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REVIEW

Cost-Effectiveness of Interventions Related to the Treatment of Women With Polycystic Ovary Syndrome: A Scoping Review

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Context: Polycystic ovary syndrome (PCOS) affects up to one-in-five reproductive-aged women and its global healthcare-related economic burden is substantial. The aim of this review was to summarise evidence of the cost-effectiveness of interventions related to the treatment of women with PCOS.

Evidence Acquisition: Six academic databases were systematically searched for relevant records. Cost data were extracted, and an interpretation statement was provided for each study based upon the cost difference or incremental cost-effectiveness ratio, and its statistical significance.

Evidence Synthesis: The search yielded 10 relevant studies. Only one study was conducted in a low- and middle-income country (LMIC), China. Nine studies focused on infertility treatment, and one study related to pregnancy care. There remains uncertainty regarding cost-effectiveness of the following infertility treatments: In vitro fertilisation (IVF) cycles compared to ovulation induction (OI) cycles in women with clomiphene citrate (CC) resistant PCOS; and urinary follicle stimulating hormone compared to recombinant follicle stimulating hormone for OI. There are likely cost savings associated with laparoscopic ovarian drilling compared to OI with gonadotropins in women with CC-resistant PCOS, as well as with artificial cycle-frozen embryo transfer (AC-FET) without gonadotropin releasing hormone agonist (GnRH-a) pre-treatment compared to AC-FET with GnRH-a pre-treatment in women with PCOS. Treatment with metformin was lower cost and more effective compared to no treatment for achieving normal glucose regulation without developing gestational diabetes mellitus.

Conclusion: The high proportion of fertility-related treatment studies reflects reproductive features often being the best-recognised feature of PCOS. However, limited evidence is available from LMICs. Further economic evidence is needed regarding PCOS treatments, particularly lifestyle interventions treating outcomes other than infertility.

Keywords: cost-effectiveness analysis, health expenditure, polycystic ovary syndrome, infertility, pregnancy

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine abnormality of reproductive-aged women.[1] The global prevalence of PCOS among this cohort is 4–20%.[2] Variability in the global prevalence is largely explained by differences in diagnostic criteria, disparities in access to medical care and education for the condition, and heterogeneity in clinical manifestations of PCOS associated with different ethnicities and socioeconomic levels.[3,4] Recent research has highlighted the disparities in PCOS diagnosis and mental health outcomes among women in low- and middle-income countries (LMICs), such as Bangladesh, where healthcare access and cultural perceptions of reproductive health influence treatment-seeking behaviour.[5] The prevalence of PCOS is also likely underestimated; notably, as much as 75% of women with PCOS remain undiagnosed even after visiting many medical institutions.[6] Notwithstanding, PCOS has become increasingly common—rising in prevalence by 4.47% between 2007 and 2017[7]—and represents a significant public health concern.

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PCOS impacts multiple facets of women's lives, including their reproductive, psychological, and metabolic health. Excess body weight, which is frequently associated with PCOS, can exacerbate the incidence, prevalence, and severity of PCOS[8] and foster other long-term morbidities including metabolic complications such as type 2 diabetes mellitus (T2DM), risks of certain types of cancer, and diminished quality of life, self-esteem, and general psychological wellbeing.[9,10] Thus, PCOS is also a high-cost disease. The total healthcare-related economic burden of PCOS in the United States (US) is estimated to be $8.5 billion annually (2022US Dollars [USD]).[11,12] Of this cost, approximately 46% ($3.9 billion 2022USD) is attributed to the cost of treating reproductive endocrine morbidities—menstrual dysfunction, hirsutism, and infertility care[11]—consistent with the high symptomatology of PCOS during the reproductive years.[2,9,13] Metabolic and vascular morbidities—strokes and T2DM—account for more than 48% ($4.1 billion 2022USD) of the economic burden of PCOS, while pregnancy-related comorbidities—gestational diabetes mellitus (GDM), hypertensive disorders, and preeclampsia—just 5% ($397 million 2022USD). Finally, the cost of the initial diagnostic evaluation of PCOS accounts for <2% ($147 million 2020USD) of the economic burden.

Given the underestimation of the reported prevalence of PCOS and high costs associated with a wide variety of PCOS-related complications and morbidities, the estimated total healthcare-related economic burden is likely a significant underestimate. Further, the global healthcare-related economic burden of PCOS is almost certainly higher, warranting prioritisation of evidence-based treatments for this major public health condition. New and existing healthcare treatments must also demonstrate value for money, or "cost-effectiveness", to ensure maximum health benefits can be achieved at a given level of expenditure, and these analyses are now a formal requirement of many healthcare systems. Yet, the cost-effectiveness of available interventions to treat women with PCOS remains unclear. To this end, the aim of this review was to identify and summarise evidence of cost-effectiveness of any intervention related to the treatment of women with PCOS. Findings from this review will inform the current update of the international guideline on the treatment and management of PCOS.

Materials and Methods

A scoping review methodology was chosen to meet these aims, as scoping reviews are best suited to provide an overview of the evidence rather than a critical appraisal of available literature.[14] The Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA ScR) was used to guide the reporting of this review.[15] The PRISMA ScR checklist is presented in Appendix 1. Since this review was a scoping review rather than a systematic review,[14] it did not fit the current PRISMA criteria to register with PROSPERO.[16]

Search Strategy and Selection Criteria

We searched for peer-reviewed studies from PubMed, National Health Service Economic Evaluation Database, Medline (OVID), Web of Science, Econlit, and the Cost Effectiveness Analysis Registry. No time limit was placed on searches. No restriction on the country where the study was conducted. Searching was conducted in October 2022. We used English search terms (see Appendix 2 for the full search strategy) only but did not limit the search to English articles. The search strategy was based upon the following two components: (1) cost-effectiveness study design; and (2) women with PCOS as the treatment population. Economic evaluations based upon systematic reviews or meta-analyses were included. Studies were excluded if they did not involve an full economic analysis of treatment options (ie, cost of illness studies, describing costs attributable to PCOS without any intervention or treatment strategy comparison, or not measuring costs per outcome of interest), did not include quantification of costs (ie, effectiveness studies only), were not empirical studies (ie, reviews, protocols, or opinion articles), or did not involve women with PCOS as the population of interest.

Data Management and Analysis

Titles and abstracts were imported into the Covidence online review management system, where duplicates were automatically removed. Two independent authors (EC and YH) screened titles and abstracts, then the full text of potentially relevant studies, to assess for eligibility. Data were extracted into a table by one author (EC) and checked by a second reviewer (YH), which included the following items: title, first author, year of publication, country the study was conducted in, treatment population, study design, intervention, comparison, analysis perspective, outcome measure, cost, or incremental cost effectiveness ratio (ICER), currency used, and if the results were based upon statistically

significant differences in costs and outcomes. Because scoping reviews do not aim to produce a critically appraised answer to a particular research question,[14] an assessment of risk of bias of the evidence was not performed.

All costs were converted from the reported currency into USD at time of reporting, and then adjusted for inflation into 2022USD.[17] An interpretation statement was provided for each study based upon the cost difference or ICER, and the statistical significance of the cost and outcome measures utilised in the study.

Results

The search yielded 987 records. The Covidence system automatically removed 513 duplicates. The title and abstract screening process resulted in 419 articles being removed, and a further 45 were excluded at full text review stage (Figure 1). A total of 10 relevant articles were identified.

Overview of Study Characteristics

Half (5/10) of included studies were more than 10 years old, with the average study age being 11 years (from the year 2022). All studies were published in English. Nine studies were conducted in high-income countries (HICs), including seven (of 10) from Europe, and one each from the US and New Zealand. Only one study was conducted in a LMIC–China. Most (7/10) studies were conducted alongside a clinical trial; one was based upon observational clinical data; and two were modelled studies using published sources to populate the model.

The most frequently utilised economic evaluation approach (8/10 studies) was cost-minimisation analysis to show the less expensive option of two treatments with assumed equal clinical efficacy. Two studies used a modelled cost-effectiveness design, where differences in outcomes and differences in costs between treatments were assessed. Supplementary Table 1 presents the basic characteristics of the included studies and their economic outcomes.

Nine of the 10 included studies focused on infertility treatment. Of these nine, five related to women with clomiphene citrate (CC)-resistant PCOS.

In vitro Fertilisation (IVF) Compared to Ovulation Induction (OI)

One 1999 study (n=28 women with CC-resistant PCOS) comparingIVF cycles with OI cycles found that the costs per pregnancy of IVF were lower compared to OI cycles, however, the statistical significance of the cost saving was not reported and there were no significant differences in outcomes between the two treatment groups.[19]

OI Using Gonadotropins Compared to Laparoscopic Ovarian Drilling (LOD)

Three studies compared LOD (using electrocautery or diathermy) with OI using gonadotropins (recombinant follicle stimulating hormone (rFSH), urinary follicle stimulating hormone (uFSH), or human Menopausal Gonadotropin (hMG). All concluded that there was no significant difference in outcomes between treatment groups, and that LOD resulted in cost-savings.[20–22]

uFSH Compared to rFSH

Three studies compared costs of using uFSH and rFSH for OI in women with PCOS undergoing infertility treatment. Two studies reported a non-statistically significant cost saving of rFSH compared to uFSH,[23,24] while a prior study from 2004 (n=170 women with PCOS and at least two years of infertility, either with CC-failure or CC-resistance) identified a statistically significant higher cost for rFSH compared to uFSH.[25]

Six Cycles of CC and a Maximum of Three Cycles of IVF, Compared to Other Treatment Patterns

One study modelled the cost-effectiveness of five different treatment options for women with PCOS and CC-failure (ie, women who ovulate on CC but do not conceive after six cycles of CC treatment), compared to six cycles of CC and a maximum of three cycles of IVF.[26] The comparator was more effective and less costly than the following three treatment scenarios: (1) a maximum of three cycles of IVF only; (2) six cycles of gonadotropins, followed by a maximum of three cycles of IVF; and (3) 12 cycles of gonadotropins, followed by a maximum of three cycles of IVF.

Six cycles of CC, six cycles of gonadotropins, and three cycles of IVF cost an additional $1,335 per additional pregnancy gained compared to six cycles of CC and a maximum of three cycles of IVF. Similarly, six cycles of CC, 12

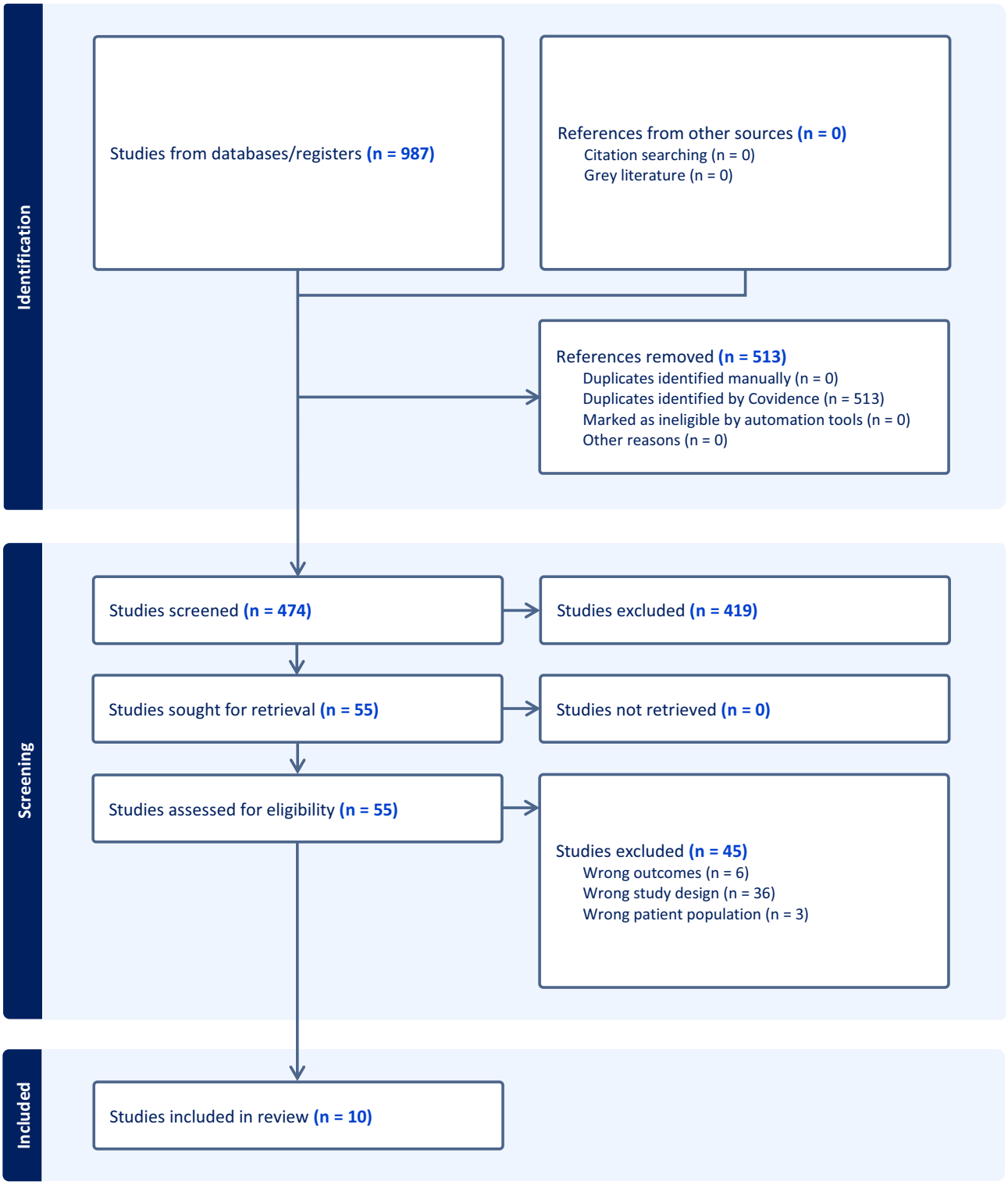

Figure 1 PRISMA 2020 Flow Diagram showing included and excluded studies. PRISMA figure adapted from Page M J, McKenzie J E, Bossuyt P M, Boutron I, Hoffmann T C, Mulrow C D, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021; 372:n71.[18]

cycles of gonadotropins, and three cycles of IVF cost an additional $1,337 per additional pregnancy gained compared to six cycles of CC and a maximum of three cycles of IVF. For these latter two comparisons, there was no significant difference in costs and a significant difference in outcomes, indicating that six cycles of CC, either six or 12 cycles of

gonadotropins, and three cycles of IVF could be dominant (more effective and cost-saving) compared to the same treatment option but without any cycles of gonadotropins.

Gonadotropin Releasing Hormone Agonist (GnRH-a) Pre-Treatment Compared to No GnRH Agonist Pre-Treatment During Artificial Cycle-Prepared Frozen Embryo Transfer (AC-FET)

One study (n=343 women with PCOS and unknown CC-treatment status) compared AC-FET with and without GnRH-a pre-treatment in women with PCOS scheduled for AC-FET and receiving no more than two blastocysts.[27] AC-FET without GnRH-a pre-treatment resulted in cost savings of $1,238 per live birth compared to AC-FET with GnRH-a pre-treatment.

Pregnancy Care

One study modelled the cost-effectiveness of treatment with metformin compared to no treatment for achieving normal glucose regulation amongst pregnant women with PCOS and not previously diagnosed with diabetes.[28] The results indicated that treatment with metformin was dominant, being lower cost and more effective than no treatment, although the statistical significance of the difference between treatment arms was not reported.

Discussion

The scoping review identified 10 studies on the cost-effectiveness of PCOS treatment and revealed several critical limitations in the existing evidence base. First, the majority of studies focused on infertility treatments, with only one study addressing pregnancy care and none evaluating lifestyle modifications. Second, most studies were conducted in HICs, with only one study from a LMIC, limiting the generalisability of findings to resource-constrained settings. Third, many studies are over a decade old, raising concerns about their relevance given recent advancements in PCOS treatment guidelines (eg, the shift from CC to letrozole for OI).

Furthermore, the findings from these 10 studies were inconsistent and provided limited conclusive evidence. For example, there remains uncertainty regarding the cost-effectiveness of IVF cycles compared to OI cycles in women with CC-resistant PCOS, as well as the cost-effectiveness of uFSH and rFSH for OI. While three studies suggested potential cost savings associated with LOD compared to gonadotropins for OI in women with CC-resistant PCOS, only one study suggested potential cost savings associated with AC-FET without GnRH-a pre-treatment compared to AC-FET with GnRH-a pre-treatment in women with PCOS. Additionally, only one study suggested that a combination of CC and IVF might be a cost-effective infertility treatment option for women with PCOS, and only one study found metformin to be a cost-effective treatment for achieving normal glucose regulation among pregnant women with PCOS without pre-gestational diabetes. Overall, the heterogeneity in treatment approaches, outcomes, and methodologies across studies makes it difficult to draw definitive conclusions or provide robust recommendations for clinical practice or policy development.

Management of PCOS requires identification and management of current symptoms, attention to infertility and emotional concerns, as well as preventive activities to minimise the risk of future associated health problems.[13] Various treatments for PCOS and its symptoms have been proposed ranging from lifestyle modifications, administration of pharmaceutical agents, the use of LOD, and the application of assisted reproduction techniques (ART).[2,13,29] While nine studies identified in this review focused on infertility treatments (eg, IVF, OI, LOD, CC, uFSH, rFSH, or AC-FET), only one study was identified in this review that focused on treatment outside of fertility care; specifically, GDM prevention.[28] Although reproductive features are often the best-recognised features in PCOS, fertility is not necessarily impaired in all PCOS cases—some women conceive without medical intervention.[30] Lifestyle change is, therefore, recommended as the first-line therapy for women with PCOS, in order to emphasise healthy lifestyles and the benefits of weight loss on reproductive, metabolic, and psychological features.[30] Then, targeted medical treatment can be given as required. However, we identified no cost-effectiveness evaluations in this area. There is a clear need for future economic evaluations of lifestyle treatments for PCOS and its symptoms.

PCOS is the most common cause of anovulatory infertility,[13] which reflects the high proportion of cost-effectiveness studies related to infertility care identified in this review. If pharmacological infertility treatment is required, the best first-line pharmacological treatment is OI with letrozole.[31] There is currently no economic evidence of the cost-effectiveness

of letrozole for the treatment of infertility in women with PCOS. Regarding other populations with unexplained subfertility undergoing intrauterine insemination, one decision-analytic model found high uncertainty regarding the cost-effectiveness of letrozole when compared to CC and gonadotropins.[32] Cost-effectiveness research for letrozole, therefore, must be prioritised to support its use for women with PCOS as a first-line pharmacological infertility treatment.

Recommended second-line pharmacological intervention is OI using CC or gonadotropins. A 2020 review of clinical trials listed on PubMed compared all the available fertility treatment options for women with PCOS and found that CC remains the lowest cost.[33] Yet, Saad-Naguib and colleagues[33] noted that additional cycles of CC may lead to patient intolerance with continued feelings of anxiety and despair after each failed attempt at conception. If a woman has CC-resistant PCOS or should CC fail to result in pregnancy, it is recommended to treat infertility with either alone, exogenous gonadotropins alone, CC with metformin, or gonadotropin with metformin.[31] This current review identified possible cost savings associated with the use of LOD compared to using OI with gonadotropins in women with CC-resistant PCOS.[20–22] Other pharmacological infertility treatments, such as gonadotropins, CC with metformin, and gonadotropins with metformin, which are less invasive than LOD have not been included in this review. Further economic evidence is needed regarding the cost-effectiveness of these infertility treatments for PCOS women.

If all of the aforementioned treatments are unsuccessful or if there are other factors contributing to infertility such as endometriosis or male factors, IVF with or without intracytoplasmic sperm injection (ICSI) is the last step in treating infertile women with PCOS. One study from 1999 (n= 28 women with CC-resistant PCOS) compared 30 IVF cycles with 41 OI cycles, and found that IVF may be dominant (lower cost and more effective) compared to OI cycles.[19] However, there were no significant differences in costs or outcomes between the two treatment groups. Saad-Naguib and colleagues[33] determined that after unsuccessful attempts at CC with timed intercourse, proceeding directly to IVF/ICSI (instead of exogenous gonadotropins or LOD) will yield a 70% live birth rate in a 5-month period—the shortest amount of time among all the protocols studied. They reported that the most cost-effective method of obtaining pregnancy was three cycles of CC followed by two cycles of IVF/ICSI.[33] This current review identified one study that determined six cycles of CC and a maximum of three cycles of IVF was more effective and cost saving in treating women with PCOS and CC-failure compared to other varying combinations of treatment cycles of CC, gonadotropins, and IVF.[26] Further, six cycles of CC, either six or 12 cycles of gonadotropins, and three cycles of IVF could be more effective and cost-saving compared to the same treatment option but without any cycles of gonadotropins.[26] For women with CC-failure, CC and IVF is cost-effective and a combination of CC, gonadotropins, and IVF may be even more so, but this needs further evidence. Regardless, in the event pharmacological treatment is required, it is recommended that physicians consider the following: the individual's personal characteristics, preferences, and values; the benefits, adverse effects, and contraindications in PCOS and general populations; and education, lifestyle, and other options including counselling alongside pharmacological therapy.[31]

Triggering final oocyte maturation with a GnRH-a pre-treatment and freezing all suitable embryos could be considered in women with PCOS having an IVF/ICSI cycle with a GnRH-a protocol and at an increased risk of developing ovarian hyperstimulation syndrome or where fresh embryo transfer is not planned.[31] However, the significantly higher hyperstimulation rate, the associated risk of multiple pregnancies, and the additional costs of administration, in the absence of substantive benefits, do not currently justify the use of GnRH-a during OI with gonadotropins in women with PCOS.[29] This review found one study reporting AC-FET without GnRH-a pre-treatment as more cost saving compared to AC-FET with GNRH-a pre-treatment.[27] Clinical recommendations also state that uFSH and rFSH can be used in women with PCOS undergoing controlled ovarian hyperstimulation for IVF/ICSI, yet there is insufficient evidence to recommend specific preparations.[31] Due to limited evidence, we could not ascertain the cost-effectiveness of uFSH and rFSH for OI in women with PCOS.

It is essential to capture the full benefits and costs of an intervention to maximise the efficiency and cost-efficacy of treatment options for women with PCOS. The most frequently utilised economic evaluation approach (8/10 studies) identified in this review was cost-minimisation analysis, which considers which intervention is the least-cost option and assumes clinical efficacy. The remaining two studies utilised a cost-effectiveness study design, which compared the differences in costs and outcomes of different intervention options. These studies were able to determine the dominant treatment, or the treatment with the lowest cost and highest efficacy. Cost-effectiveness evidence can be considered by

decision-makers against competing claims for healthcare resources across a multitude of medical conditions,[34] and by physicians to determine the optimal method to meet the needs of women with PCOS. In addition to cost-effectiveness analysis, other economic analyses that incorporate both benefits and costs of an intervention include cost-utility analysis and cost-benefit analysis.[35] It is recommended that future trials incorporate an economic evaluation component to build the evidence base for the cost-efficacy of PCOS treatments, alongside their clinical effectiveness.

Limitations

While this scoping review provides a comprehensive synthesis of cost-effectiveness research on PCOS treatments, limitations should be noted. First, due to the nature of scoping reviews, we did not conduct a formal quality assessment of the included studies, which limits our ability to comment on the robustness of the evidence. Second, due to the limited available evidence and heterogeneity in study outcomes, we were unable to conduct a meta-analysis.

Conclusion

The limited number of studies identified in this review highlights significant gaps in the current evidence base for cost-effectiveness analyses of PCOS interventions. While nine studies focused on infertility treatments, only one study addressed pregnancy care, and none evaluated lifestyle modifications—despite their status as first-line therapy for PCOS. Furthermore, the majority of studies were conducted in HICs, with only one study from a LMIC.

The existing evidence is too limited to draw definitive conclusions or provide robust recommendations for clinical practice or policy development. Until more robust evidence becomes available, healthcare decision-makers should interpret the current findings with caution and prioritise research investments to address these critical gaps.

Abbreviations

PCOS, Polycystic ovary syndrome; T2DM, Type 2 diabetes mellitus; USD, United States Dollars; PRISMA ScR, Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews; ICER, Incremental cost effectiveness ratio; LOD, Laparoscopic ovarian drilling; AC-FET, Artificial cycle-prepared frozen embryo transfer; GnRH-a, Gonadotropin releasing hormone agonist; GDM, Gestational diabetes mellitus; IVF, In vitro fertilisation; rFSH, Recombinant follicle stimulating hormone; uFSH, Urinary follicle stimulating hormone; hMG, Human Menopausal Gonadotropin; ART, Assisted reproductive therapy; HP-uFSH, Highly-purified urinary follicle stimulating hormone; ICSI, Intracytoplasmic sperm injection; OI, Ovulation induction; CC, Clomiphene citrate; NICU, Neonatal intensive care unit.

Data Sharing Statement

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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Disclosure

The authors declare that they have no competing interests.

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