

Combined Oral Contraceptives (COCs) Management on symptoms of Polycystic Ovary Syndrome: A Systematic Review

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Abstract. Polycystic Ovary Syndrome (PCOS) has been proved could affect the health of reproductive-aged patients from the physically and emotionally, becoming a major concern of international public health. Meanwhile, PCOS is considered as associated with various severe symptoms, among which infertility is the most of those. The literature argues combined oral contraceptives (COCs) are the first-line treatment modality for PCOS. However, the link between COCs and the symptoms management of PCOS should be bridged. **Purpose:** This study aims to conduct a systematic review to evaluate the impact of intaking COCs on the management of all relevant symptoms. **Method:** This review will adhere to the JBI SUMARI guidelines for systematic reviews, and the search method is built to give access to both published and unpublished research. For searching recently released publications, databases like CINAHL plus (EBSCOhost), PubMed, Ovid Emcare, Ovid MEDLINE, and Scopus (Elsevier) are available. Quantitative studies published in English within the last 10 years are intended to be included in the system review. **Outcomes:** The outcome will present a clear proof between COCs treatment and PCOS symptoms management, including hirsutism, acne, menstrual irregularity and infertility. It could be as the evidence for surgical nurse provide further interventions, which are more tailored and effective, for specific PCOS patients.

Keywords: PCOS; COCs; relevant symptoms management, acne.

1. Introduction

1.1. Background

Polycystic ovary syndrome (PCOS) is considered as the most common endocrine disorder for those reproductive-aged female patients, which is the reason of developing menstrual irregularity and ovarian dysfunction, with 8%-13% prevalence, globally [1]. According to the research, the clinical diagnosis requires it come with more than two out of three all the symptoms, including clinical and or biochemical hyperandrogenism, oligo/anovulation with irregular menstrual cycles and polycystic ovarian morphology (PCOM) on ultrasound, in adults [2]. Furthermore, when diagnosing PCOS in adolescent patients, it's essential to identify both hyperandrogenism and ovulatory disruption as criteria, as the presence of polycystic ovarian morphology (PCOM) alone is not a distinctive characteristic in this age group [3]. Meanwhile, due to the existing hormonal imbalances, despite not all patients will experience the same set of symptoms or to the same degree, they are still with series of common performances and features associated. Which with hyperandrogenism characterized by, or even much worse with symptoms on hirsutism or/and acne or/and infertility or/and oligo/anovulation. However, for those PCOS patients, utilizing combined oral contraceptives (COCs) with modifications of health lifestyle are considered as first-line treatment in most female's patients if fertility is undesired, which could improve the clinical signs of hyperandrogenism and regulate the menstrual cycle for the long-period treatment [4]. According to the research, utilizing COCs could come with series of benefits, including restore menstrual cyclicity, improve hyperandrogenism and reduce the risk of endometrial [4].

To provide further detail, it's important to note that COCs consist of a blend of low-dose estrogens and various progestins. These combinations work by releasing the progestin component they contain, which serves to block the release of gonadotropin-releasing hormone (GnRH) and reduce the occurrence of the luteinizing hormone (LH) peak. This, in turn, encourages patients to undergo ovulation [4]. Meanwhile, through hormone replacement therapy, oestrogen/progesterone is down

regulated the hypothalamus–pituitary axis, which thereby enable regulation of menstrual cycles [2]. Which means if the utilization of COCs is ceased (usually monthly discontinuous for 4–7 days) a withdrawal bleed is induced, which is the result of regular bleeding pattern [2].

1.2. Purpose

This review intends to collect and review current exist research and papers, in order to critically explore the evidence to prove the relationship between utilization COCs as medical treatment and all relevant symptoms management for PCOS patients.

The significance of this review is because those PCOS symptoms, including irregular periods, hirsutism, acne and infertility, could significantly impact the quality of life for affected individuals. Therefore, understanding the extent to which COCs alleviate these symptoms is essential for providing effective care and improving patients' well-being. Meanwhile, PCOS is a complex and heterogeneous condition with various symptoms, as discussed earlier. Understanding the effectiveness of COCs in managing these symptoms is essential because they are a common treatment choice. By reviewing the existing literature, healthcare providers and researchers can gain insights into the benefits and limitations of COCs as part of the treatment strategy for PCOS. Moreover, COCs can help regulate hormonal imbalances in PCOS, particularly by reducing androgens (male hormones) and promoting regular menstrual cycles. Investigating how COCs affect hormone levels and their impact on symptom management is crucial for optimizing treatment plans.

The latest similar systematic review was published in March of 2023, aiming at comparing the effects of taking combined oral contraceptive pills (COCP) as medical treatment with controls, including no medical treatment, placebo and/or lifestyle treatment in the PCOS management. This review is not restricted focusing on adult patients, but comprehensively included adolescent patients, and also considered possibly relative effects including hirsutism, irregular cycles, quality of life, body mass index (BMI) and weight, however, those low certainty of evidence makes the results of research with untrustworthiness. Therefore, there's a need for a systematic review that brings together the most recent trials to establish the connection between COCs and all the pertinent symptoms associated with PCOS. This process begins with a comprehensive search for relevant literature across various databases, including but not limited to the Cochrane Database of Systematic Reviews and the JBI EBP Database.

2. Method

2.1. PICO Elements

Using PICO format to construct all previously mentioned review elements, presented in Table 1.

Table 1. PICO elements

Table 1: PICO elements			
P (population)	I (intervention)	C (comparison)	O (outcome)
PCOS patients	COCs	Controls	Relevant symptoms management
		OR	
		Placebo	
		OR	
		Lifestyle treatment	

The utilization of the PICO template enables the creation of a well-structured research question. This is achieved by identifying the specific patient population, investigating the context, making comparisons, and specifying the expected outcomes [6, 7]. According to the research, it could be utilized for constructing further systematic review questions [6, 8].

2.2. Search Strategy

In order to ensure the accuracy of the system review, the search strategy is designed to access current published and unpublished studies [5]. The purpose of the system review is through searching the relevant studies or research to identify the relationship of conducting COCs for PCOS patients and the relevant symptoms, including hirsutism, acne, infertility and oligo/anovulation. In addition, assess the statuses and symptoms after conducting COCs. Therefore, to maximize the search for current published articles, the research team will conduct database searches in CINAHL Plus (EBSCOhost), PubMed, Ovid Emcare, Ovid MEDLINE, and Scopus (Elsevier). Afterward, they will explore specific subcategories related to PCOS in the MeSH (Medical Subject Headings) database. For this purpose, the team has chosen the following keyword combinations:

((Polycystic ovary syndrome or PCOS or polycystic ovarian syndrome or polycystic ovaries).mp. or Polycystic Ovary Syndrome/ or (ovarian syndrome, polycystic or ovary syndrome, polycystic or polycystic ovarian syndrome or polycystic ovary syndrome or polycystic ovary syndrome 1).mp.) AND (Combined oral contraceptive or COCs or (combined oral contraceptive or combined oral contraceptives or contraceptive agents, female, combined or contraceptive, combined oral or contraceptives, combined oral or contraceptives, oral, combined or oral contraceptive, combined or oral contraceptives, combined).mp. or (Contraceptives, Oral, Combined/ or Contraceptives, Oral, Hormonal/ or Contraceptives, Oral, Sequential/ or Contraceptives, Oral, Synthetic/)) AND (Controls or Placebo or Life-style treatment or Health lifestyle modifications or (hrqol or "health related quality of life" or life quality or "quality of life").mp. or Control Groups/ or (control group or control groups or group, control or groups, control).mp. or "Controlled Clinical Trials as Topic"/ or (effect, placebo or placebo effect or placebo response or response, placebo).mp.)

This transparent reporting of the utilized search strategy is designed to provide researchers with access to individually evaluate each key term and ensure the effectiveness of the search terms [9]. Consequently, if any key terms yield are not relevant with results, researchers can reevaluate the search strategy and make necessary modifications. When constructing the search strategy in the CINAHL plus (EBSCOhost) database, which 40 articles are identified for potential inclusion.

Given our inclusion criteria, which encompasses a ten-year timeframe, peer-reviewed status, and publication in English, we applied relevant filters in the database to specify the time period and language restrictions. This process allowed us to filter out results that did not meet these criteria. Additionally, we considered further requirements for both inclusion and exclusion criteria. Subsequently, we manually scrutinized the reference lists of the filtered publications to identify any studies that may have been missed during the initial database search and to include them in this review.

2.3. Eligibility or Inclusion Criteria

Establishing a clear demarcation between what is included and excluded in the criteria for the literature review is essential. This ensures that the review is thorough and unbiased, aligning with the research questions previously outlined [8].

2.3.1 Types of studies

The aim of this review is to explore the correlation between the use of COCs and the alleviation of symptoms associated with PCOS. Therefore, this systematic review will encompass a diverse range of research types, including observational and experimental quantitative studies. These may involve quasi-experimental inquiries, randomized controlled trials, prospective and retrospective cohort investigations, case-control studies, and cross-sectional studies. Considering studies that employ multiple research methods for further examination. However, the primary focus will be on extracting quantitative data. To ensure the inclusion of the latest and most relevant evidence, the selection criteria will prioritize contemporary studies published in English within the past decade, from 2013 to the present.

2.3.2 Participants

All patients who diagnosed as PCOS, with the presence of symptoms being studied (e.g., hirsutism, acne, infertility, oligo/anovulation). Gender eligibility criteria must be limited exclusively to females, and the age range should encompass both adults and adolescents. However, there will be no restrictions imposed on the medical history and family history of the patients.

2.3.3 Intervention

Implement standardized COCs treatment regimens.

2.3.4 Outcome

The primary outcomes that the study aims to assess changes in symptom severity, hormone levels, and menstrual regularity. Which could include changes in hirsutism scores (e.g., using the Ferriman-Gallwey score), acne severity (e.g., using a standardized acne grading system), menstrual regularity (e.g., frequency and regularity of menstrual cycles), and fertility markers (e.g., ovulation rates). Meanwhile, it is essential to consider assess the long-term effects and sustainability of symptom management with COCs. In addition, secondary outcome measures which provide additional insights into the effects of COCs on other aspects of PCOS, such as metabolic markers, hormonal profiles, and quality of life.

2.3.5 Exclusion criteria

Studies will be excluded from the review, if:

- 1) Patients are prepubertal children or postmenopausal women.
- 2) Patients are in the period of being pregnant or lactating.
- 3) Patients with other significant medical conditions which could confound the study results or interact with COCs.
- 4) Patients with contraindication to COC usage.
- 5) Patients are intaking other medications.
- 6) Patients have recently used or are currently using hormonal treatments for PCOS.
- 7) Patients with recent surgical interventions related to PCOS.
- 8) Individuals with severe psychological conditions or mental illness.
- 9) Individuals with severe substance abuse disorders or heavy alcohol consumption.
- 10) Individuals with hyperandrogenism due to conditions other than PCOS.
- 11) Patients with acne or hirsutism unrelated to PCOS.
- 12) Individuals who do not provide informed consent to participate in the study.
- 13) The research papers have not undergone the peer-review process.
- 14) The research papers do not include the necessary data in their reporting.
- 15) The sources are credited to books and book reviews.

2.4. Study Selection

After completing the search strategy, the entire search results will be exported to Endnote to effectively manage the database and eliminate duplicate articles. These exported articles will undergo an initial screening based on the inclusion criteria, which involves evaluating their titles and abstracts. The potentially relevant studies will be segregated into a separate Endnote library. Subsequently, access to the full manuscripts of these potentially relevant articles will be sought, and they will be thoroughly reviewed.

To ensure a systematic and transparent study selection process, it is crucial to employ a standardized selection strategy. Therefore, we will combine the PRISMA 2020 abstract checklist with a flow diagram to guide the study selection process [10]. The PRISMA 2020 statement outlines 27 items that must be addressed for a systematic review of the studies, categorizing them into different aspects, including titles, abstracts, methods, results, discussions, and other relevant information. Furthermore, the utilization of the PRISMA flow diagram will aid researchers in visually representing the intricacies of the search procedure. This diagram will document the precise count of screened

studies, followed by the evaluation of reports, excluded studies, including the rationales for their exclusion, and ultimately, the determination of the studies that were included in the final analysis [11]. The comprehensive disclosure of the screening procedure offers readers the opportunity to evaluate the suitability of the employed methodologies and bolsters the credibility of the results. Moreover, it simplifies the task for healthcare professionals to gauge the relevance of the findings within their particular setting and reinforces the prospects for subsequent replication and the updating of reviews.

2.5. Data Extraction

The data extraction process should encompass specific details for all included studies. This information should encompass the study's design, characteristics, outcomes, data analysis methods, results, and any comments made by the reviewers. The study details should encompass the author's name, publication year, and the journal in which it was published. Study characteristics should encompass the study type, contextual setting, participant demographics, recruitment methods, follow-up duration, and exposure variables. Outcomes should encompass both primary and secondary outcomes, along with the measurement scales or tools used. Data analysis methods should include the statistical techniques employed and any adjustments made. Study results should include effect size measurements (such as risk ratio, relative risk ratio, or odds ratio), p-values, and 95% confidence intervals. The data extraction process will be carried out independently by two reviewers. In case of any discrepancies between the two reviewers, a discussion will be initiated to resolve them. If necessary, a third reviewer may be consulted to help with resolution. Additionally, efforts will be made to contact authors or researchers via email to request missing data or clarification on any ambiguous information.

2.6. Evidence Appraisal

Those studies will categorize eligible studies based on study design. Two separate reviewers will evaluate these studies for their credibility, relevance, and methodological rigor using critical appraisal tools from JBI. In case of any discrepancies between the two reviewers, engaging in discussions or involve another reviewer to reach a consensus. Additionally, contacting the authors via email to clarify any missing data or unclear information. The findings from this assessment will be presented both in a table format and narrative format. This system review process is essential, as the quality of the included studies significantly impacts the reliability and validity of our results.

2.7. Data Analysis

According to the research, meta-analysis is employed to consolidate the quantitative data. This involved combining the data through statistical meta-analysis using JBI SUMARI [12,13]. In case the data represents categorical variables, they will express the effect size as the odds ratio. Conversely, if the data represents continuous variables, the effect size will be conveyed as either the weighted mean difference or standardized mean difference, accompanied by their respective 95% confidence intervals. As a result, they addressed the heterogeneity by subjecting it to statistical evaluation using the Chi-square (χ^2) test and delved into it further by conducting subgroup analyses that took into account the specific attributes of the quantitative studies included in the review [14]. The meta-analysis itself was conducted using Review Manager (RevMan) Version 5, which is a freely available software designed to assist in the creation of protocols and systematic reviews.

2.8. Research Rigour

To enhance the clarity and rigor of the review, a series of actions should be taken. Initially, it is crucial to register this review protocol with reputable review databases such as PROSPERO. This registration serves the purpose of preventing other researchers from conducting a similar review simultaneously. Subsequently, it is advisable to arrange a consultation with an expert librarian and seek their guidance on refining the literature search strategy for the review protocol, ensuring its

accuracy and comprehensiveness. Furthermore, in order to minimize potential biases in the procedures, it is important to subject the processes of literature search, evidence assessment, and study selection to peer review. This step aims to identify and rectify any possible sources of bias. Additionally, it is imperative to choose appropriate, trustworthy, and validated tools to be used in the stages of research evaluation, data extraction, and data analysis. Therefore, in order to ensure the efficient future reference, it is recommended to store the extracted data in an EndNote library, facilitating further examination and utilization.

2.9. Ethical Considerations

While systematic reviews serve as a comprehensive approach to gather and analyze existing data, ethical considerations are of paramount importance to guarantee the precision and credibility of the cumulative evidence [15,16]. Consequently, this systematic review will prioritize recognizing contributors, upholding academic integrity, and incorporating well-vetted studies with ethical approval. This approach aims to safeguard the accuracy of the findings.

3. Result

Although in total 40 papers after conducting searching, there are some searching results are irrelevant.

There are 4 searching results are introducing the definition, diagnosis, management and relevant treatment of PCOS, focusing on the hyperandrogenic adolescents screening and management. One article focuses on how the level of miT-451a is affected by different approaches of PCOS treatments. One is focusing on the usage of GLP-1 receptor agonists in obesity, polycystic ovary syndrome, and infertility. One examines markers of short-term cardiovascular risk in women with PCOS, emphasizing impact of treatment on cardiovascular and metabolic health. One explores whether red blood cell distribution width (RDW) could be used as a screening tool for metabolic abnormalities in women with PCOS. One proves the Metformin directly affects those PCOS patients on the expression of key glycolytic enzyme proteins and mitochondrial function. Two provide insights into assisted reproductive technologies and oocyte development.

One discusses lifestyle, environmental, and nutritional aspects of PCOS in adolescents, providing insights into non-pharmacological aspects of PCOS management.

there are 7 articles focuses on the regulation of menstrual cycles. They all indicate that COCs could regulate the hormonal cycle, including a monthly withdrawal bleed, in order to help regulate periods for PCOS patients. Which can be particularly helpful in reducing irregular and unpredictable menstrual cycles. Moreover, 11 papers are focusing on the management of Hyperandrogenism (Elevated Male Hormones). COCs could be effective in causing a decrease in free androgens, addressing severe situation with excessive androgen levels for adolescents. Meanwhile, for those young infertile women, COCs also reduces testosterone and improves the levels of sex hormone-binding globulin (SHBG), which binds to androgens and reduces their bioavailability. In addition, through decreasing the level of free androgens, which results in decreased new hair development and the growth of terminal hair. Which means lowering androgen levels can lead to a reduction in symptoms like hirsutism and acne. COCs can further be effective in reducing hirsutism by suppressing the production of androgens (male hormones), which are often elevated in individuals with PCOS. The estrogen component of COCs can help counterbalance the effects of excess androgens. Meanwhile, COCs could significantly decrease PCOS-VAS1 (facial-hirsutism) and decline all PCOS-VAS items. However, the extent of hair reduction can vary, and it may take several months of consistent use to notice a significant improvement. COCs can be beneficial in managing acne associated with PCOS. They help by regulating hormone levels, reducing the production of sebum (skin oil), and minimizing the inflammation that contributes to acne. Improvement in acne may take several months, and not all individuals will experience the same degree of improvement.

4. Conclusion

Compared to other chronic disease, most aspects for PCOS are focused on the improvement of Hirsutism, and the IVF outcomes, therefore, lack of adequate data makes the result with less confidence. In addition, because of releasing exogenous estrogen and progestin, COCs provide temporary relief from PCOS symptoms as long as they are being taken. However, once a patient stops taking it, the symptoms may return. COCs can be recommended as a primary treatment option for PCOS patients experiencing symptoms such as irregular menstrual cycles, hirsutism (excess hair growth), and acne. They are effective in regulating menstrual cycles and reducing androgen-related symptoms. Moreover, COCs containing anti-androgenic progestins can be considered for patients with hirsutism and acne. These formulations can help reduce excess hair growth and improve skin conditions. Although life-style modification is associated with HRQoL improvement, the improve of HRQoL is likely to be attributed to weight loss and Ferriman-Gallwey (FG)-score decrease during the period of COCs utilization. Therefore, it should be considered exclude those relatively lean and less hirsute study population on the relationship between COCs treatment and HROoL improvement. Compared to other chronic disease, most aspects for PCOS are focused on the improvement of Hirsutism, and the IVF outcomes. Meanwhile, lack of references focusing on the the effects on fertility after stopping the COCs on the system review, as the impact on acne is more than 6 months. Therefore, the effect of conducting COCs on fertility could be further constructed.

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Appendix 1

# ▲ Searches	Results
1  (Polycystic ovary syndrome or PCOS or polycystic ovarian syndrome or polycystic ovaries).mp. or Polycystic Ovary Syndrome/ or (ovarian syndrome, polycystic or ovary syndrome, polycystic or polycystic ovarian syndrome or polycystic ovary syndrome or polycystic ovary syndrome 1).mp.	79626
2  (Combined oral contraceptive or COCs or (combined oral contraceptive or combined oral contraceptives or contraceptive agents, female, combined or contraceptive, combined oral or contraceptives, combined oral or contraceptives, oral, combined or oral contraceptive, combined or oral contraceptives, combined)).mp. or (Contraceptives, Oral, Combined/ or Contraceptives, Oral, Hormonal/ or Contraceptives, Oral, Sequential/ or Contraceptives, Oral, Synthetic/) [mp=ti, ot, ab, tx, ct, sh, kw, fx, de, md, sd, hw, bt, sw, tn, dm, mf, dv, kf, dq, cw, ac, ip, vo, pg, jn, yr, dp, ey, cd, cl, pb, sa, pu, ib, is, et, ar, bs, cf, ja, pj, pa, dt, rf, so, pi, pl, ry, st, mo, op, os, ta, te, nm, ox, px, rx, an, ui, ds, on, sy, ux, mx, tc, id, tm]	84130
3  (Controls or Placebo or Life-style treatment or Health lifestyle modifications or (hrqol or "health related quality of life" or life quality or "quality of life")).mp. or Control Groups/ or (control group or control groups or group, control or groups, control).mp. or "Controlled Clinical Trials as Topic"/ or (effect, placebo or placebo effect or placebo response or response, placebo).mp. [mp=ti, ot, ab, tx, ct, sh, kw, fx, de, md, sd, hw, bt, sw, tn, dm, mf, dv, kf, dq, cw, ac, ip, vo, pg, jn, yr, dp, ey, cd, cl, pb, sa, pu, ib, is, et, ar, bs, cf, ja, pj, pa, dt, rf, so, pi, pl, ry, st, mo, op, os, ta, te, nm, ox, px, rx, an, ui, ds, on, sy, ux, mx, tc, id, tm]	7745428
4  1 and 2 and 3	590
5  limit 4 to english [Limit not valid in DARE,CLCMR,CLEED,Books@Ovid,JBI EBP Database; records were retained]	575
6  limit 5 to full text [Limit not valid in Your Journals@Ovid,Books@Ovid; records were retained , Limit not valid in DARE,CDSR,ACP Journal Club,CCA,CLCMR,CLHTA,CLEED,APA PsycBooks,Transport Database; records were eliminated]	105
7  limit 6 to peer reviewed journal [Limit not valid in Your Journals@Ovid,DARE,CDSR,ACP Journal Club,CCA,CCTR,CLCMR,CLHTA,CLEED,Books@Ovid,Journals@Ovid,JBI EBP Database,Embase,Ovid Emcare,Global Health,HAPI,ICONDA,Ovid MEDLINE(R),APA PsycBooks,Transport Database; records were retained]	105
8  limit 7 to last 10 years	40