syndrome, deranged lipid profile, and clomiphene resistance were statistically more common in the obese PCOS group (P < 0.05). Hypertension, deranged blood sugar profile, testosterone, androstenedione levels, and endometrial hyperplasia were more common in obese PCOS group but the results were not statistically significant. No significant differences were found in the luteinizing hormone (LH), follicle-stimulating hormone (FSH), LH–FSH ratio, and 17-hydroxyprogesterone (17-OHP) levels between the two groups.

Conclusion: Obese PCOS have a higher risk of adverse outcomes like hypertension, IR, metabolic syndrome, and endometrial hyperplasia. So, targeting obesity in PCOS women will not only help to prevent adverse outcomes but also improve responsiveness to clomiphene citrate.

Keywords: Body mass index, hypertension clomiphene, metabolic syndrome, polycystic ovarian syndrome

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrinological disorder seen in 6–10% of the women. In nearly 20% of the infertile women, PCOS is said to be the key reason behind infertility.[1] The diagnosis is based on the Rotterdam’s criteria[2] which includes two of the three findings – polycystic ovaries, anovulatory cycles, and hyperandrogenism. Other features that have been associated with PCOS include insulin resistance (IR) and metabolic syndrome.[3]

There is a bi-directional relationship between obesity and PCOS. Both exacerbate each other in a never-ending cyclical manner.[4] The prevalence of obesity in PCOS women is reported to be 30–75%.[5]

In clinical practice, we come across two types of PCOS patients – one group who are obese and the other group of non-obese PCOS.[6] We have seen that these patients differ in their clinical, metabolic, and hormonal parameters. Also, they respond differently to ovulation induction treatment.

PCOS has been associated with menstrual irregularity, hyperandrogenism, hypertension, metabolic syndrome, IR,[7] endometrial hyperplasia,[8] and clomiphene citrate resistance. This study aims to find the prevalence of these parameters in the PCOS women and compare them between...
the two PCOS phenotypes – obese and non-obese PCOS groups.

**MATERIALS AND METHODS**

This prospective observational study was conducted in the Department of Obstetrics and Gynecology at a government hospital. The period of study was 1 year and 164 patients with PCOS-related infertility were enrolled.

Consecutive sampling method was adopted for this study. Data collection were done for 1 year. In each week two days were fixed for sample collection which was done during OPD time. Each day, first three patients were contacted for the study. Thus, total of 312 patients were contacted in the study. But, 96 patients were excluded after primary evaluation (they fell in the exclusion criteria). Fifty-two patients lost to follow up during the course of the study. So, the final sample size was 164 patients with PCOS-related infertility [Figure 1].

Approval was taken for this study from the ethical committee of the institution before starting the study.

Inclusion criteria included women with PCOS-related infertility (based on the Rotterdam’s criteria\(^2\)) of age <40 years. Women on any insulin-sensitizing agent, lipid-lowering agent, having an endocrine disorder, anorexia nervosa/bulimia nervosa, or with hypothalamic or pituitary dysfunction were excluded.

All PCOS women desirous of pregnancy were evaluated after a written informed consent. Relevant history was taken to rule out the exclusion criteria. The physical examination included her blood pressure (BP), weight in kilograms using a beam balance, and height in upright posture without shoes using a stadiometer to the nearest 0.5 cm was recorded. The body mass index (BMI) was recorded from the above measurements. Owing to the differences in body fat distribution between the Asian and Western population, the World Health Organization (WHO) expert committee in 2004\(^9\) has proposed BMI cut-offs for the Asian population which was used in this study.

These PCOS women were divided into two groups: one who were overweight and other who were obese based on the Asian criteria\(^9\) with BMI $\geq$23 kg/m$^2$ were included in the obese PCOS group and the other group included those women with BMI $<23$ kg/m$^2$ (normal and underweight women) designated as non-obese PCOS group.

Various clinical, metabolic, and hormonal parameters were compared in the two groups. Clinical parameters included signs of androgen excess like excessive hair growth, acne, or alopecia. Excessive hair growth was evaluated by the modified Ferriman and Gallwey\(^10\) score.

The Federation of Gynecology and Obstetrics (FIGO) classification\(^11\) was used to characterize menstrual irregularity. The cycle length of 24–38 days was considered normal and length $>$38 days were included in the oligomenorrheic group.

The patients enrolled in the study were called on Day 2 of her next cycle for the investigations [follicle-stimulating hormone (FSH), luteinizing hormone (LH), 17-hydroxyprogesterone levels (17-OHP), testosterone, androstenedione, 75 g oral glucose tolerance test, fasting insulin, fasting triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and cholesterol levels]. The results were compared in the obese and non-obese PCOS groups.

The diagnosis of hypertension (BP $>$130/80) was based on the AHA/ACC 2017 criteria\(^12\) and that of metabolic syndrome was based on the ATP III criteria.\(^13\) Their presence or absence was compared between the obese and non-obese PCOS group.

The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR),\(^14\) a surrogate marker of IR was used in this study. Patients with HOMA-IR $>$2\(^7\) were defined as having IR. IR was compared between obese and non-obese PCOS group.

Endometrial biopsy was done on Day 1 of the cycle and the presence or absence of hyperplasia was compared between obese and non-obese PCOS groups.

All these patients were treated with clomiphene citrate starting with 50 mg/day on the Day 2–5 of their cycle for 5 days. In case of failure of ovulation, the dose will be increased by 50 mg in subsequent cycles to a maximum dose of 150 mg over three cycles.

Response to clomiphene citrate was assessed by ovulation. Transvaginal scan (TVS) was done by the same observer using a Philips ultrasound machine, model IU22. A scan was done starting from Day 10 of the cycle and until follicle size $>$18 mm or Day 20 of the cycle. Patients were called after 2–3 days of development of dominant follicle to look for the rupture of the follicle.
Those who did not ovulate with 150 mg clomiphene were classified as CC-resistant. Presence or absence of CC-resistance was compared between the obese and non-obese PCOS group.

The various parameters of the patients were recorded as mean ± SD. Normality of quantitative data were checked by measures of Kolmogorov–Smirnov tests of normality. If data were normally distributed independent t-test was applied for comparison of two groups (clomiphene-sensitive and clomiphene-resistant). Mann–Whitney U-test was used for statistical analysis of skewed continuous variables. Proportions were compared using the Chi-square or Fisher’s exact test, whichever applicable. All statistical tests were two-sided and performed at a significance level of α = 0.05. The analysis was conducted using the IBM SPSS STATISTICS (version 24.0).

RESULTS

Of the total 164 PCOS women, 124 (75.61%) were in overweight and obese group with BMI ≥23 kg/m² and 40 (24.39%) were in the non-obese and normal weight PCOS group. BMI distribution in the study population is shown in [Table 1].

Clinical hyperandrogenism as calculated by Ferriman–Gallwey score was significantly higher in the obese group (14.23 ± 3.84 vs. 12.604.01, P = 0.02). Biochemical hyperandrogenism (total testosterone and androstenedione) was higher in obese as compared to non-obese PCOS but the results were not statistically significant [Table 2].

Menstrual irregularity was statistically more common in obese PCOS group as compared to non-obese PCOS (86.29% vs. 70%, P = 0.019). The prevalence of IR (HOMA-IR >2) was 59.76% in the PCOS women. Fasting insulin (12.63 ± 6.84 vs. 9.5 ± 96.36, P = 0.012) and HOMA-IR (2.91 ± 1.84, 2.18 ± 1.63, P = 0.014) were significantly more common in the obese group as compared to non-obese PCOS. Fasting and 2-h postprandial blood sugar were more common in the obese group but the results were not statistically significant [Table 2].

Hypertension was seen in 3.66% of the PCOS women and it was more common in the obese group as compared to non-obese PCOS but the result was not statistically significant [Table 3].

Metabolic syndrome was seen in 24.39% of the PCOS women and was statistically more common in the obese group as compared to non-obese PCOS (29.03% vs. 10%, P = 0.015) [Table 4].

The prevalence of impaired glucose tolerance and diabetes mellitus in the study population were 40.24% and 6.71%, respectively, and was more common in the obese PCOS group [Table 4].

Endometrial hyperplasia was seen in 7.93% of the PCOS women. Endometrial hyperplasia with atypia (seen in 1.6%) was limited to the obese group [Table 4]. There were no statistically significant differences related to LH, LH–FSH ratio, 17-OHP among the obese and non-obese PCOS group.

BMI distribution amongst the CC-resistant and CC-sensitive groups is given in Table 5. CC-resistance was statistically more common in the obese PCOS group (58.87% vs. 37.5%, P = 0.018).

DISCUSSION

In the present study, the Ferriman–Gallwey score, menstrual irregularity, IR (fasting insulin and HOMA-IR), metabolic syndrome, deranged lipid profile, and clomiphene resistance were statistically more common in the obese PCOS group (P < 0.05). Hypertension, deranged blood sugar profile, testosterone, androstenedione levels, and endometrial hyperplasia were more common in obese PCOS group but the results were not statistically significant. No significant differences were found in the LH, FSH, LH–FSH ratio, and 17-OHP levels between the two groups.

Prevalence of overweight and obese population in PCOS women in the current study was 75.61%. This was in accordance with the study conducted by Essah and Nestler.[13] In the present study, the prevalence of hyperandrogenism and menstrual irregularity were higher in the obese PCOS group. Obesity results in increase in the androgens and decrease in sex hormone binding globulin (SHBG) levels, thus increasing free androgen level.[15] Similar results were observed in the study by Kim et al.[16] who found a higher hyperandrogenism in women with high BMI. Obesity results in hormonal imbalances resulting in hyperandrogenism and hyperinsulinemia.[17] This explains the higher Ferriman–Gallwey score, testosterone, and androstenedione in the obese PCOS group.

Hyperandrogenism leads to hyperinsulinemia and vice versa. Insulin acts on the theca cells, increasing androgen production. Also, theca cells of the PCOS women are more responsive to the insulin-secreting action of insulin.[18] Insulin has synergistic action like gonadotropins in increasing LH-induced androgen synthesis by theca cells. It also increases GnRH-mediated LH synthesis and release.[19]

Using the HOMA-IR to estimate IR, the prevalence of IR in the present study was 59.76%. These results were consistent with the study conducted by DeUgarte et al.[7] and Carmina and Lobo.[20] Also, IR was higher in the obese PCOS group.

| BMI category (kg/m²) | Definition | Distribution (n=164) (%) |
|----------------------|------------|------------------------|
| <18-5                | Underweight| 3 (1.8)                |
| 18-5-23              | Normal     | 37 (22.6)              |
| 23-27.5              | Increased risk for metabolic syndrome | 69 (42.1) |
| >27.5                | High risk for metabolic syndrome      | 55 (33.5) |

BMI: Body mass index, PCOS: Polycystic ovarian syndrome, WHO: World Health Organization
The prevalence of impaired glucose tolerance and diabetes mellitus in the obese PCOS group were 41.9% and 8.06%, respectively, and in the non-obese group were 35% and 2.5%. This risk is higher than in the general population.[21]

It has been suggested that PCOS women have an intrinsic risk of developing IR.[22] Obesity and higher BMI further adds to the risk of IR and metabolic syndrome by defective secretion or action of insulin. Same has been noted in the present study.

Definitely, this study shows that obese PCOS have a higher risk of IR, metabolic syndrome, and hypertension. But, due to lack of control population, this study fails to clarify if this increased risk is entirely due to obesity or the synergistic effect of PCOS and obesity. One thing is very clear from this study that if we target obesity, we will be able to prevent the development of IR and metabolic syndrome in PCOS patients.

Both obesity and PCOS leading to anovulation are known risk factors for endometrial hyperplasia and endometrial carcinoma.[23] The various mechanisms by which obesity results in endometrial hyperplasia are hyperestrogenism caused by the peripheral conversion of androstenedione to estrone, by decreasing SHBG and increasing anovulation.[24] PCOS-related obesity, infertility, nulliparity, IR, and metabolic syndrome are also independent risk factors of endometrial hyperplasia.[25] Patients with BMI >40 kg/m² have 13 times more risk of endometrial hyperplasia.

### Table 2: Comparison of clinical, metabolic and hormonal parameters amongst obese and lean PCOS group

| PARAMETERS | MEAN DISTRIBUTION (n=164) (MEAN±SD) | OBESE PCOS1 BMI² ≥23 kg/m² (MEAN±SD) (n=124) | LEAN PCOS1 BMI² <23 kg/m² (MEAN±SD) (n=40) | P (MANN-WHITNEY TEST) |
|------------|-----------------------------------|---------------------------------------------|----------------------------------|---------------------|
| Age in years | 27.98 | 28.083.80 | 27.683.57 | 0.748 |
| Waist-hip ratio | 62.24 | 0.890.04 | 0.860.05 | 0.001* |
| SBP3 in mmHg | 117.32 | 117.277.63 | 117.457.65 | 0.954 |
| DBP4 in mmHg | 74.755.805 | 74.845.60 | 74.5.0 | 0.831 |
| Ferriman Gallwey Score | 13.98 | 14.23.3.48 | 12.604.01 | 0.02* |
| Testosterone (nmol/l) | 2.74 | 2.79 | 2.58 | 0.281 |
| Androstenedione (ng/ml) | 2.97 | 3.05 | 2.74 | 0.226 |
| FBS5 (mg/dl) | 90.14 | 90.8513.59 | 87.9511.19 | 0.292 |
| PPBS6 (mg/dl) | 130.73 | 132.5130.13 | 125.2326.48 | 0.197 |
| Fasting Insulin (mIU/L) | 11.89 | 12.636.84 | 9.596.36 | 0.012* |
| HOMA-IR7 | 2.73 | 2.911.84 | 2.181.63 | 0.014* |
| Serum Triglycerides (mg/dl) | 133.11 | 139.53.53 | 114.4636.37 | 0.005* |
| Serum Cholesterol (mg/dl) | 171.12 | 175.1940.44 | 158.4948.55 | 0.019* |
| LDL8 (mg/dl) | 110.55 | 113.3925.14 | 101.7174.3 | 0.023* |
| HDL9 (mg/dl) | 47.98 | 47.169.01 | 49.538.25 | 0.182 |
| Baseline FSH10 (IU/l) | 5.84 | 5.8±2.71 | 5.8±1.75 | 0.347 |
| Baseline LH11 (IU/l) | 13.53 | 13.33±7.56 | 14.13±6.78 | 0.370 |
| Baseline LH11/FSH10 | 2.48 | 2.6±1.69 | 3.0±2.30 | 0.529 |
| 17 OHP12 (ng/dl) | 1.38 | 1.37±0.73 | 1.43±0.88 | 0.748 |

*Chi-square test, #Fisher’s exact test

### Table 3: Comparison between the obese and lean PCOS group

| Parameter | Category | Mean distribution (n=164) (mean±SD) (%) | Obese PCOS1 BMI² ≥23 kg/m² (mean±SD) (n=124) (%) | Lean PCOS1 BMI² <23 kg/m² (mean±SD) (n=40) (%) | P |
|-----------|----------|-----------------------------------|---------------------------------------------|----------------------------------|---------------------|
| Menstrual irregularity | Present | 135 (82.34) | 107 (86.29) | 28 (70) | 0.019* |
| | Absent | 29 (17.68) | 17 (13.71) | 12 (30) | 0.547* |
| Hypertension (BP >130/80) | Present | 6 (3.66) | 5 (4.03) | 1 (2.5) | 0.069* |
| | Absent | 158 (96.34) | 119 (95.97) | 39 (97.5) | |
| Insulin resistance (HOMA-IR >2) | Present | 98 (59.76) | 79 (63.71) | 19 (47.5) | 0.069* |
| | Absent | 66 (40.24) | 45 (36.29) | 21 (52.5) | |
| Metabolic syndrome | Present | 40 (24.39) | 36 (29.03) | 4 (10) | 0.015* |
| | Absent | 124 (75.6) | 88 (70.97) | 36 (90) | |
| Endometrial hyperplasia | Present | 13 (7.93) | 11 (8.87) | 2 (5) | 0.342* |
| | Absent | 151 (92.07) | 113 (91.13) | 38 (95) | |
| Outcome | CC-resistant | 88 (53.66) | 73 (58.87) | 15 (37.5) | 0.018* |
| | CC-sensitive | 76 (46.34) | 51 (41.13) | 25 (62.5) | |

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hyperplasia with atypia and 23 times higher risk of endometrial hyperplasia without atypia.\(^{27}\)

The prevalence of endometrial hyperplasia among the PCOS women in this study was 7.93% and it was more in the obese PCOS group. In fact, hyperplasia with atypia was seen exclusively in the obese PCOS group. The risk of endometrial cancer in hyperplasia without atypia is <1% and in those with endometrial hyperplasia with atypia is as high as 33%.\(^{28}\) Thus, managing obesity in PCOS females will help decrease the risk of endometrial hyperplasia and endometrial cancer.

Obesity and high BMI have been associated with the poor fertility outcomes.\(^{29}\) It decreases the number of follicles, decreases fertilization rates, and increases the time of conception. In the present study, CC-resistance was also higher in the obese PCOS group. So, targeting obesity will improve fertility outcome and response to clomiphene.

**Conclusion**

Obese PCOS have a higher risk of adverse outcomes like hypertension, IR, metabolic syndrome, and endometrial hyperplasia. These women should be screened for the same. Targeting obesity in PCOS women will not only help to prevent adverse outcomes but also improve responsiveness to clomiphene citrate.

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**Table 4: Menstrual irregularity, blood sugar abnormalities, and endometrial biopsy distribution among the obese and lean PCOS\(^1\) group**

| Mean distribution (n=164) (mean±SD) (%) | Obese PCOS\(^1\) BMI\(^1\) ≥23 kg/m\(^2\) (n=124) (%) | Lean PCOS\(^1\) BMI\(^1\) <23 kg/m\(^2\) (n=40) (%) |
|---------------------------------------|---------------------------------------------|---------------------------------------------|
| Menstrual cycle distribution (days)   |                                             |                                             |
| 24-38 days                           | 29 (17.68)                                  | 17 (13.71)                                  |
| 38-60 days                           | 31 (18.90)                                  | 23 (18.55)                                  |
| >60 days                             | 104 (63.42)                                 | 84 (67.74)                                  |
| Blood sugar abnormalities            |                                             |                                             |
| Normal                               | 77 (46.95)                                  | 62 (50)                                     |
| Impaired glucose tolerance           | 66 (40.24)                                  | 52 (41.94)                                  |
| Diabetes mellitus                    | 11 (6.71)                                   | 10 (8.06)                                   |
| Endometrial biopsy on Day 1 of cycle |                                             |                                             |
| Secretary                            | 123 (75)                                    | 92 (74.19)                                  |
| Proliferative                        | 28 (17.07)                                  | 21 (16.94)                                  |
| Simple hyperplasia without atypia    | 10 (6.10)                                   | 8 (6.45)                                    |
| Complex hyperplasia without atypia   | 1 (0.61)                                    | 1 (0.8)                                     |
| Simple hyperplasia with atypia       | 1 (0.61)                                    | 1 (0.8)                                     |
| Complex hyperplasia with atypia      | 1 (0.61)                                    | 1 (0.8)                                     |
| Total                                | 164 (100)                                   | 124                                          |

\(^1\)CC: Clomiphene citrate

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**Table 5: BMI\(^1\) categorization in CC\(^{-}\)sensitive and CC\(^{-}\)resistant groups**

| BMI\(^1\) | CC\(^{-}\)resistant (n=88) (%) | CC\(^{-}\)sensitive (n=76) (%) |
|-----------|-------------------------------|------------------------------|
| <18.5     | 1 (1.13)                      | 2 (2.63)                     |
| 18.5-23   | 22 (25)                       | 14 (18.42)                   |
| 23-27.5   | 35 (39.77)                    | 34 (44.74)                   |
| >27.5     | 30 (34.10)                    | 25 (32.89)                   |

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**Conflicts of interest**

There are no conflicts of interest.

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Sachdeva, et al.: Obese and non-obese PCOS comparison

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