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Original Research Article

To Study the Effect of Oral Contraceptives and Metformin on Metabolic and Endocrine Parameters in Individuals with Polycystic Ovarian Syndrome: a Prospective Interventional Study

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Abstract:

Background: Polycystic ovarian syndrome (PCOS) is the predominant endocrine condition among women in the reproductive age range. PCOS is defined by the presence of excessive levels of male hormones, prolonged absence of ovulation, abnormal uterine bleeding, and changes in the structure of the ovaries.

Aim: To study the impact of oral contraceptives and metformin on metabolic and endocrine parameters in individuals with polycystic ovarian syndrome.

Materials and Methods: The patients were categorised into two groups based on the clinician's evaluation of their profile. Group A consisted of 70 patients, whereas Group B also included 70 patients. Group A was given a combination of lifestyle modification and oral metformin. At the beginning of the trial, a 500 mg dose was administered, and, based on the patient's reaction and clinical assessment, the metformin dosage was modified to a maximum of 2000 mg per day for a duration of 6 months. Group B received lifestyle modification and was administered OCP (a fixed dosage combination of ethinyl estradiol 50 micrograms and cyproterone acetate 2 milli grammes per day) for a duration of six months. Every patient included in the trial was monitored for a duration of six months, with regular assessments of all pertinent clinical and laboratory indicators.

Results: The mean HbA1c levels among the study subjects in group A at the end of the study were 7.23 ± 0.28% as compared to 5.66 ± 0.15% among the group B study population. The difference was found to be highly significant (p = 0.01). Among the lipid profiles, the differences in total cholesterol, LDL, and TG were statistically significant. The mean testosterone levels among the study subjects in group A at the end of the study were 2.89± 0.55 mmol/L as compared to 2.95± 0.23 mmol/L among the group B study population. The difference was found to be statistically significant (p-value = 0.02). A total of 27 (38.57%) of the study patients in group A had USG changes suggestive of PCOS before initiation of the treatment, which got reduced to 23 (32.86%) and 25 (35.71%) at the end of the 2nd and 6th months of treatment, respectively. The rate of improvement of the USG changes in PCOS among the study population was found to be not statistically significant (p-value = 0.08). Similarly, 43 (61.43%) of the study population in group B had USG changes suggestive of PCOS before initiation of the treatment, which got reduced to 34 (48.57%) and 26 (37.14%) at the end of the 2nd and 6th months of treatment, respectively. The rate of improvement of the USG changes in PCOS among the study population was found to be highly significant (p-value <0.001).

Conclusion: Both oral metformin and oral contraceptive tablets are effective therapy options for people with PCOS and result in considerable improvement in menstruation symptoms within six months of starting medication. Individuals with worse metabolic parameters have had more benefits from oral metformin treatment, whereas individuals with excellent metabolic parameters and worse endocrinological profiles have shown comparable improvements with oral contraceptive tablets.

Keywords: Oral Contraceptive Pill, Metformin, Polycystic Ovarian Syndrome.

Introduction

Polycystic ovarian syndrome (PCOS) is the predominant endocrine condition among women in the reproductive age range. PCOS is defined by the presence of excessive levels of male hormones, prolonged absence of ovulation, abnormal uterine bleeding, and changes in the structure of the ovaries [1]. Polycystic ovary syndrome (PCOS) is a persistent condition that has lasting effects on both reproductive and metabolic functions. Insulin resistance (IR) is a consistent characteristic of

polycystic ovary syndrome (PCOS), and only a small number of studies have documented the metabolic distinctions between PCOS patients who are fat and those who are lean [2]. The pathophysiology of polycystic ovary syndrome (PCOS) is complex, which makes it difficult to establish definitive recommendations for its care. The treatment strategy differs depending on the age and the specific complaints of the patients [3]. Furthermore, there is a significant divergence in the approach to PCOS among endocrinologists, gynaecologists, and ermatologists. The pharmacological treatments typically prescribed for PCOS include insulin sensitizers, oral contraceptive pills (OCP), and anti-androgens [4].

The need for extended pharmacological treatment places a significant psychological burden on adolescent girls and their parents. An all-encompassing perspective on therapy is necessary, and the patient's participation in choosing the treatment aids in enhancing adherence. Prior publications have shown contradictory findings regarding clinical, hormonal, and reproductive outcomes [5–7]. The researchers were driven to explore other therapy approaches due to the perplexing variability noticed in the outcomes. The treatments being evaluated include the administration of vitamin D, acarbose, berberine, pioglitazone, and other preparations at different stages of assessment [8–10].

Aims and Objectives: To study the impact of oral contraceptives and metformin on metabolic and endocrine parameters in individuals with polycystic ovarian syndrome.

Materials and Methods

The present prospective study was conducted on 140 patients with Polycystic Ovary Syndrome (PCOS) attaining outpatient department (OPD) of the Department of Obstetrics and Gynaecology, Sri Krishna Medical College & Hospital, Muzaffarpur, Bihar, India.

The study duration was from July 2023 to February 2024. The Institutional Ethics Committee gave the study its approval. All enrolled patients provided written informed consent. Data such as name, age, etc. was recorded.

Inclusion Criteria: The study included individuals with Polycystic Ovary Syndrome (PCOS) between the ages of 15 and 35 who were not pregnant at the time of enrollment or at any point throughout the trial. Individuals who were not taking any drugs that may affect glucose or sex hormone levels, such as oral contraceptives or metformin, were also included.

Exclusion Criteria: The research excluded women with pre-existing or co-existing gynaecological disorders, as well as those with pre-existing diabetes, hypertension, dyslipidemia, or any other medical problems.

Sampling Size Determination and Sampling Technique: The PCOS patients were diagnosed using the Rotterdam criteria [11].

The following simple formula would be used for calculating the adequate sample size in a prevalence study:

$N= Z^2 P (1-P)/d^2$

N= sample size, Z= level of confidence, P= prevalence, d= Absolute error or precision

Z = Is standard normal variate (at 5% type 1 error (P< 0.05) it is 1.96 and at 1% type 1 error (P<0.01) it is 2.58). As in majority of studies P values are considered significant below 0.05 hence 1.96 is used in formula. p = Expected proportion in population based on previous studies or pilot studies.

The sample size was calculated using a single population proportion formula by considering a 95% confidence level, a 5% margin of error, and a 9.1% estimated proportion of overall prevalence [12].

Sample size $= 1.96^2 \times 0.091 (1-0.091)/0.05^2$

$=126$

Considering a 10% non-response rate, the total minimum sample size for the study was 138 patients. We included 140 (more than the minimum required number of cases) patients with PCOS in the present study.

Nidhi R et al. [12] observed in 2011 that the prevalence of PCOS in Indian adolescents is 9.13%. This draws attention to the issue of early diagnosis in adolescent girls.

The patients were categorised into two groups based on the clinician's evaluation of their profile. Group A consisted of 70 patients, whereas Group B also included 70 patients. All chosen patients received counselling on adopting a healthy lifestyle and were provided with nutritional suggestions to aid in weight loss. They were offered counselling on maintaining a balanced diet and engaging in sufficient activity. The recommendation is to follow a diet that is low in carbohydrates and rich in fiber. Additionally, it is encouraged to engage in 150 minutes of moderate activity per week, according to the RCOG norm.

Group A was given a combination of lifestyle modification and oral metformin. At the beginning of the trial, a 500 mg dose was administered, and based on the patient's reaction and clinical assessment, the metformin dosage was modified to a maximum of 2000 mg per day for a duration of 6 months.

Group B received lifestyle modification and was administered OCP (a fixed dosage combination of ethinyl estradiol 50 micrograms and cyproterone acetate 2 milligrammes per day) for a duration of six months. Every patient included in the trial was monitored for a period of six months. During the subsequent monitoring period, patients had evaluations at the second and sixth months after the commencement of the targeted therapy. There were no instances of severe adverse reactions among the individuals who received the medicine.

Upon obtaining written informed consent, the following data were gathered from the participants: demographic profile of the patient, weight, hirsutism; comprehensive menstrual history including cycle duration, intermenstrual spotting, dysmenorrhoea; amount of flow determined by number of pads used and presence of clots; symptoms of androgen excess; and drug history. The Body Mass Index (BMI) was determined by dividing the weight in kilogrammes by the square of the height in metres.

An extensive, comprehensive examination was performed to identify acne, hirsutism, and acanthosis nigricans.

Polycystic ovaries on ultrasound sonography (USG) are characterised by the existence of 12 or more follicles in each ovary, with a diameter ranging from 2 to 9 mm and/or an ovarian volume exceeding 10 mL. The criteria for improvement in ultrasonography (USG) were met if the number of follicles fell to fewer than 12 and/or the ovarian volume declined to less than 10 cc during the two planned follow-up visits.

The metabolic parameters observed were fasting blood sugar (FBS), post-prandial blood sugar (PPBS), haemoglobin A1C (HbA1c), and lipid profile (total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides). Testosterone, prolactin, and thyroid stimulating hormone (TSH) levels were evaluated for the endocrine parameters.

Statistical Analysis: The statistical analysis was conducted using the Statistical Package for the Social Sciences software, version. The data were reported as the mean value plus or minus the standard deviation, as well as percentages represented as numbers. The Student's t-test, Chi-square test, and ANOVA test were used to compare the results. A p-value less than 0.05 was deemed to have statistical significance.

Results

The current research recruited a total of 140 patients. The average age in group A was 24.48±1.23 years, whereas in group B it was 23.33±1.42 years. Group A, consisting of 70 patients, got a combination of lifestyle intervention and metformin. Group B, also consisting of 70 patients, received a combination of lifestyle intervention and oral contraceptive pills (OCP). There was no discernible disparity in the socioeconomic position between the two groups. The initial mean weight of group A at the beginning of the therapy was 59.65±1.96 kg. After 6 months, the mean weight decreased to 54.56±1.13 kg (p = 0.001) [Table 1].

Table 1: Clinical parameters in Group A before and after treatment (n=70)

Clinical parameters	Before treatment	At 2nd month	At 6th month	p-value
Weight (kg) (mean±SD)	59.65±1.96	58.25±2.12	54.56±1.13	<0.001
BMI (kg/m2) (mean±SD)	30.12±1.85	29.31±1.74	27.78±1.87	<0.001
Waist/hip ratio	1.11±0.01	1.09±0.02	1.05±0.05	0.02
Acanthosis Nigricans n (%)	23(32.85%)	21(30%)	26 (37.14%)	0.45
Hirsutism	34 (48.57%)	32 (45.71%)	31 (44.28%)	0.10
Acne	42(60%)	40(57.14%)	38 (54.28%)	0.11

Table 2: Clinical parameters in Group B before and after treatment (n=70)

Clinical parameters	Before treatment	At 2nd month	At 6th month	p-value
Weight (kg) (mean±SD)	50.23±1.85	51.12±2.28	52.96±2.06	<0.001
BMI (kg/m2) (mean±SD)	25.32±1.96	26.13±2.51	27.52±2.25	<0.001
Waist/hip (mean±SD)	1.05±0.01	1.21±0.02	1.33±0.06	<0.001
Acanthosis Nigricans	25 (35.71%)	19 (27.14%)	15(21.43%)	0.36
Hirsutism	40(57.14%)	38 (54.29%)	37 (52.87%)	0.37
Acne n (%)	42 (60%)	35 (50%)	32 (45.71%)	<0.001

The initial mean weight of group B at the beginning of the therapy was 50.23±1.85 Kg. This weight climbed to 52.96±2.06 Kg at ix months (p<0.001). This disparity was once again statistically significant. Group B had a higher incidence of hirsutism and acne at the start of the therapy. At the end of the therapy in both groups, there was a decrease in hirsutism and acne. However, the decrease in the occurrence of acne in group B at the conclusion of the therapy was statistically significant [Table 2].

Table 3: Metabolic parameters in Group A before and after treatment (n=70)

Metabolic parameters	Before treatment	At 2nd month	At 6th month	p-value
FBS (mmol/L)	5.86± 0.20	5.22 ±0.55	4.98 ±0.39	0.02
PPBS (mmol/L)	6.02 ±0.32	5.84± 0.18	5.62 ±0.11	0.01
HbA1c (%)	7.85 ±0.74	7.63± 0.32	7.23± 0.28	0.02
Total cholesterol (mmol/L)	5.96± 0.15	5.88 ±0.11	5.70 ±0.19	0.41
HDL (mmol/L)	1.02 ±0.12	0.98± 0.12	1.04 ±0.08	0.32
LDL (mmol/L)	4.85± 0.41	5.13±0.58	4.92± 0.41	0.33
TG (mmol/L)	3.01 ±0.38	2.97 ±0.47	2.93 ±0.21	0.51

BMI: Body mass index, FBS: Fasting blood sugar, PPBS; potprandial blood sugar, HDL: High density lipoprotein, LDL: Low density lipoprotein, TG: Triglycerides; *p value<0.05(Significant)

The mean HbA1c levels of group A before the initiation of the treatment were found to be 7.85 ±0.74%, which were reduced to 7.63 ± 0.32% and 7.23 ± 0.28% at the end of two months and six months, respectively (p-value = 0.02) [Table-3].

Table 4: Endocrine parameters in Group A before and after the treatment (n=70)

Endocrine parameters	Before treatment	At 2nd month	At 6th month	p-value
Testosterone (mmol/L)	3.12± 0.61	3.02 ±0.86	2.89± 0.55	0.09
Prolactin (ng/mL)	20.03± 1.32	19.84± 1.22	19.62 ±1.13	0.07
TSH (IU/L)	4.02 ±0.32	4.21 ±0.21	3.92 ±0.20	0.23

Before the initiation of treatment, the mean TSH level of group A was found to be 4.02 ±0.32 IU/L, which marginally increased to 4.21 ±0.21 IU/L and then reduced to 3.92 ±0.20 IU/L at the end of the 2nd and 6th months, respectively (p-value = 0.23); Table 4.

Table 5: Metabolic parameters in group B before and after treatment

Metabolic parameters	Before treatment	At 2nd month	At 6th month	p-value
FBS (mmol/L)	5.23 ±0.12	5.56 ±0.12	5.56± 0.12	0.61
PPBS (mmol/L)	6.12± 0.19	6.24± 0.15	6.02 ±0.10	0.53
HbA1c (%)	5.85± 0.28	5.90 ±0.21	5.66 ±0.15	0.85
Total cholesterol (mmol/L)	6.09± 0.36	6.02± 0.56	6.13± 0.47	0.30
HDL (mmol/L)	1.84± 0.25	1.78 ±0.19	1.64± 0.13	0.46
LDL (mmol/L)	3.96 ±0.29	4.12 ±0.22	4.45 ±0.35	0.11
TG (mmol/L)	3.02± 0.12	3.21 ±0.39	2.91 ±0.28	0.73

The mean HbA1c levels of group B before the initiation of the treatment were found to be 5.85 ± 0.28 %, which became 5.90 ± 0.21 % and 5.66 ± 0.15 % at the end of 2nd and 6th months, respectively (p-value = 0.85) [Table-5].

Table 6: Endocrine parameters in group B

Endocrine parameters	Before treatment	At 2nd month	At 6th month	p- value
Testosterone (mmol/L)	3.25± 0.39	3.14 ±0.11	2.95± 0.23	0.01
Prolactin (ng/mL)	19.65 ±0.98	19.41 ±1.21	19.26 ±1.22	0.35
TSH (IU/L)	4.39 ±0.21	4.18 ±0.45	4.64± 0.20	0.79

Among the endocrine parameters, only serum testosterone was significantly reduced at the end of the treatment in group B [Table 6].

Table 7: Comparative analysis of metabolic parameters between group A and group B at the end of the study

Metabolic parameters	Group A (n=60)	Group B (n=60)	p-value
FBS (mmol/L)	4.98 ±0.39	5.56± 0.12	0.01
PPBS (mmol/L)	5.62 ±0.11	6.02 ±0.10	0.02
HbA1c (%)	7.23± 0.28	5.66 ±0.15	0.01
Total cholesterol (mmol/L)	5.70 ±0.19	6.13± 0.47	0.02
HDL (mmol/L)	1.04 ±0.08	1.64± 0.13	0.03
LDL (mmol/L)	4.92± 0.41	4.45 ±0.35	0.04
TG (mmol/L)	2.93 ±0.21	2.91 ±0.28	0.01

The mean HbA1c levels among the study subjects in group A at the end of the study were 7.23± 0.28 % as compared to 5.66±0.15 % among the group B study population. The difference was found to be highly significant (p = 0.01). Among the lipid profiles, the differences in total cholesterol, LDL, and TG were statistically significant [Table 7].

Table 8: Comparative analysis of endocrine parameters

Endocrine parameters	Group A	Group B	p-value
Testosterone (mmol/L)	2.89± 0.55	2.95± 0.23	0.02
Prolactin (ng/mL)	19.62 ±1.13	19.26 ±1.22	0.36
TSH (IU/L)	3.92 ±0.20	4.64± 0.20	0.89

The mean testosterone levels among the study subjects in group A at the end of the study were 2.89± 0.55 mmol/L as compared to 2.95± 0.23 mmol/L among the group B study population. The difference was found to be statistically significant (p-value = 0.02) [Table 8].

A total of 27 (38.57%) of the study patients in group A had USG changes suggestive of PCOS before initiation of the treatment, which got reduced to 23 (32.86%) and 25 (35.71%) at the end of the 2nd and 6th months of treatment, respectively. The rate of improvement of the USG changes in PCOS among the study population was found to be not statistically significant (p-value = 0.08). Similarly, 43 (61.43%) of the study population in group B had USG changes suggestive of PCOS before initiation of the treatment, which got reduced to 34 (48.57%) and 26 (37.14%) at the end of the 2nd and 6th months of treatment, respectively. The rate of improvement of the USG changes in PCOS among the study population was found to be highly significant (p-value <0.001).

Discussion

Polycystic ovarian syndrome is a prevalent endocrine disorder that mostly affects women in their reproductive years. Lifestyle modification, which includes dietary and activity changes, is the first treatment approach for all women diagnosed with PCOS [13]. Lifestyle management is especially crucial for patients who have dyslipidemia [14, 15]. A meta-analysis conducted by Sirmans SM et al. revealed that the prevalence of PCOS is subject to variation depending on the diagnostic criteria used but may reach levels as high as 15-20% [16]. The research also emphasised that women with PCOS are more susceptible to metabolic abnormalities and difficulties associated with infertility. In addition, they highlighted that individuals with PCOS are more likely to have elevated coronary artery calcium scores and increased carotid intima-media thickness. The research found that the average metabolic difference in fasting blood sugar (FBS) between the two study groups was 5.86 ± 0.20 mmol/L and 5.23 ± 0.12 mmol/L (p = 0.0001), respectively. Similarly, the average postprandial blood sugar (PPBS) was 6.02 ±0.32 mmol/L and 6.12 ± 0.19 mmol/L (p = 0.0001), respectively, at the start of the study.

Research done by Kocer D et al. in Turkey has shown that metformin reduces oxidative stress and enhances insulin resistance, dyslipidemia, and endothelial dysfunction [17]. The current research has also shown that the combination of lifestyle modification with oral metformin enhances the management of blood sugar levels and abnormal lipid levels in individuals with polycystic ovary syndrome (PCOS).

A study conducted by Aydogmus H et al. found that PCOS patients had significantly higher levels of total testosterone (p-value = 0.01), LH (p-value <0.00), total cholesterol (p-value = 0.02), insulin (p-value <0.00), and triglyceride (p-value <0.00) compared to healthy women with polycystic ovarian morphology and regular menstrual cycles [18].

Tao T. et al. conducted another investigation in an urban area in Northern China, focusing on institutions. This investigation was designed as a randomised, parallel, open-label trial. A total of 63 patients were randomly assigned to three treatment groups. The first group got metformin, the second group received saxagliptin, and the third group received both medicines. In the third group, there was a significant decrease in HbA1c compared to the first and second groups (saxagliptin vs. combination therapy vs. metformin: -1.1 vs. -1.3 vs. -1.1%, p-value = 0.016). However, there was no significant difference in HbA1c reduction between the first and second groups (p-value > 0.05) [19].

All three groups exhibited a substantial decrease in the homeostasis model assessment-insulin resistance index and a significant rise in the deposition index (p-value <0.01 for all). The Homeostasis Model Assessment—Insulin Resistance Index (HOMA-IR) showed no significant change in cell activity across the metformin and combo groups. Furthermore, there was no significant change in the insulinogenic index across the three groups (p-value > 0.05 for all). Nevertheless, the saxagliptin and metformin groups exhibited a substantial reduction in both BMI and high-sensitivity C-reactive protein levels (p-value <0.01 for both) [19].

In the same way, the current research also showed that taking metformin orally had a substantial positive effect on the glycaemic indices (p-value = 0.01). Metformin, however, did not provide substantial improvements in the endocrinological parameters (p-value > 0.05). The duration of the current research's follow-up period was limited to six months, in contrast to the 24-month follow-up period of the study done by Tao et al. [19]. Due to logistical constraints, the current research was unable

to assess HOMA-IR and other advanced indicators of insulin resistance.

Medeiros SF et al. did a meta-analysis in Brazil to investigate the influence of subclinical hypothyroidism on the features of individuals with polycystic ovary syndrome (PCOS) [20]. A total of 1,537 PCOS individuals with normal thyroid function and 301 PCOS patients with subclinical hypothyroidism were chosen from nine studies. Both groups had comparable anthropometric measurements. Patients diagnosed with subclinical hypothyroidism and polycystic ovary syndrome (PCOS) had elevated levels of total cholesterol and triglyceride (p-value = 0.036 and p-value = 0.012, respectively), as well as reduced levels of high-density lipoprotein cholesterol (p-value = 0.018). In those with euthyroid PCOS, the fasting glucose levels were lower (p-value = 0.022). The androgen levels in both groups were comparable, with a p-value greater than 0.05. The current investigation has shown that the average TSH levels did not exhibit any substantial enhancement at the conclusion of the study period while using oral metformin and implementing lifestyle modifications (p-value = 0.23). The research population that got oral contraceptive pills (OCP) together with lifestyle change showed similar results (p-value = 0.79) during a six-month trial period. There was no significant difference in the mean TSH at the conclusion of the study period when comparing the two groups (p-value = 0.89). These data indicate that the commonly used treatments, metformin and OCP, do not have a substantial impact on the thyroid profile of individuals with PCOS.

The metabolic and endocrine sequelae of PCOS, as explained, are morbid and incur high mortality rates. Diabetes affects macro- and microvasculature, leading to organ damage in the eyes, kidneys, and heart. Dyslipidaemia accounts for premature atherosclerosis and a prothrombotic state, which is life-threatening. Central obesity causes obstructive sleep apnea, which is itself an independent risk factor for cardiac failure, pulmonary arterial hypertension, and arrhythmias that severely impair quality of life. Most women tend to ignore these co-morbidities once menstrual irregularities are relieved with OCPs or fertility is achieved with ovulation induction drugs like metformin and clomiphene [21–24]. It is important to highlight that the care of PCOS should also aim to rectify or avoid these clinical implications by timely screening of patients at high risk. A little decrease in weight (2–5%) might lead to substantial enhancement in metabolic and endocrine factors, hence mitigating the advancement of diseases. Engaging in regular, moderate exercise and following a low-calorie diet may significantly decrease the likelihood of acquiring diabetes and cardiovascular illnesses [25]. Nevertheless, the therapy options now accessible, such as oral contraceptive pills (OCP) and metformin, may provide clear advantages in addressing monthly irregularities and infertility in individuals with polycystic ovary syndrome (PCOS). However, these treatment methods are often ineffective in managing these health concerns after they have already arisen, as seen by the findings of this research.

Limitations of the Study: Selection bias may have resulted from the lack of randomization throughout the subject recruiting process. The short follow-up period and logistical constraints of the present centre may have been limitations of the present study.

Conclusion

Both oral metformin and oral contraceptive tablets are effective therapy options for people with PCOS and result in considerable improvement in menstruation symptoms within six months of starting medication. Individuals with worse metabolic parameters have had more benefits from oral metformin treatment, whereas individuals with excellent metabolic parameters and worse endocrinological profiles have shown comparable improvements with oral contraceptive tablets. Additional treatment options may include a combined medication of oral contraceptive pills (OCP) and metformin, or the inclusion of statins along with lifestyle change.

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