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Assessing the Physiological Impacts of Commonly Prescribed Medications for Polycystic Ovary Syndrome (PCOS): A Comprehensive Review

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Abstract: Polycystic ovary syndrome (PCOS) is a multifaceted endocrine and metabolic disorder that predominantly impacts women of reproductive age. The systematic review and meta-analysis focused on the treatments prescribed for PCOS, examining the prescribing patterns, side effects, and physiological impacts. The study analyzed medication choices, classifications, the type of therapy, its physiological impacts on patients, and the effect of these medications with the different parameters, such as testosterone, sex hormone-binding globule, dehydroepiandrosterone sulfate, and fasting glucose in patients. The research targets women diagnosed with PCOS, focusing on interventions like metformin and oral contraceptives, with outcomes related to hormonal, anthropometric, and metabolic parameters. The study also employed the PEDro scale to assess the quality and validity of the selected studies, and PRISMA guidelines ensured a thorough evaluation of the methodological rigor and reliability of the research findings. The search results identified various medications and interventions used for PCOS treatment, including metformin, oral contraceptives, spironolactone, myo-inositol, and selective estrogen receptor modulators (SERMs). Metformin and oral contraceptives had mixed effects on hormonal profiles, metabolic markers, and reproductive outcomes. Furthermore, metformin had a nonsignificant impact on HDL cholesterol levels compared to oral contraceptives alone, while triglyceride levels were not significantly different between the two groups. The systematic review and meta-analysis provided valuable insights into the treatments prescribed for PCOS, highlighting the importance of monitoring side effects and long-term impacts. The study underscores the need for a comprehensive approach to PCOS management, incorporating medication choices, lifestyle changes, and ongoing monitoring to ensure optimal patient outcomes.

Key Words: PCOS; medications; reproductive outcomes; physiological impacts; prescription practices

1. INTRODUCTION

According to Gu et al. (2022), a multifaceted disease that predominantly impacts women at different ages, especially childbearing and conceptional ages is commonly known as polycystic ovary syndrome (PCOS). This disorder is classified as a metabolic and endocrine disease. The pathophysiology is influenced by the mutual aggravation of hyperandrogenism and insulin resistance throughout PCOS development while also being impacted by malfunctioning the hypothalamus-pituitary-ovarian axis. Moreover, PCOS is recognized as a highly heritable condition, with individuals possessing a genetic predisposition susceptible to its manifestation under certain environmental factors (Harada, 2022).

According to Liu et al. (2021), there were 1.55 million incident cases of PCOS among women of reproductive age (15-49) years worldwide. Between 2007 and 2017, there was a considerable growth of 4.47%. In 2017, the global age-standardized incidence rate of PCOS among women of reproductive age was 82.44 per 100,000 population, showing a 1.45% rise from 2007.

The objective of this study is to analyze the prescribing patterns of OB-GYN doctors in terms of the conditions in the management of the symptoms of PCOS through its medications, classifications, and monotherapy or combination. It also aims to determine the physiological impacts of medications used in PCOS management, and how these affect the patients' BMI status, cholesterol and triglyceride levels, insulin levels, and insulin resistance. Moreover, it aspires to examine the effects of PCOS medications on the Sex hormone-binding globule (SHBG), Dehydroepiandrosterone sulfate (DHEAS), and Fasting glucose (FG) parameters in individuals.

The study primarily focused on the physiological parameters of only the commonly prescribed medicines for PCOS and only applicable to patients ranging in age from 12 to 45 years old, independent of marital status or employment, and not address additional issues that are not necessarily related to the physiological effects.

Although the exact cause of PCOS is still not fully understood, it is believed to have origins in epigenetic factors. Currently, there is no medical cure for PCOS; however, it is possible to manage the symptoms associated with the condition (Khadilkar, 2019). According to Glendining et al. (2023), several number of therapies have been showing effectiveness in managing PCOS. These include addressing the patient's hyperandrogenism, central neuroendocrine dysfunction and metabolic pathophysiology. Due to this emerging PCOS medications, these could help improve patient's overall health outcomes.

2. METHODOLOGY

2.1 Research Design

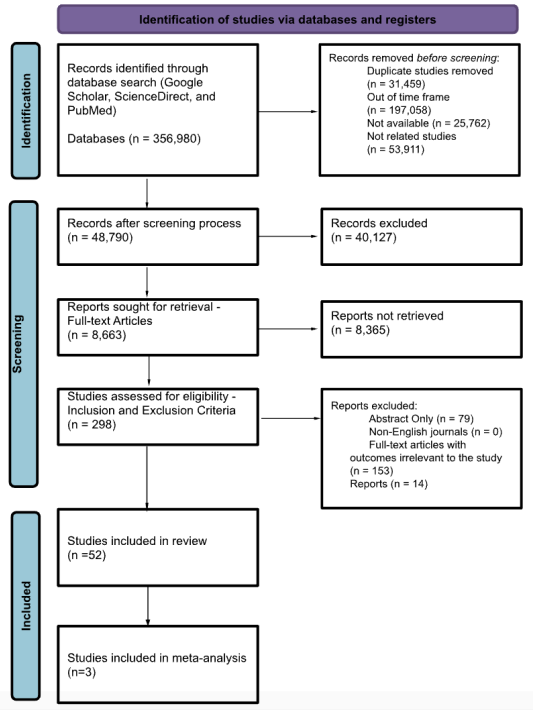

Fig. 1. PRISMA Flow Diagram

The study is a systematic review and meta-analysis involving studies on prescription practices, physiological effects, and conditions associated with PCOS. Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021), researchers systematically searched electronic databases, including MEDLINE from PubMed, ScienceDirect, and Google Scholar, to identify relevant journal articles and research studies spanning the period from 2014 to 2023.

2.1 Data Gathering Procedures

Boolean operators were strategically employed to create focused and productive search strategies. Subsequently, the inclusion criteria were: (a) observational (retrospective and prospective) and randomized controlled trials (RCTs) involving humans as the clinical subjects, (b) included women diagnosed with PCOS, (c) assessed the effect metformin or OCP/COCP alone or combined with other intervention, (d) were originally published in English language between 2014 and 2023, and (e) assessed outcomes on hormonal, anthropometric, and metabolic parameters. In addition to a full-text screening procedure, the Physiotherapy Evidence Database (PEDro) Scale Criteria was utilized to ensure the overall quality of the selected studies. Furthermore, the Cochrane Collaboration Risk of Bias (RoB v2) tool was used for quality of randomized controlled trials (RCTs) in terms of the following domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other bias.

2.2 Statistical Treatment

Meta-analyses were performed using Rev-Man version 5.4. Heterogeneity (I^2) among the trials were examined wherein if there was substantial heterogeneity (I^2>50%) (Higgins and Green, 2011) among the studies, a random-effect model was applied. Otherwise, a fixed-effects model was used. Cochrane Q test and the I^2 statistics were generated to assess heterogeneity among studies, and $p < 0.1$ or $I^2 > 50\%$ was considered as statistically significant heterogeneity. Forest plots were generated and standardized mean difference (SMD) were reported for pooled analysis using the Mantel–Haenszel method for all outcome measures. Publication bias was evaluated qualitatively using funnel plots for assessment of asymmetry and quantitatively using the Eggers' test in Stata 17.0 if there were at least ten studies included. Accordingly, $p < 0.1$ was considered as significant publication bias.

2.3 Publication Bias

Due to study paucity ($k < 10$), publication bias assessment either qualitatively using the funnel plot or quantitatively using Egger's linear regression nor Begg's rank tests was not conducted. As a rule of thumb, the Cochrane Handbook for Systematic Reviews of Interventions, Higgins and Green (2011) suggests that tests for funnel plot asymmetry should be used only when there are at least ten (10) studies included in the meta-analysis. Accordingly, when there are fewer studies, the power of the tests is too low to distinguish chance from real asymmetry .

3. RESULTS AND DISCUSSION

3.1 Results

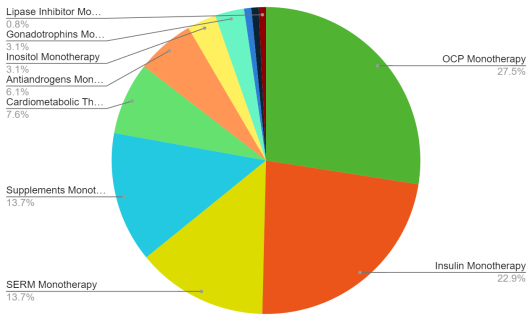

Fig. 2. Commonly Prescribed PCOS Medications

Among the different drug classifications used for the management of PCOS, as seen in Figure 2, insulin is the primary regimen used worldwide. It can be used as a monotherapy to address a variety of medical diseases, and it can also be combined with other medications from different classifications since the majority of the studies emphasized its significance as a sensitizing agent when used in combination. Some studies stated that combining it with OCPs can decrease the patient's BMI. Furthermore, unlike other classifications, it only possesses minimal side effects, specifically metformin, which is predominantly used due to its favorable safety profile and only produces sleepiness and tiredness as its side effects; however, it has a consistent side effect on the gastrointestinal tract (GIT). Aside from insulin, OCPs such as progestin and estrogen are frequently utilized as they play a major role in fertility programs. It is used mainly in combination with other classifications, such as with insulin, antiandrogens, and SERMs to increase its effectiveness. The monotherapy of OCP had a particularly significant impact on reducing free testosterone. However, when compared to insulin, OCPs possess undesired side effects and severe reactions such as ectopic pregnancy.

In addition, SERMs like Clomid are also used in fertility programs as they induce ovulation which leads to higher conception rates. To provide additional benefits, it is usually combined with insulin and gonadotropins. Only some patients will experience flushing and GIT discomfort while using this medication. Moreover, to manage the symptoms associated with hyperandrogenism, antiandrogens such as spironolactone, cyproterone, and finasteride are used. Inositol, supplements, and gonadotrophins are also used as monotherapy or part of a combination as they trigger the effectiveness of other medications, and they also help in the management of the symptoms of PCOS.

PCOS also exists in women with existing comorbidities, specifically CVD, dyslipidemia, hypertension, and type 2 DM. The association between these diseases and having PCOS was not yet established, but Glintborg (2015) stated that metabolic risk may further increase due to hyperandrogenism and hyperandrogenemia in PCOS. Therefore, other medications such as steroids, lipase inhibitors, and dopamine receptor antagonists are used to treat these diseases alongside with regulation and management of symptoms caused by PCOS.

In conducting meta-analysis, homogeneity is crucial to assess if the outcomes of many trials are comparable enough to one another to justify their combination into the overall result (Sedgwick, 2015). RCTs are carefully structured to minimize the risk of bias. Only three studies were eligible for inclusion in the meta-analysis because the other studies demonstrated heterogeneity with other datasets or studies, possessed a high risk of bias, studies conducted on different population groups, lacked data at specific follow-up time points, and cases where no further data extraction was possible.

BMI Status

Metformin vs. OCP

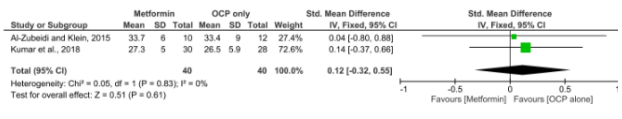

Fig. 3. Forest plots comparing the Body Mass Index (BMI) in women with PCOS receiving Metformin and OCP alone. The pooled SMD are derived from the fixed-effects model. CI, confidence interval; SMD, standardized mean difference.

Three randomized clinical trial studies (Al-Zubeidi and Klein, 2015; Dursun et al., 2016; Kumar et al., 2018) recorded the mean (SD) for BMI status at baseline and follow-up after treatment initiation at the sixth month of therapy. However, only the study of Al-Zubeidi and Klein (2015) noted the mean (SD) weight loss between baseline and follow-up time. In Figure 3, the results of the two studies were combined and it shows that metformin-treated women had a non-significant higher BMI score than women treated with OCP only (SMD = 0.12; 95% CI: -0.32, 0.55; p = 0.61) at 6 months follow up. In addition, no heterogeneity was observed in both studies (X^2=0.05; p = 0.83; I^2 = 0%); with this, a fixed effects model was used.

Combination of OCP and Metformin vs. OCP alone

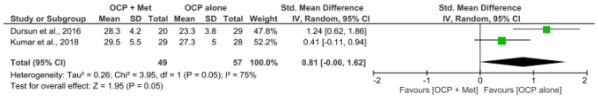

Fig. 4. Forest plots comparing the BMI in women patients receiving metformin + OCP and OCP alone. The pooled SMD are derived from the random-effects model. CI, confidence interval; SMD, standardized mean difference.

On the other hand, a combination therapy of OCP and metformin was compared to the therapy of OCP alone were the interventions in the studies of Dursun et al. (2016) and Kumar et al. (2018). The review of the two therapies showed a non-significantly higher BMI score among women treated with OCP and metformin when compared to women treated with OCP alone (SMD = 0.81; 95% CI: 0.00, 1.62; p = 0.05). However, substantial heterogeneity was observed between the two studies as shown in Figure 4 (Tau^2= 0.26; X^2=3.95; p = 0.05; I^2 = 75%); hence, a random-effects model was adopted.

Insulin Level

Metformin vs. OCP

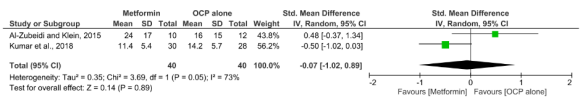

Fig. 5. Forest plots comparing the insulin level (uIU/mL) in women patients receiving Metformin and OCP alone. The pooled SMD are derived from the random-effects model. CI, confidence interval; SMD, standardized mean difference.

In the analysis of insulin levels (uIU/mL) two studies (Al-Zubeidi and Klein, 2015; Dursun et al., 2016) recorded women patients treated with metformin have a nonsignificant combined effect of lower insulin levels when compared to women treated with OCP only (SMD = -0.07; 95% CI: -1.02, 0.89; p = 0.89) at 6 months follow up. Moreover, substantial heterogeneity was observed between the two studies (Tau^2=0.35; X^2=3.69; p = 0.05; I^2 = 73%); hence, a random effects model was used.

Combination of OCP and Metformin vs. OCP alone

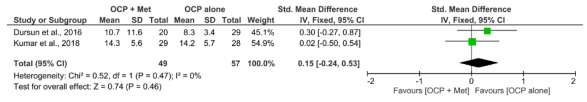

Fig. 6. Forest plots comparing the insulin level (uIU/mL) in women patients receiving combined OCP + Metformin and OCP alone. The pooled SMD are derived from the fixed-effects model. CI, confidence interval; SMD, standardized mean difference.

On the other hand, the combined results of the two studies (Dursun et al., 2016; Kumar et al., 2018) recorded that patients treated with combined OCP and metformin had higher insulin levels as compared to patients treated with OCP alone (SMD = 0.15; 95% CI: -0.24, 0.53; p = 0.46). This, however, was not significant. A fixed effects model was used in the analysis as no heterogeneity was observed in both studies (X^2=0.52; p = 0.47; I^2 = 0%).

Insulin Resistance

Metformin vs. OCP

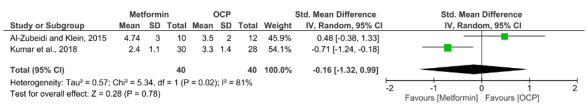

Fig. 7. Forest plots comparing the HOMA score in women patients receiving metformin and OCP. The pooled SMD are derived from the random-effects model. CI, confidence interval; SMD, standardized mean difference.

HOMA-IR score, also known as the Homeostatic Model Assessment for Insulin Resistance, was utilized to assess insulin resistance in the study. The comparison of OCP alone and combined OCP with metformin from the two studies showed that two patients treated with metformin had non-significant lower HOMA-IR scores as compared to patients treated with OCP (SMD = -0.16; 95% CI: -1.32, 0.99; p = 0.78). A substantial heterogeneity was observed between the studies (Tau^2=0.57; X^2=5.37; p = 0.02; I^2 = 81%); hence, a random-effects model was used.

Cholesterol and Triglyceride Levels

Metformin vs. OCP

a. High density lipoprotein (HDL)

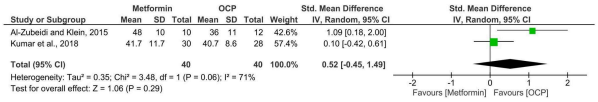

Fig. 8a. High-density lipoprotein (HDL) x OCP and Metformin vs OCP only. Forest plots comparing the High-density lipoprotein (HDL) levels in patients receiving Metformin-OCP and OCP alone. The pooled SMD are from the random-effects model. CI, confidence interval; SMD, standardize mean difference.

In the examination of HDL levels (mg/dL), two studies (Al-Zubeidi and Klein, 2015; Kumar et al., 2016) documented that women diagnosed with polycystic ovary syndrome (PCOS) who received MET-OCP treatment exhibited a statistically insignificant combined effect of elevated HDL levels in comparison to women who received OCP alone (SMD = 0.52; 95% CI: -0.45, 1.49; p = 0.29) at the 6-month follow-up period. Furthermore, there was significant variation across the two investigations (Tau^2 = 0.42; Chi^2 = 4.10; p = 0.06; I^2 = 71%). Therefore, a random effects model was employed.

b. Trigylceride (TG)

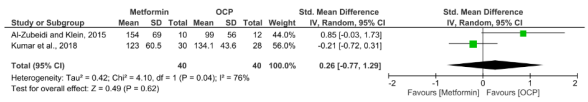

Fig. 8b. TG x Met vs OCP only random. Forest plots comparing the Triglycerides (TG) levels (mg/dL) in women patients receiving MET and OCP alone. The pooled SMD are derived from the random-effects model. CI, confidence interval; SMD, standardized mean difference.

In the examination of TG (mg/dL), two studies (Al-Zubeidi and Klein, 2015; Dursun et al., 2016) documented that female patients who received metformin treatment exhibited a statistically insignificant impact of reduced TG levels in comparison to women who received only oral contraceptive pills (OCP) (standard mean difference = 0.26; 95% confidence interval: -0.77, 1.29; p = 0.62) during the 6-month follow-up period. Furthermore, there was significant heterogeneity across the two investigations (Tau^2 = 0.42; Chi^2 = 4.10; p = 0.04; I^2 = 76%). Therefore, a random effects model was employed.

Sex Hormone-Binding Globulin (SHBG)

OCP vs. combination of OCP + metformin or metformin alone

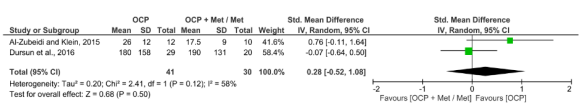

Fig. 9. SHBG x OCP and Metformin vs. OCP only Random. Forest plots comparing the Sex Hormone-Binding Globulin (SHBG) levels in patients receiving MET-OCP and OCP alone. The pooled SMD are from the random-effects model. CI, confidence interval; SMD, standardized mean difference.

In the analysis of SHBG levels (nmol/L), two studies (Al-Zubeidi and Klein, 2015; Dursun et al., 2016) documented that women who received MET-OCP treatment showed a statistically insignificant combination effect of reduced SHBG in comparison to women who received OCP only (SMD = 0.28; 95% CI: -0.52, 1.08; p = 0.50). A substantial heterogeneity was observed between the studies (Tau^2 = 0.20; Chi^2 = 2.41; p = 0.12; I^2 = 58%). Therefore, a random effects model was employed.

Dehydroepiandrosterone sulfate (DHEAS)

OCP vs. OCP + Metformin

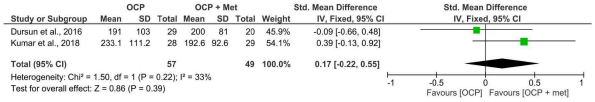

Fig. 10. Forest plots comparing the DHEAS levels in women patients receiving OCP alone and women receiving combined OCP + metformin. The pooled SMD are derived from the fixed-effects model. CI, confidence interval; SMD, standardized mean difference.

Based on the combined effects of the studies of Dursun et al. (2016) and Kumar et al. (2018), it shows that the women patients under the monotherapy of OCP had nonsignificant higher DHEAS levels compared to the group of women patients under the combined therapy of OCP + metformin (SMD = 0.17; 95% CI: -0.22, 0.55; p = 0.39). Additionally, heterogeneity was not observed in both studies (X^2=1.50; p = 0.22; I^2 = 33%); hence, a fixed effects model was used.

Fasting Glucose

OCP vs. OCP + Metformin

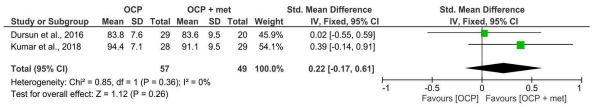

Fig. 11. Forest plots comparing the FG levels in women patients receiving OCP alone and women receiving combined OCP + metformin. The pooled SMD are derived from the fixed-effects model. CI, confidence interval; SMD, standardized mean difference.

At six months follow-up, Dursun et al. (2016) and Kumar et al. (2018) both measured the FG levels (mg/dL). With their combined results, Figure 11 showed that women patients under monotherapy of OCP had nonsignificant higher FG levels compared to the group of women patients under combined OCP + metformin (SMD = 0.22; 95% CI: -0.17, 0.61; p = 0.26). Furthermore, no heterogeneity was observed between the two studies

(X^2 = 0.85; p = 0.36; I^2 = 0%); hence, a fixed-effects model was used.

3.2 Discussion

After conducting a meta-analysis, it was found that metformin-treated women and women treated with combination therapy (Metformin + OCP) have a slightly higher BMI after six months compared to OCP-treated women, although it is not statistically significant. Clearly, women using monotherapy of metformin or combined therapy with metformin tend to have higher BMI scores. This may be due to several factors such as diet and lifestyle, which might not been controlled while conducting the studies, genetic factors since it can influence the response of the patient to the treatment, and patients may have pre-existing conditions that can predispose them to much higher BMI. Change in BMI would have been used to assess the effectiveness of a drug in terms of weight loss however only one study (Al-Zubeidi and Klein, 2015) reported a mean (SD) for weight loss between baseline and follow-up time after treatment.

On the other hand, both low insulin levels and insulin resistance were seen in women treated with metformin than those treated with OCP alone after six months; however, it was insignificant. Metformin-treated women have lower HOMA scores than the OCP-treated group, indicating low insulin resistance. Substantial heterogeneity was observed between the studies therefore, there might be variability in the effects of the two treatments. Furthermore, the combined therapy of metformin and OCP shows slightly higher insulin levels, though insignificant, compared to the monotherapy of OCP. Unlike the aforementioned results, no heterogeneity was observed.

Cholesterol and triglyceride levels are also measured to see the effectiveness of the medications used for PCOS. Although there was no significant difference, women treated with metformin tended to have lower levels of HDL than those with OCP monotherapy. Likewise, no significant difference was observed in the TG levels of women treated with monotherapy of metformin and OCP. Substantial heterogeneity was observed between the comparison of studies.

Monotherapy of OCP and metformin and a combination of both medications were compared for various parameters such as SHBG levels, DHEAS levels, and FG levels. Women treated with monotherapy of OCP exhibited nonsignificantly higher SHBG levels. Similarly, OCP-treated patients displayed elevated DHEAS levels without significant heterogeneity across the studies. Additionally, it shows nonsignificant differences in the FG levels as compared to groups with combined treatment, with also no observed heterogeneity.

4. CONCLUSIONS

There are variety of medications used to manage the symptoms of polycystic ovary syndrome (PCOS). Among these classifications, the most commonly prescribed medication by physicians is Metformin, which is an insulin-sensitizing agents. Oral contraceptives (OCPs) such as Estrogen/Progestin and SERMs, specifically Clomiphene Citrate are also prescribed along with Metformin and sometimes as combination to manage different symptoms while inducing fertility and such. Among these medications, Metformin increases the patient's BMI, while lowering the insulin levels, insulin resistance, and cholesterol, mainly high-density lipoprotein (HDL). Moreover, OCPs aids in increasing the sex hormone-binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEAS), and fasting glucose (FG). By this, combination therapy of Metformin and OCPs can be more effective among the adolescents and women suffering from PCOS.

More research on PCOS is needed globally due to its rising prevalence. Researchers should focus on understanding OB-GYN prescribing practices and the effects of PCOS medications. Consistent data sets and standardized measurement procedures are essential for future studies to ensure uniform and comparable results.

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