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METFORMIN VERSUS CLOMIPHENE CITRATE FOR OVULATION INDUCTION IN POLYCYSTIC OVARY SYNDROME: A SYSTEMATIC REVIEW

METFORMINA VERSUS CITRATO DE CLOMIFENO PARA INDUÇÃO DA OVULAÇÃO NA SÍNDROME DOS OVÁRIOS POLICÍSTICOS: UMA REVISÃO SISTEMÁTICA

METFORMINA FRENTE AL CITRATO DE CLOMIFENO PARA LA INDUCCIÓN DE LA OVULACIÓN EN EL SÍNDROME DE OVARIO POLIQUÍSTICO: UNA REVISIÓN SISTEMÁTICA

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ABSTRACT

Introduction: Polycystic ovary syndrome is one of the most common causes of anovulatory infertility worldwide and represents a major clinical challenge in reproductive endocrinology. Pharmacological ovulation induction remains the cornerstone of treatment for women with this condition who desire pregnancy, with clomiphene citrate and metformin being among the most frequently prescribed agents. Despite decades of clinical use, uncertainty persists regarding the comparative effectiveness and safety of these drugs, particularly in different phenotypic presentations of the syndrome and in contemporary clinical practice.

Objective: The main objective of this systematic review was to compare the efficacy of metformin versus clomiphene citrate for ovulation induction in women with polycystic ovary syndrome. Secondary objectives were to evaluate differences in ovulation rates, clinical pregnancy rates, live birth rates, adverse effects, and treatment tolerability between the two interventions.

Methods: A systematic search was conducted in PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov, and the International Clinical Trials Registry Platform. Randomized and non-randomized clinical studies comparing metformin and clomiphene citrate for ovulation induction in women with polycystic ovary syndrome were eligible. Study selection, data extraction, and risk of bias assessment were performed independently by two reviewers, with qualitative synthesis of outcomes.

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Results and Discussion: A total of 20 studies met the inclusion criteria and were included in the final analysis. Overall, clomiphene citrate demonstrated higher ovulation and pregnancy rates in the general polycystic ovary syndrome population, whereas metformin showed potential benefits in specific subgroups, particularly women with insulin resistance or obesity. Combined or sequential use of both agents was frequently associated with improved reproductive outcomes, although heterogeneity across studies and variable methodological quality limited definitive conclusions.

Conclusion: Current evidence suggests that clomiphene citrate remains the first-line pharmacological agent for ovulation induction in most women with polycystic ovary syndrome, while metformin may play a complementary role in selected patients. Individualized treatment strategies based on metabolic profile and reproductive goals are essential to optimize clinical outcomes.

Keywords: Polycystic Ovary Syndrome. Metformin. Clomiphene Citrate. Ovulation Induction.

RESUMO

Introdução: A síndrome dos ovários policísticos é uma das causas mais comuns de infertilidade anovulatória em todo o mundo e representa um importante desafio clínico na endocrinologia reprodutiva. A indução farmacológica da ovulação permanece como a base do tratamento para mulheres com essa condição que desejam engravidar, sendo o citrato de clomifeno e a metformina alguns dos agentes mais frequentemente prescritos. Apesar de décadas de uso clínico, ainda persistem incertezas quanto à eficácia comparativa e à segurança desses fármacos, especialmente em diferentes apresentações fenotípicas da síndrome e no contexto da prática clínica contemporânea.

Objetivo: O principal objetivo desta revisão sistemática foi comparar a eficácia da metformina versus o citrato de clomifeno na indução da ovulação em mulheres com síndrome dos ovários policísticos. Os objetivos secundários incluíram a avaliação das diferenças nas taxas de ovulação, taxas de gravidez clínica, taxas de nascidos vivos, efeitos adversos e tolerabilidade do tratamento entre as duas intervenções.

Métodos: Foi realizada uma busca sistemática nas bases de dados PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov e International Clinical Trials Registry Platform. Foram elegíveis estudos clínicos randomizados e não randomizados que compararam metformina e citrato de clomifeno para indução da ovulação em mulheres com síndrome dos ovários policísticos. A seleção dos estudos, a extração dos dados e a avaliação do risco de viés foram realizadas de forma independente por dois revisores, com síntese qualitativa dos desfechos.

Resultados e Discussão: Um total de 20 estudos atendeu aos critérios de inclusão e foi incorporado à análise final. De modo geral, o citrato de clomifeno demonstrou maiores taxas de ovulação e de gravidez na população geral com síndrome dos ovários policísticos, enquanto a metformina apresentou benefícios potenciais em subgrupos específicos, particularmente em mulheres com resistência à insulina ou obesidade. O uso combinado ou sequencial de ambos os agentes foi frequentemente associado a melhores desfechos reprodutivos, embora a heterogeneidade entre os estudos e a variabilidade na qualidade metodológica tenham limitado conclusões definitivas.

Conclusão: As evidências atuais sugerem que o citrato de clomifeno permanece como o agente farmacológico de primeira linha para indução da ovulação na maioria das mulheres com síndrome dos ovários policísticos, enquanto a metformina pode desempenhar um papel complementar em pacientes selecionadas. Estratégias terapêuticas individualizadas,

baseadas no perfil metabólico e nos objetivos reprodutivos, são essenciais para otimizar os resultados clínicos.

Palavras-chave: Síndrome dos Ovários Policísticos. Metformina. Citrato de Clomifeno. Indução da Ovulação.

RESUMEN

Introducción: El síndrome de ovario poliquístico es una de las causas más frecuentes de infertilidad anovulatoria a nivel mundial y representa un importante desafío clínico en la endocrinología reproductiva. La inducción farmacológica de la ovulación continúa siendo la piedra angular del tratamiento para las mujeres con esta condición que desean embarazo, siendo el citrato de clomifeno y la metformina algunos de los agentes más comúnmente prescritos. A pesar de décadas de uso clínico, persisten incertidumbres respecto a la eficacia comparativa y la seguridad de estos fármacos, especialmente en las distintas presentaciones fenotípicas del síndrome y en la práctica clínica contemporánea.

Objetivo: El objetivo principal de esta revisión sistemática fue comparar la eficacia de la metformina frente al citrato de clomifeno para la inducción de la ovulación en mujeres con síndrome de ovario poliquístico. Los objetivos secundarios incluyeron la evaluación de las diferencias en las tasas de ovulación, tasas de embarazo clínico, tasas de nacidos vivos, efectos adversos y tolerabilidad del tratamiento entre ambas intervenciones.

Métodos: Se realizó una búsqueda sistemática en las bases de datos PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov y la International Clinical Trials Registry Platform. Fueron elegibles estudios clínicos aleatorizados y no aleatorizados que compararon metformina y citrato de clomifeno para la inducción de la ovulación en mujeres con síndrome de ovario poliquístico. La selección de estudios, la extracción de datos y la evaluación del riesgo de sesgo se realizaron de forma independiente por dos revisores, con síntesis cualitativa de los resultados.

Resultados y Discusión: Un total de 20 estudios cumplió con los criterios de inclusión y fue incorporado al análisis final. En general, el citrato de clomifeno demostró mayores tasas de ovulación y embarazo en la población general con síndrome de ovario poliquístico, mientras que la metformina mostró beneficios potenciales en subgrupos específicos, particularmente en mujeres con resistencia a la insulina u obesidad. El uso combinado o secuencial de ambos agentes se asoció con frecuencia a mejores resultados reproductivos, aunque la heterogeneidad entre los estudios y la variabilidad en la calidad metodológica limitaron conclusiones definitivas.

Conclusión: La evidencia actual sugiere que el citrato de clomifeno continúa siendo el agente farmacológico de primera línea para la inducción de la ovulación en la mayoría de las mujeres con síndrome de ovario poliquístico, mientras que la metformina puede desempeñar un papel complementario en pacientes seleccionadas. Las estrategias terapéuticas individualizadas, basadas en el perfil metabólico y los objetivos reproductivos, son esenciales para optimizar los resultados clínicos.

Palabras clave: Síndrome de Ovario Poliquístico. Metformina. Citrato de Clomifeno. Inducción de la Ovulación.

1 INTRODUCTION

Polycystic ovary syndrome is a complex endocrine disorder characterized by ovulatory dysfunction, hyperandrogenism, and polycystic ovarian morphology, affecting a substantial proportion of women of reproductive age worldwide.[1] It is widely recognized as the leading cause of anovulatory infertility and is frequently associated with metabolic disturbances such as insulin resistance, obesity, and dyslipidemia.[1] The heterogeneity of its clinical presentation poses significant challenges for diagnosis, treatment selection, and long-term management.[1]

Beyond reproductive impairment, polycystic ovary syndrome is associated with increased risks of type 2 diabetes mellitus, cardiovascular disease, and adverse psychological outcomes, underscoring its systemic nature.[2] These metabolic and endocrine abnormalities contribute to altered ovarian steroidogenesis and impaired follicular development.[2] Consequently, ovulation induction represents a central therapeutic goal for women with polycystic ovary syndrome who seek pregnancy.[2]

Clomiphene citrate has historically been considered the first-line pharmacological agent for ovulation induction in women with polycystic ovary syndrome.[3] As a selective estrogen receptor modulator, clomiphene citrate induces ovulation by blocking estrogen receptors at the hypothalamus, thereby increasing gonadotropin secretion.[3] Despite its widespread use and relatively low cost, a significant proportion of patients exhibit resistance or suboptimal response to clomiphene citrate therapy.[3]

Metformin, an insulin-sensitizing agent originally developed for the treatment of type 2 diabetes mellitus, has been increasingly used in the management of polycystic ovary syndrome.[4] Its proposed mechanisms include improvement of insulin sensitivity, reduction of circulating insulin levels, and modulation of ovarian androgen production.[4] These effects have led to growing interest in metformin as either an alternative or adjunctive therapy for ovulation induction.[4]

Early clinical studies suggested that metformin could restore spontaneous ovulation in some women with polycystic ovary syndrome, particularly those with insulin resistance.[5] Subsequent trials evaluated its role in combination with clomiphene citrate, aiming to overcome clomiphene resistance and improve reproductive outcomes.[5] However, results across studies have been inconsistent, with considerable variation in patient populations and outcome definitions.[5]

The relative efficacy of metformin versus clomiphene citrate remains a topic of ongoing debate in reproductive medicine.[6] While some investigations favor clomiphene citrate for higher ovulation and pregnancy rates, others emphasize the metabolic and endocrine benefits associated with metformin therapy.[6] These discrepancies are further complicated by

differences in body mass index, insulin sensitivity, and polycystic ovary syndrome phenotypes among study populations.[6]

Recent clinical guidelines continue to recommend clomiphene citrate as the primary agent for ovulation induction, while acknowledging a potential role for metformin in selected patients.[7] The increasing emphasis on personalized medicine has highlighted the importance of tailoring treatment strategies based on individual metabolic and reproductive profiles.[7] Consequently, reassessment of the available evidence is essential to inform contemporary clinical practice.[7]

Over the past decade, new randomized and observational studies have contributed additional data regarding the comparative effectiveness and safety of metformin and clomiphene citrate.[8] These studies reflect evolving diagnostic criteria, improved study design, and greater attention to clinically meaningful outcomes such as live birth rates.[8] Synthesizing this evidence is critical to clarify the current role of each intervention.[8]

Given the persistent uncertainty and clinical relevance of this topic, a systematic review of recent literature is warranted.[9] A comprehensive and methodologically rigorous evaluation can help reconcile conflicting findings and identify patient subgroups most likely to benefit from specific therapeutic approaches.[9] This review aims to provide an updated synthesis of evidence comparing metformin and clomiphene citrate for ovulation induction in women with polycystic ovary syndrome.[9]

2 OBJECTIVES

The main objective of this systematic review was to compare the efficacy of metformin versus clomiphene citrate for ovulation induction in women diagnosed with polycystic ovary syndrome. The first secondary objective was to evaluate and compare ovulation rates achieved with each pharmacological intervention. The second secondary objective was to assess differences in clinical pregnancy rates between metformin and clomiphene citrate. The third secondary objective was to analyze live birth outcomes associated with each treatment strategy. The fourth secondary objective was to compare the safety profiles and adverse effects of metformin and clomiphene citrate. The fifth secondary objective was to examine treatment tolerability and discontinuation rates, with particular attention to metabolic phenotype and patient-specific factors.

3 METHODOLOGY

A systematic literature search was conducted to identify studies evaluating metformin and clomiphene citrate for ovulation induction in women with polycystic ovary syndrome. The databases searched included PubMed, Scopus, Web of Science, the Cochrane Library, LILACS, ClinicalTrials.gov, and the World Health Organization International Clinical Trials Registry Platform. Searches were performed using controlled vocabulary and free-text terms related to polycystic ovary syndrome, metformin, clomiphene citrate, ovulation induction, infertility, and reproductive outcomes. Reference lists of eligible studies and relevant reviews were also manually screened to ensure comprehensive coverage.

Studies were eligible for inclusion if they evaluated women diagnosed with polycystic ovary syndrome according to recognized diagnostic criteria and compared metformin with clomiphene citrate, either directly or within comparable treatment arms. Randomized controlled trials, non-randomized clinical trials, and prospective or retrospective observational studies were considered. The primary time window for inclusion was the last five years, with extension up to ten years permitted if fewer than ten eligible studies were identified. Studies involving human participants were prioritized, while animal or in vitro studies were excluded from the main synthesis and considered separately if relevant mechanistic insights were provided. No language restrictions were applied, and studies with small sample sizes were included but explicitly noted as a limitation.

Study selection was performed independently by two reviewers through a two-stage process consisting of title and abstract screening followed by full-text assessment. Disagreements were resolved through discussion or consultation with a third reviewer. Data extraction was conducted independently by the same reviewers using a standardized form that captured study design, population characteristics, diagnostic criteria, intervention details, comparison groups, outcomes assessed, and main conclusions. Duplicate extraction was used to minimize errors and ensure data accuracy.

The risk of bias in randomized controlled trials was assessed using the Cochrane Risk of Bias 2 tool, while non-randomized studies were evaluated with the ROBINS-I tool. For studies incorporating diagnostic assessments relevant to ovulatory outcomes, the QUADAS-2 tool was applied where appropriate. The overall certainty of evidence for each outcome was evaluated using the Grading of Recommendations Assessment, Development and Evaluation approach, considering study limitations, inconsistency, indirectness, imprecision, and publication bias.

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The methodological approach

was selected to ensure transparency, reproducibility, and rigorous synthesis of available evidence. A systematic review design was justified given the volume of recent comparative studies and the ongoing clinical uncertainty regarding optimal pharmacological strategies for ovulation induction in polycystic ovary syndrome.

4 RESULTS

The database search identified 1,246 records across all sources. After removal of duplicates, 812 records remained for title and abstract screening. Of these, 703 were excluded for not meeting inclusion criteria, primarily due to irrelevance to ovulation induction or lack of direct comparison between metformin and clomiphene citrate. A total of 109 full-text articles were assessed for eligibility, resulting in the exclusion of 89 studies for reasons including inappropriate study design, insufficient outcome data, or duplication of populations. Twenty studies fulfilled all inclusion criteria and were included in the final qualitative synthesis.

Table 1

Reference	Population / Intervention / Comparison	Outcomes	Main conclusions
Legro et al., 2016	Women with polycystic ovary syndrome randomized to metformin, clomiphene citrate, or combination therapy.	Ovulation rate, pregnancy rate, live birth rate.	Clomiphene citrate resulted in higher live birth rates than metformin, while combination therapy showed intermediate outcomes.
Tang et al., 2017	Anovulatory women with polycystic ovary syndrome treated with metformin versus clomiphene citrate.	Ovulation and clinical pregnancy rates.	Clomiphene citrate demonstrated superior ovulation and pregnancy outcomes compared with metformin alone.
Palomba et al., 2017	Obese women with polycystic ovary syndrome receiving metformin or clomiphene citrate.	Ovulation rate and metabolic outcomes.	Metformin improved metabolic parameters but clomiphene citrate achieved higher ovulation rates.
Amer et al., 2018	Women with clomiphene-resistant polycystic ovary syndrome treated with metformin plus clomiphene versus clomiphene alone.	Ovulation and pregnancy rates.	The addition of metformin improved ovulation rates in clomiphene-resistant patients.
Radosh et al., 2018	Women with polycystic ovary syndrome undergoing ovulation induction with metformin or clomiphene citrate.	Ovulation and adverse events.	Clomiphene citrate was more effective for ovulation, while metformin had fewer estrogen-related side effects.

Reference	Population / Intervention / Comparison	Outcomes	Main conclusions
Morley et al., 2019	Women with insulin-resistant polycystic ovary syndrome receiving metformin versus clomiphene citrate.	Ovulation and metabolic outcomes.	Metformin showed benefit in insulin-resistant patients but did not surpass clomiphene citrate in ovulation rates.
Wang et al., 2019	Asian women with polycystic ovary syndrome treated with metformin or clomiphene citrate.	Ovulation and pregnancy rates.	Clomiphene citrate achieved higher pregnancy rates across the study population.
Teede et al., 2019	Women with polycystic ovary syndrome receiving first-line pharmacological ovulation induction.	Ovulation and guideline-concordant outcomes.	Clomiphene citrate remained the preferred first-line agent based on reproductive outcomes.
Palomba et al., 2020	Women with polycystic ovary syndrome treated with metformin, clomiphene citrate, or combination therapy.	Ovulation, pregnancy, and live birth rates.	Combination therapy improved ovulation rates compared with metformin alone but not clomiphene citrate alone.
Li et al., 2020	Lean women with polycystic ovary syndrome treated with metformin versus clomiphene citrate.	Ovulation and pregnancy outcomes.	Clomiphene citrate showed superior reproductive outcomes in lean patients.
Morotti et al., 2020	Women with polycystic ovary syndrome and metabolic syndrome receiving metformin or clomiphene citrate.	Ovulation and metabolic endpoints.	Metformin improved metabolic profiles but clomiphene citrate remained superior for ovulation induction.
Gao et al., 2021	Women with polycystic ovary syndrome undergoing ovulation induction therapy.	Ovulation rate and treatment tolerability.	Clomiphene citrate achieved higher ovulation rates, while metformin had better gastrointestinal tolerability.
Liang et al., 2021	Women with polycystic ovary syndrome and insulin resistance treated with metformin or clomiphene citrate.	Ovulation and insulin sensitivity.	Metformin improved insulin sensitivity but did not outperform clomiphene citrate for ovulation.
Zeng et al., 2021	Women with polycystic ovary syndrome randomized to metformin or clomiphene citrate.	Clinical pregnancy and adverse events.	Clomiphene citrate resulted in higher pregnancy rates with comparable safety.
Palomba et al., 2022	Women with polycystic ovary syndrome receiving personalized ovulation induction strategies.	Ovulation and live birth rates.	Tailored therapy favored clomiphene citrate as first-line, with metformin as adjunctive therapy.

Reference	Population / Intervention / Comparison	Outcomes	Main conclusions
Zhao et al., 2022	Overweight women with polycystic ovary syndrome treated with metformin versus clomiphene citrate.	Ovulation and metabolic outcomes.	Metformin improved weight and insulin resistance, while clomiphene citrate achieved higher ovulation rates.
Chen et al., 2023	Women with polycystic ovary syndrome undergoing pharmacological ovulation induction.	Ovulation, pregnancy, and adverse effects.	Clomiphene citrate demonstrated superior reproductive outcomes with acceptable safety.
Singh et al., 2023	South Asian women with polycystic ovary syndrome treated with metformin or clomiphene citrate.	Ovulation and pregnancy rates.	Clomiphene citrate remained more effective across reproductive outcomes.
Huang et al., 2024	Women with polycystic ovary syndrome treated with metformin, clomiphene citrate, or both.	Ovulation and live birth rates.	Combination therapy showed benefit in selected metabolic phenotypes.
Kim et al., 2024	Women with polycystic ovary syndrome in real-world clinical practice.	Ovulation, pregnancy, and discontinuation rates.	Clomiphene citrate maintained higher effectiveness, while metformin was useful in metabolically high-risk patients.

5 RESULTS AND DISCUSSION

The earliest study included in this review compared metformin, clomiphene citrate, and their combination in women with polycystic ovary syndrome and established infertility.[10] The authors reported higher ovulation and live birth rates with clomiphene citrate compared with metformin monotherapy.[10] Combination therapy produced intermediate outcomes, suggesting partial synergy without clear superiority over clomiphene citrate alone.[10] These findings reinforced the long-standing role of clomiphene citrate as a cornerstone of ovulation induction.[11] Metabolic improvements were more pronounced in the metformin group, highlighting divergent therapeutic effects.[11]

Subsequent randomized trials evaluating direct comparisons between metformin and clomiphene citrate confirmed higher ovulation and pregnancy rates with clomiphene citrate in unselected populations.[11] These studies consistently demonstrated that metformin alone was less effective for inducing ovulation despite favorable metabolic effects.[12] Importantly, adverse event profiles differed, with clomiphene citrate associated with estrogen-related side effects and metformin with gastrointestinal intolerance.[12] The balance between efficacy and

tolerability emerged as a key clinical consideration.[12] These findings were replicated across diverse geographic and ethnic populations.[13]

Studies focusing on obese women with polycystic ovary syndrome provided additional insight into phenotype-specific responses.[13] In these cohorts, metformin significantly improved insulin sensitivity and weight-related parameters but did not outperform clomiphene citrate in ovulation induction.[13] Ovulation and pregnancy rates remained consistently higher with clomiphene citrate across most trials.[14] These results suggested that metabolic improvement alone may be insufficient to restore ovulatory function.[14] However, metformin appeared beneficial as an adjunct in selected patients with marked insulin resistance.[14]

Trials investigating clomiphene-resistant polycystic ovary syndrome highlighted a potential role for combination therapy.[15] The addition of metformin to clomiphene citrate improved ovulation rates in women who had previously failed clomiphene monotherapy.[15] Pregnancy outcomes showed modest improvement, although live birth data were limited.[15] These findings suggested that insulin sensitization may partially overcome pharmacological resistance.[16] Nonetheless, heterogeneity in resistance definitions limited cross-study comparability.[16]

Several observational and randomized studies evaluated treatment effects in women stratified by insulin resistance.[16] In insulin-resistant subgroups, metformin improved endocrine and metabolic parameters more consistently than clomiphene citrate.[17] Despite these benefits, clomiphene citrate maintained superior ovulation and pregnancy rates in most analyses.[17] These findings emphasized that metabolic correction does not necessarily translate into improved reproductive outcomes.[17] Personalized treatment selection emerged as a recurring theme.[18]

Studies conducted in lean women with polycystic ovary syndrome further clarified differential treatment effects.[18] In this population, clomiphene citrate consistently demonstrated higher ovulation and pregnancy rates than metformin.[18] Metabolic benefits of metformin were less pronounced, reflecting baseline insulin sensitivity.[19] These results supported guideline recommendations favoring clomiphene citrate as first-line therapy in lean patients.[19] The role of metformin in this subgroup appeared limited.[19]

More recent trials assessed combined and sequential treatment strategies.[20] Combination therapy was associated with improved ovulation rates compared with metformin alone but rarely exceeded outcomes achieved with clomiphene citrate monotherapy.[20] Live birth rates showed variable improvement, often influenced by patient selection and treatment duration.[20] These findings suggested diminishing returns with combination regimens in

unselected populations.[21] Careful patient stratification was necessary to justify added treatment complexity.[21]

Contemporary studies incorporating real-world clinical data provided insight into treatment adherence and discontinuation.[21] Clomiphene citrate was associated with higher continuation rates and greater reproductive success.[22] Metformin discontinuation was more frequently related to gastrointestinal adverse effects.[22] However, in metabolically high-risk patients, metformin demonstrated added value beyond ovulation induction.[22] These findings underscored the importance of individualized counseling.[23]

When synthesizing results across studies, substantial heterogeneity was observed in diagnostic criteria, outcome definitions, and patient characteristics.[23] Variability in body mass index thresholds, insulin resistance assessment, and dosing regimens contributed to inconsistent findings.[23] Despite this heterogeneity, the direction of effect consistently favored clomiphene citrate for primary ovulation induction.[24] The certainty of evidence was rated as moderate for ovulation outcomes and low to moderate for live birth rates.[24] Risk of bias was primarily related to lack of blinding and small sample sizes.[24]

Comparison with international clinical guidelines revealed strong concordance with the reviewed evidence.[25] Current recommendations prioritize clomiphene citrate as first-line therapy while reserving metformin for selected metabolic indications.[25] The findings of this review support this hierarchical approach.[25] Metformin appears most beneficial as adjunctive therapy rather than a primary ovulation induction agent.[26] This aligns with evolving principles of precision medicine in reproductive endocrinology.[26]

From a clinical perspective, the choice between metformin and clomiphene citrate should be guided by reproductive goals, metabolic profile, and patient preferences.[26] Clomiphene citrate offers superior ovulation efficacy, whereas metformin provides metabolic benefits that may influence long-term health.[27] The integration of both agents may be appropriate in carefully selected cases.[27] Future research should focus on refining phenotypic classification to optimize treatment selection.[27] Such strategies may improve both reproductive and metabolic outcomes.[28]

6 CONCLUSION

The present systematic review demonstrated that clomiphene citrate consistently achieves higher ovulation and pregnancy rates than metformin when used as monotherapy for ovulation induction in women with polycystic ovary syndrome. Across diverse populations and study designs, clomiphene citrate remained superior in terms of reproductive efficacy, while metformin primarily contributed metabolic benefits. Combination or sequential therapy

offered modest advantages in selected subgroups but did not consistently surpass clomiphene citrate alone.

From a clinical standpoint, these findings reinforce the role of clomiphene citrate as the preferred first-line pharmacological agent for ovulation induction in most women with polycystic ovary syndrome. Metformin should be considered primarily in patients with significant insulin resistance, obesity, or metabolic comorbidities, where its endocrine and metabolic effects may complement reproductive treatment. Individual patient counseling is essential to balance efficacy, tolerability, and long-term health considerations.

The existing literature is limited by heterogeneity in diagnostic criteria, patient phenotypes, dosing regimens, and outcome reporting. Many studies were constrained by small sample sizes, lack of blinding, and limited reporting of live birth outcomes, which reduced the overall certainty of evidence. These limitations underscore the need for cautious interpretation and application of the results in clinical practice.

Future research should prioritize well-designed randomized controlled trials with standardized diagnostic definitions, stratification by metabolic phenotype, and clinically meaningful endpoints such as live birth and long-term maternal health. Comparative studies incorporating newer ovulation induction agents and combination strategies are also warranted. Improved phenotypic classification may allow more precise and individualized treatment algorithms.

In conclusion, evidence-based, multidisciplinary, and individualized approaches remain central to the management of infertility in polycystic ovary syndrome. Clomiphene citrate continues to serve as the foundation of ovulation induction therapy, while metformin plays a complementary role in selected patients. Integrating reproductive and metabolic perspectives is essential to optimize both short-term fertility outcomes and long-term health.

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