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Demographic Representation in Clinical Trials of Pharmacotherapy Fertility Treatments in Women with Polycystic Ovary Syndrome (PCOS): A Cross-Sectional Analysis

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A Thesis Presented to:
The Faculty of the Yale School of Public Health
Yale University

In partial fulfillment of the requirements for the Master's in Public Health Degree

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Under the supervision of:

Dr. Trace Kershaw (Primary Advisor)
Dr. Melinda Irwin (Secondary Advisor)

ABSTRACT

Background: While Polycystic Ovary Syndrome (PCOS) is a medical condition that impacts women of childbearing age, prior research has shown that women of color are at a disproportionately higher risk. The goal of this meta research project is to closely model a systematic process to assess demographic characteristics of participants recruited and enrolled in clinical trials and RCTs in PCOS-related research studies. **Methods:** An exhaustive electronic database search was performed through *Ovid MEDLINE, PubMed, Scopus, Ovid Embase, and Web of Science* to identify studies that focused on PCOS-related infertility. Out of the 2,883 records identified in the initial search strategy, eight studies met the final search criteria. **Results:** Among the eight studies identified in the final search criteria, three studies (37.5%) failed to report the race or ethnicity of the enrolled participants. Meanwhile, while five studies (62.5%) did provide information about the patients' racial and demographic characteristics, only two studies (25%) included population samples that were vastly women of color. The remaining three studies (37.5%) involved an overwhelming majority of white women in the recruitment sample. None of the eight studies reported or stratified findings across race or ethnicity metrics.

Discussion: None of the authors outlined the recruitment methodology nor sampling techniques when selecting participants for these clinical trials. For the five studies who reported on patient demographics, the only information provided was a baseline characteristics table, which outlined characteristics such as average age, BMI, and race/ethnicity of the study subjects. The findings from this study highlight the critical need for future clinical trials to account for racial and ethnic diversity in the sampling methodology and inclusion of research participants.

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BACKGROUND

Polycystic Ovary Syndrome (PCOS) is a medical condition that impacts 10% of women of childbearing age, characterized by an imbalance in reproductive hormones which can cause various metabolic abnormalities, infertility, and other gestational/physical complications.¹ There are five major hormones that play a role in PCOS related complications: 1) Androgens, also known as male sex hormones. While androgens are present in the bodies of both males and females, women with PCOS tend to produce an abnormal amount of androgens, which can cause menstrual cycle irregularities, hinder ovulation, increase production of facial/body hair/acne, and lead to the development of ovarian cysts.² 2) Insulin, which plays a major role in managing blood glucose levels in the body. Women with PCOS are more likely to be insulin resistant - their bodies can produce insulin, but they can't use it effectively or efficiently which increases their risk for Type II Diabetes.³ 3) Luteinizing hormone (LH) and 4) Follicle-stimulating hormones (FSH) - both of which are secreted by the pituitary gland. LH helps to control the production of estrogen and progesterone in the ovary, while FSH controls the development and release of the eggs in a woman's ovary.⁴ Women with PCOS tend to have lower levels of both FSH and LH, which contributes to difficulties with ovulation and higher rates of infertility. 5) Progesterone, which is a hormone released by the ovaries and influences the menstrual cycle and pregnancy. Women with PCOS tend to suffer from an imbalance in progesterone, which can cause menstrual cycle irregularities and an increased risk for infertility.⁵

While PCOS can affect women of all racial and ethnic backgrounds, prior research studies have shown that minority women of color may present an elevated risk of PCOS-related infertility and

other health disparities compared with non-minority white women.⁶ According to researchers Braveman et al., health disparities are health differences that adversely affect socially disadvantaged groups and are systemic, plausibly avoidable health differences on the basis of race/ethnicity, colorism, religion, nationality, socioeconomic status, education, occupation, gender/gender identity, sexual orientation, age, geography, disability, illness, or other characteristics associated with discrimination or marginalization.⁷ Over the years, social science researchers have highlighted the pervasive role that historical systems of oppression, structural inequities, and racism have played in generating social disadvantage and health disparities among minority people of color. Researchers Link and Phelan have asserted that both racism and socioeconomic status are fundamental causes of social inequities and mortality because they influence multiple disease outcomes, are associated with multiple risk factors, are reproduced over time, and involve access to resources that can be used to minimize or avoid such risks.⁸ Additionally, researchers Fullilove et al. have explained how the spillover effects of racism have generated and contributed to racial residential segregation, whereby policymakers, housing authorities, and community planners have used tactics such as redlining, serial forced displacement, urban renewal, and gentrification to push minority people of color out of historically white neighborhoods.⁹ Consequently, these communities of color are often forced to relocate into concentrated areas that are frequently under-resourced, low-income, and suffer from high rates of food insecurity, limited job opportunities, and poorer access to healthcare. The inverse hazards law posits that these types of negative consequences accumulate inversely with power and resources, which typically affects minority communities of color and places them at higher risk for disease-related illness and mortality.¹⁰ The compounding effects of structural and

systemic injustices have generated elevated risks for these minority communities of color, placing them at higher risks for various chronic and long-term illnesses. Despite progressive changes in disease management and treatment, it is clear that race-related disparities have continued to persist over time, with detrimental costs to individual-level health.

The National Institutes of Health estimates that 40 to 85% of women with PCOS are either overweight or obese, which is a risk factor to PCOS.¹¹ Furthermore, The Centers for Disease Control and Prevention (CDC) have reported that non-white people of color have the highest rates of obesity in the U.S. Specifically, their most recent report released in 2021 revealed that Non-Hispanic Black adults had the highest age-adjusted prevalence of obesity (49.6%), followed by Hispanic adults (44.8%).¹² With knowledge that Black and Hispanic Americans have higher morbidity and mortality rates due to cardiovascular diseases and diabetes mellitus in the general population than white Americans, a 2017 study by researchers Engmann et al. studied the effects of racial and ethnic differences in PCOS metabolic phenotypes as it relates to insulin resistance, metabolic syndrome, and hyperandrogenemia. The study found that Hispanic women with PCOS had a significantly higher prevalence of hirsutism (93.8 vs. 86.8%), abnormal free androgen index (75.8 vs. 56.5%), abnormal homeostasis model assessment (52.3 vs. 38.4%), hyperglycemia (14.8 vs. 6.5%), and lower sex hormone binding globulin compared to non-Hispanic Whites. Furthermore, Non-Hispanic Black women had a significantly lower prevalence of metabolic syndrome (24.5 vs. 42.2%) compared with Hispanic women, and lower serum triglyceride levels compared to both Hispanics and non-Hispanic Whites (85.7 ± 37.3 vs. 130.2 ± 57.0 vs. 120.1 ± 60.5 mg/dL, $p < 0.01$), and a lower prevalence of hypertriglyceridemia

(5.1 vs. 28.3 vs. 30.5%, $p < 0.01$) compared to the other two groups.¹³ These findings highlight the critical need to understand the racial and ethnic differences in metabolic syndrome for women with PCOS in identifying effective prevention and treatment strategies.¹⁴

Over the years, various clinical trials on pharmacotherapy drug treatments have been assessed in treating infertility-related PCOS in women. Currently, the four most common and effective drug treatments for ovulation induction used by physicians include: 1) Clomiphene: An estrogen modulator used to induce egg production among infertile women; 2) Letrozole: A non-steroidal aromatase inhibitor commonly used to treat breast cancer but also works to stimulate ovaries; 3) Metformin: An oral medication commonly used to treat type II diabetes but also serves as an effective ovulation induction agent for non-obese women with PCOS; and 4) Gonadotropins: Peptide hormonal injection shots that can regulate the reproductive system and stimulate ovulation.^{15,16,17,18,19} However, with knowledge that PCOS tends to disproportionately affect minority women of color, it is important to uncover whether previous clinical trials and randomized controlled trials (RCTs) have considered patient demographic characteristics in the study design, methodology, and enrollment of patients into these clinical trials.

A 2015 article by researchers Oh et al. assessed diversity representation in clinical and biomedical research. Their findings illustrated that while racial and ethnic minorities comprise nearly 40% of the U.S. population, they remain severely under-represented in many clinical trials.²⁰ Citing one example, the study found that less than 5% of NIH-funded respiratory research reported inclusion of racial and ethnic minorities.²¹ By failing to include racial and

ethnic representation in these clinical trials, there continues to be a significant gap in understanding and research regarding the factors that contribute to inequitable and disproportionate burdens of health among minority populations.

Despite ample studies and research of PCOS in academic discourse, there have been no identified studies to date that have critically assessed racial representation in the methodology and recruitment of these PCOS-related clinical trials. The goal of this meta research project is to fill this gap in research by closely modeling a systematic process to assess demographic characteristics of the study subjects recruited and enrolled in clinical trials and RCTs researching the efficacy of pharmacotherapy fertility treatments for women with Polycystic Ovary Syndrome (PCOS). The primary objective of this thesis is to conduct a comprehensive meta research assessment of prior clinical trial studies and randomized controlled trials in order to assess whether the studies reflect representative samples of the U.S. population - specifically with regard to race and ethnicity-related factors. Understanding the patient demographics of the various studies will help understand whether the clinical trials and RCTs that evaluate the treatments for PCOS are representative of the true populations who need treatment. As a secondary objective, this thesis will also assess the ovulatory, pregnancy, and fertility-related outcomes associated with the various pharmacotherapy drug treatments for PCOS in order to deduce any striking patterns stratified across race or ethnicity, such as whether certain drug treatments tended to be disproportionately prescribed to or utilized by certain racial or ethnic groups. I hypothesize that study recruitment across the reviewed studies will illustrate an overall non-representative sample of the U.S. population affected by PCOS. The findings generated in

this paper are critical in ensuring that fertility treatment and population health outcomes are optimized across all patient demographics. The results from this meta research project will have the potential to inform the design and methodology of future clinical studies in this field in order to improve racial and ethnic representation in these trials and improve population health equity.

METHODS

Study selection and methods for this meta research project followed the procedures outlined by the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020* Checklist and the *Consolidated Standards for Reporting Trials (CONSORT)* Flow Diagram.^{22,23} Given that this meta research project involved a critical appraisal and critique of previous research studies and did not involve any direct clinical trials or new research on human subjects, Institutional Review Board (IRB) approval was not required. Additionally, because my primary outcome of interest involved patient demographic information and representation, effect measures (such as risk or odds ratios), data synthesis methods, and certainty assessments were out of scope for the purposes of this meta research project..

Eligibility Criteria

In 1998, The American Medical Association's Council on Long Range Planning and Development drafted a healthcare policy (H-350.974) declaring racial and ethnic disparities to be a major public health problem.²⁴ Part of their policy resolution included the development of evidence-based performance measures to reduce health disparities across various socioeconomic and racial/ethnic groups, including greater representation of people of color in medicine and clinical trials. In order to assess whether recent clinical trials and RCTs have effectively incorporated greater diversity in study recruitment, the database searches in this meta research project were limited to that of RCTs and clinical trials published in or after 1999 (one year after the policy's inception) through 2021. With our

population base being U.S. patients with PCOS-related infertility, these studies were limited to English language studies conducted within the United States and therefore, excluded any non-English studies conducted outside the U.S. This search strategy was also restricted to only include full-text publications and excluded studies with pre-trial registries or pre-prints.

Inclusion Criteria

When considering search terms and search criteria for this meta research project, only articles that focused on the primary health condition of PCOS-related infertility were included. PCOS-related infertility can be defined and broken down into the following two components: 1) PCOS is a condition that affects women of reproductive age, which is defined as women who are biologically capable of conceiving children. This includes adolescents who have reached pubertal maturation all the way to fertile adult women who have not yet reached the stage of menopause. 2) This meta research project only focuses on women who have been clinically diagnosed with Polycystic Ovary Syndrome and struggle to conceive children naturally due to fertility-related complications. Furthermore, while there are various methods and ways of treating PCOS-related infertility, this search strategy was constrained to only include the four most common pharmacotherapy drug treatments, which include: Clomiphene, Letrozole, Metformin, and Gonadotropins. Streamlining the search to these four drug treatments ensures consistency across the various database searches and helps to keep a more refined and focused search. Finally, as defined in our study selection criteria, this meta research project only included RCTs and clinical trials

published between the years of 1999-2021 that were written in English-language and conducted in the United States.

Exclusion Criteria

In order to focus and optimize the results of this meta research project, there were various study characteristics and terms that were excluded from the search strategy. First, given that this research project focuses on PCOS-related infertility among women of reproductive age, studies that included young people who have not yet reached pubertal maturation age and post-menopausal women were excluded from this search. Additionally, while there are an array of different drug treatments and interventions for the treatment of PCOS-related infertility, this study has taken a focused review of the four most common pharmacotherapy drug treatments of Clomiphene, Letrozole, Metformin, and Gonadotropins. As such, any other pharmacotherapy drug treatments outside of these four medications were excluded from the search criteria. While the primary intervention involves pharmacotherapy drug treatments, it is possible to encounter studies that also incorporate lifestyle modifications or other non-drug treatment therapies as secondary interventions in treating PCOS-related infertility, which were excluded from our study. Finally, non-clinical trials and non-RCT studies published before 1999 and non-English studies conducted outside of the U.S. were excluded, as well as any pre-trial registries, pre-prints without full-text publications, or clinical trials in pre-publication phases.

Information Sources

Working with public health advisors and trained medical librarians, I as a solo researcher conducted searches for primary research studies across five expanded electronic databases and registries, which included *Ovid MEDLINE*, *PubMed*, *Scopus*, *Ovid Embase*, and *Web of Science*. The publication dates for study selection across all five search bases were restricted to 1999 - 2021, as justified in the eligibility criteria above. The rationales for selecting each database or registries are outlined as follows:

Ovid MEDLINE: Compiled by the U.S. National Library of Medicine, Ovid MEDLINE is the world's most comprehensive source of life sciences and biomedical bibliographic information, containing publications from 1965 to present.²⁵ Despite similarities to PubMed, Ovid MEDLINE offers a more structured and flexible interface, thus yielding more focused search results.

PubMed: Developed and maintained by the National Institutes of Health, PubMed is a free and comprehensive literature search base, primarily across biomedical, healthcare, and life sciences literature. With more than 33 million citations, abstracts, and full-text journal articles, PubMed is one of the largest scientific databases in medicine and healthcare, which will yield a high degree of relevant academic journal articles for my selected research topic.²⁶ Furthermore, PubMed has a very streamlined and user-friendly search experience due to its automatic term mapping feature, has excellent system response speeds, and is widely accessible to both researchers and the general public.

Scopus: Launched in 2004, Scopus is the largest abstract and citation database for peer-reviewed literature in the fields of science, technology, medicine, social sciences, arts, and humanities.²⁷ Through institutional access via Yale University, this database will allow for an expansive and comprehensive search for relevant studies within the defined inclusion and exclusion criteria.

Ovid Embase: Produced by Elsevier, Ovid Embase is a biomedical and pharmacological database, yielding over 32 million abstracts, indexes, and full-text articles.²⁸ This database utilizes *Emtree* to index full-text content and search terms in order to uncover all relevant and current publications. With my thesis project involving studies of pharmacotherapy drug treatments in treating infertility-related PCOS, Ovid Embase will serve as a key database for searching studies involving pharmacological treatments.

Web of Science: Owned and produced by Clarivate, Web of Science is a multi-disciplinary research and citation database that allows users to search across almost 1.9 billion cited references and over 171 million records across a wide range of medical, social science, and humanities disciplines.²⁹

Search Strategies

Comprehensive and expansive literature searches were conducted via *Ovid MEDLINE*, *PubMed*, *Scopus*, *Ovid Embase*, and *Web of Science* databases. Through institutional student access through the Harvey Cushing/John Hay Whitney Medical Library at Yale University, I

was granted expanded access to a wide range of biomedical publications to support this meta research project. In building my database search strategy, I gained inspiration from a research publication by author Showell et al. in their 2018 publication, *Inositol for Subfertile Women with Polycystic Ovary Syndrome*.³⁰

While each database contains unique search and filtering techniques (such as the use of Map Term to Medical Subject Heading (MeSH) in Ovid MEDLINE and PubMed, and the use of Emtree for controlled vocabulary and full-text indexing in Ovid Embase), a general protocol was followed in order to ensure search consistency across all databases. First, a comprehensive search across all databases involved searching for the main condition of interest, *Polycystic Ovary Syndrome*. When applicable, I refined this search to include title/abstract, keyword, or text word searches of this term in order to retrieve more focused results. This also included the various or alternative iterations or abbreviations of the term, disease synonyms, and relevant exploded MeSH entry terms. Such examples included disease abbreviations “PCOS,” “PCOD,” or the formal medical terminology of the condition, “Stein-Leventhal Syndrome.” Next, searches for each of the four major pharmacotherapy drug treatments (Clomiphene, Letrozole, Metformin, and Gonadotropins) were conducted. In order to capture the maximum possible studies, I also searched for these drug treatment terms as medical subject headings via MeSH or Emtree when the drug treatment was part of a controlled vocabulary, as well as keyword and text word searches. Additionally, searches in all fields were conducted for the terms ‘ovulation,’ ‘ovulation induction,’ ‘fertility,’ and ‘infertility’ in order to identify studies that focus on PCOS

patients that suffer from infertility. Depending on the database, I either searched for ‘randomized controlled trials’ and ‘clinical trials’ as well as any relevant synonyms or abbreviations of the term, or I applied a filter to these studies following the conclusion of my search. I also excluded all studies that were conducted on animal subjects and only included studies that focused on human subjects. A date filter for studies conducted between 1999 - 2021 was applied, as well as a filter for English language studies. The boolean operators ‘AND’/’OR’/’NOT’ were used to combine the above search strategies to generate the final search strategy outlined in Appendices A-E below. The above search strategies for the five databases were conducted on December 3, 2021 and are accurate to this date. In sum, 303 studies were identified in Ovid MEDLINE, 386 studies were identified in PubMed, 1,866 studies were identified in Scopus, 47 studies were identified in Ovid Embase, and 281 studies were identified in Web of Science. This resulted in a total combined pool sum of 2,883 studies to be further filtered through.

Study Selection Process

After compiling a preliminary list of 2,883 studies from the initial search strategy above, I as an independent researcher leveraged a systematic process to select studies to be included in the final review. *Figure 1* below provides a visual outline of this study selection process and is explained in greater detail in the following steps:

1. EndNote X9 was downloaded to be used as a reference and citation manager tool to streamline the screening and selection of studies to be included in the final meta research project. EndNote X9 is the preferred citation manager platform due

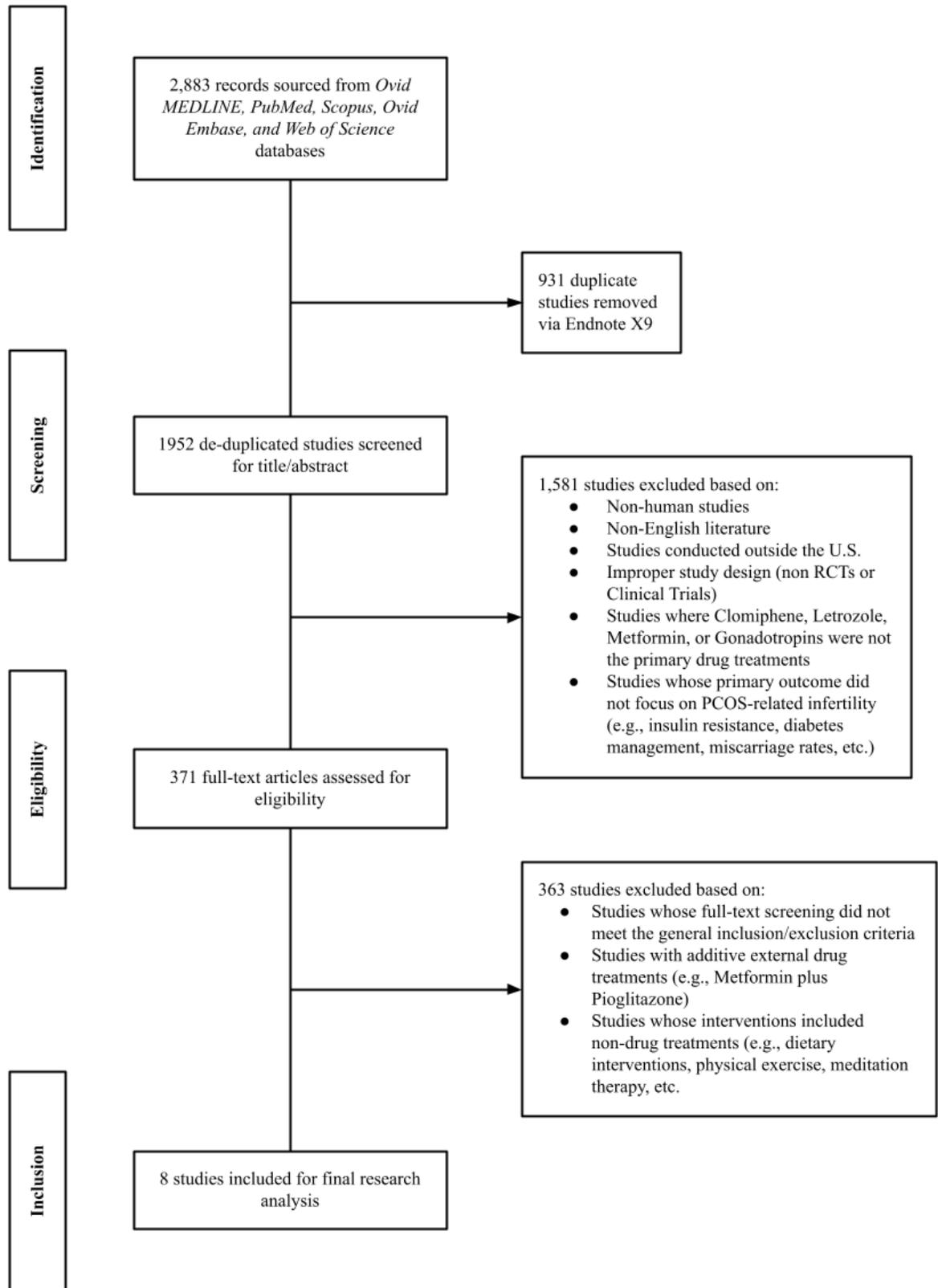
to its robust and comprehensive information sourcing from individual studies, its advanced functions such as auto-complete, edit/create your own filters, and the many customizable fields, displays, and options. Furthermore, EndNote X9 supports the direct export of references directly from the individual database sites into the citation manager, and also allows users to manually upload any additional citations. The ‘find full text or PDF’ feature also allows for available PDF documents or links to full-text web publications to be linked directly to EndNote X9 for easy access and referencing.

2. After conducting the search strategies outlined in Appendices A-E and identifying the 2,883 eligible studies, I downloaded and exported the references of these studies into EndNote X9. The ‘remove duplicates’ feature in EndNote X9 was used to automatically remove identical studies that were identified across multiple databases. If duplicative studies still remained, I manually removed them from the software. This filtering step removed 931 duplicate studies, leaving 1,952 remaining studies for further screening.
3. This stage in the filtering process involved a full screening of the title/abstract of the 1,952 remaining de-duplicated studies. While non-RCT and non-clinical trial studies should have been filtered out during the initial search strategy in the five different database searches, I manually ensured accuracy and removed any studies that did not fall within this inclusion criteria. Additionally, I manually removed

any studies conducted outside of the U.S., published outside the years of 1999 - 2021, were not written in English language, and involved non-human subjects. In addition, studies that did not include the four primary drug treatments of interest (Clomiphene, Letrozole, Metformin, or Gonadotropins) were removed. Finally, studies whose primary outcome did not focus on PCOS-related infertility (such as insulin resistance, diabetes management, miscarriage rates, etc.) were also removed. This resulted in the exclusion of 1,581 studies, leaving 371 remaining studies for additional screening and appraisal.

4. From the remaining 371 remaining studies, I conducted a full-text screening of each study and manually removed any studies that did not meet the inclusion and exclusion criteria. During this stage of the screening, studies whose primary and/or secondary interventions included additive external drug treatments (such as Metformin in combination with Pioglitazone; or Clomiphene in combination with oral contraceptives) were excluded. Additionally, studies whose primary or secondary interventions included non-drug treatments, such as dietary interventions, physical exercise, meditation therapy, or surgery, were removed.
5. After conducting a full-text analysis of all remaining studies, 8 studies were included for final research analysis in this meta-research project.

Figure 1: CONSORT diagram outlining the study selection process



Data Collection Process

After conducting independent and separate study searches in the five electronic databases and registries (including *Ovid MEDLINE*, *PubMed*, *Scopus*, *Ovid Embase*, and *Web of Science*), I exported and managed all studies in *EndNote X9* - Clarivate's online citation and reference manager to de-duplicate citations, screen the titles, abstracts, and full-text of papers, and extract important and relevant data.³¹ Despite being an independent researcher for this meta-research project, I leveraged partnerships with public health advisors and trained medical library staff at the Yale School of Public Health to ensure the data collection process was conducted accurately and efficiently.

Data Items

In order to assess individual study characteristics for each of the final 8 studies, *Table 1* below includes a summary of each publication, as well as demographic information of the study participants to be critically assessed in the results section. Each independent study has its own row in the table matrix. The table below includes information about the primary author, year of publication, study title, study design, study location, sample size, participant demographics (including age, BMI, and race/ethnicity), primary/secondary interventions, and primary/secondary outcomes. The study findings from each of the 8 studies will be reported in a separate table in the results section.

The study characteristics table includes basic publication information, such as the name of the primary author, the year the study was published, and the title of the study. The table

also reports on study characteristics, such as the study design, study location, sample size, and the participant demographics of the study, including factors such as age, BMI, and race/ethnicity. The primary and/or secondary interventions, including the drug treatments used in these studies are reported under the ‘primary/secondary interventions’ column, along with primary/secondary outcomes in the final column.

Table 1: Summary of Reviewed Studies

Author & Year	Title	Study Design	Study Location	Sample Size	Participant Demographics	Primary/Secondary Interventions	Primary/Secondary Outcomes
Aubuchon et al. (2009). ³²	Metformin Does Not Improve the Reproductive or Metabolic Profile in Women with Polycystic Ovary Syndrome (PCOS)	Randomized, double-blind, placebo controlled crossover clinical trial	General Clinical Research Center (GCRC) at the Albert Einstein College of Medicine (Bronx, NY)	8 women diagnosed with PCOS (4 women randomly assigned to intervention group, 4 women assigned to control group)	Age Range: 18-38; mean age of 25.6 ± 3.0 years Mean Weight: 98.5 ± 24.4 kg; BMI: 37.3 ± 9.6 kg/m ² . Race/Ethnicity: 5 African American participants, 2 Caucasian participants, 1 Southeast Asian participant	Intervention Group: 8 week treatment of Metformin (administered in a stepwise fashion; starting at 500mg/week and increasing by 500mg/week until maximum dose of 2000mg daily was achieved) Control Group: Placebo pills administered in the same stepwise fashion as the Metformin intervention group	Primary Outcome: To determine whether metformin promotes folliculogenesis (maturation of the ovarian follicle) through a rise in FSH levels among women with PCOS. Secondary Outcomes: Weight/BMI status, glucose use, suppression of endogenous glucose production, FFA, lipids, androgens, urinary pregnanediol glucuronide (Pdg) elevation, LH secretion, and SHBG
Cataldo et al. (2008). ³³	Extended-Release Metformin Does Not Reduce the Clomiphene Citrate Dose Required to Induce Ovulation in Polycystic Ovary Syndrome	Prospective, double-blind, placebo controlled multicenter clinical trial	Data gathered from multiple academic medical centers in the U.S. (locations not specified)	418 women with PCOS and elevated serum testosterone (n = 209 women randomized to intervention group, n = 209 women randomized to control group)	Age Range: <ul style="list-style-type: none"> ● Intervention Group: 28.3 ± 4.0 ● Control Group: 27.9 ± 4.0 BMI: <ul style="list-style-type: none"> ● Intervention Group: 34.2 ± 8.4 ● Control Group: 36.0 ± 8.9 Race/Ethnicity: Not reported	Intervention Group: Clomiphene Citrate at 50mg daily for 5 days (increased to 100 or 150mg if ovulation was not achieved) PLUS metformin XR (100mg, twice daily); continued for up to 30 weeks (6 ovulation cycles) or until first pregnancy Control Group: Clomiphene Citrate at 50mg daily for 5 days (increased to 100 or	Primary Outcome: To determine if co-treatment with Metformin XR can lower the threshold dose of clomiphene needed to induce ovulation in women with PCOS. Ovulation was confirmed by a serum progesterone more than or equal to 5ng/ml, drawn every 1-2 weeks

						150mg if ovulation was not achieved) PLUS a placebo pill	
Khorrām et al. (2006). ³⁴	Two Weeks of Metformin Improves Clomiphene Citrate-Induced Ovulation and Metabolic Profiles in Women with Polycystic Ovary Syndrome	Randomized prospective control trial	Harbor-UCLA Medical Center (Torrance, California)	31 women with PCOS-related infertility (n = 16 women randomized to intervention group, n = 15 randomized to control group)	<p>Age Range:</p> <ul style="list-style-type: none"> ● Intervention Group: 28.4 ± 0.78 ● Control Group: 28 ± 1.1 <p>BMI:</p> <ul style="list-style-type: none"> ● Intervention Group: 35.3 ± 0.99 ● Control Group: 38.8 ± 1.6 <p>Race/Ethnicity:</p> <ul style="list-style-type: none"> ● Intervention Group: 15 Hispanic, 1 Caucasian ● Control Group: 14 Hispanic, 1 African American 	<p>Intervention Group: Study subjects were prescribed 500mg of Metformin three times a day, given on cycle days 1-14 (cycle day 1 = first day of menses) in combination with Clomiphene Citrate (100mg) per day taken on days 5-9 of cycle. Intervention lasted 2 weeks</p> <p>Control Group: Patients were prescribed Clomiphene Citrate (100mg/day) on cycle days 5-9 only. Intervention lasted 2 weeks</p>	Primary Outcome: Ovulation as determined by serum P, serum insulin, and total and free T.
Legro et al. (2007). ³⁵	Clomiphene, Metformin, or Both for Infertility in the Polycystic Ovary Syndrome	Randomized control trial	Department of Obstetrics and Gynecology at Pennsylvania State University College of Medicine	626 infertile women with PCOS (n = 209 in cohort 1, n = 208 in cohort 2, n = 209 in cohort 3)	<p>Age Range:</p> <ul style="list-style-type: none"> ● Clomiphene Group: 27.9 ± 4.0 ● Metformin Group: 28.1 ± 4.0 ● Combination Therapy Group: 28.3 ± 4.0 <p>BMI:</p> <ul style="list-style-type: none"> ● Clomiphene Group: 36.0 ± 8.9 ● Metformin Group: 35.6 ± 8.5 ● Combination Therapy Group: 34.2 ± 8.4 <p>Race/Ethnicity:</p>	<p>Cohort 1: Clomiphene Citrate (50mg tablets) plus placebo; one tablet a day for 5 days, beginning on day 3 of menses</p> <p>Cohort 2: Metformin XR (500mg tablets) plus placebo; taken in stepwise increments until maximum dose of 2 tablets twice a day was achieved</p> <p>Cohort 3: Combination Metformin XR (500mg tablets); taken in stepwise increments until maximum</p>	<p>Primary Outcome: To assess the efficacy of Clomiphene Citrate, Metformin XR, or a combination treatment of Metformin XR plus Clomiphene Citrate on live birth rates</p> <p>Secondary Outcomes: Conception, pregnancy, rates of pregnancy loss, singleton birth, and ovulation (a serum progesterone level above 5ng per milliliter during a cycle)</p>

					<ul style="list-style-type: none"> ● Clomiphene Group: <ul style="list-style-type: none"> ○ White: 147/209 (70.7%) ○ Hispanic/Latino: 53/209 (25.4%) ○ Black: 37/209 (17.8%) ○ Asian: 5/209 (2.4%) ○ American Indian/Alaska Native: 21/209 (10.1%) ○ Native Hawaiian/Pacific Islander: 1/209 (0.5%) ● Metformin Group: <ul style="list-style-type: none"> ○ White: 140/208 (67.6%) ○ Hispanic/Latino: 61/208 (29.3%) ○ Black: 40/208 (19.3%) ○ Asian: 5/208 (2.4%) ○ American Indian/Alaska Native: 27/208 (13%) ○ Native Hawaiian/Pacific Islander: 0/208 (0%) ● Combination Therapy Group: <ul style="list-style-type: none"> ○ White: 148/209 (71.2%) ○ Hispanic/Latino: 50/209 (23.9%) ○ Black: 32/209 (15.4%) ○ Asian: 7/209 (3.4%) 	<p>dose of 2 tablets twice a day was achieved; PLUS Clomiphene Citrate (50mg tablets); one tablet a day for 5 days, beginning on day 3 of menses</p>	
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					<ul style="list-style-type: none"> ○ American Indian/Alaska Native: 24/209 (11.5%) ○ Native Hawaiian/Pacific Islander: 0/209 (0%) 		
Legro et al. (2014). ³⁶	Letrozole Versus Clomiphene for Infertility in the Polycystic Ovary Syndrome	Double-blind, randomized control trial	Department of Obstetrics and Gynecology at Pennsylvania State University College of Medicine	750 women with PCOS-related infertility (n = 376 randomized to Clomiphene Group, n = 374 randomized to Letrozole Group)	<p>Age Range:</p> <ul style="list-style-type: none"> ● Clomiphene Group: 28.8 ± 4.0 ● Letrozole Group: 28.9 ± 4.5 <p>BMI:</p> <ul style="list-style-type: none"> ● Clomiphene Group: 35.1 ± 9.0 ● Letrozole Group: 35.2 ± 9.5 <p>Race/Ethnicity:</p> <ul style="list-style-type: none"> ● Clomiphene Group: <ul style="list-style-type: none"> ○ White: 302/376 (80.3%) ○ Black: 44/376 (11.7%) ○ Asian: 12/376 (3.2%) ○ Mixed Race: 12/376 (3.2%) ○ Hispanic or Latino: 68/376 (18.1%) ● Letrozole Group: <ul style="list-style-type: none"> ○ White: 288/374 (77%) ○ Black: 56/374 (15%) ○ Asian: 12/374 (3.2%) ○ Mixed Race: 15/374 (4.0%) 	<p>Intervention Group 1: 376 women with PCOS-related infertility received Clomiphene Citrate (50mg daily) in permuted blocks of 2, 4, or 6, beginning on cycle day 3 for 5 days and lasting up to five menstrual cycles. If patient was non-responsive to treatment, dose was increased (max dose of 150mg). Couples were instructed to have sexual intercourse 2-3 times per week and keep an intercourse diary</p> <p>Intervention Group 2: 374 women with PCOS-related infertility received Letrozole (2.5mg daily) in permuted blocks of 2, 4, or 6, beginning on cycle day 3 for 5 days and lasting up to five menstrual cycles. If patient was non-responsive to treatment, dose was increased (max dose of 7.5mg). Couples were instructed to have sexual intercourse 2-3 times</p>	<p>Primary Outcome: Live birth rates during the treatment period</p> <p>Secondary Outcomes: Ovulation rates, pregnancy loss among women who conceived, conception rates among subjects who ovulated, and congenital anomalies</p>

					○ Hispanic or Latino: 60/374 (16%)	per week and keep an intercourse diary	
Mejia et al. (2019). ³⁷	A Randomized Controlled Trial of Combination Letrozole and Clomiphene Citrate or Letrozole Alone for Ovulation Induction in Women with Polycystic Ovary Syndrome	Randomized control trial	Two clinic sites at academic medical centers in the U.S.	70 women with PCOS-related infertility (n = 35 randomized to Letrozole treatment group, n = 35 randomized to Letrozole + Clomiphene treatment group)	<p>Age Range:</p> <ul style="list-style-type: none"> ● Letrozole Group: 31 ± 3.9 ● Letrozole + Clomiphene Group: 30 ± 4.4 <p>BMI:</p> <ul style="list-style-type: none"> ● Letrozole Group: 33 ± 8.7 ● Letrozole + Clomiphene Group: 34 ± 7.0 <p>Race/Ethnicity:</p> <ul style="list-style-type: none"> ● Letrozole Group: <ul style="list-style-type: none"> ○ White: 29/35 (83%) ○ Black: 2/35 (6%) ○ Asian: 1/35 (3%) ○ Hispanic/Latino: 2/35 (6%) ○ Mixed Race: 1/35 (3%) ● Letrozole + Clomiphene Group: <ul style="list-style-type: none"> ○ White: 30/35 (86%) ○ Black: 1/35 (3%) ○ Asian: 1/35 (3%) ○ Hispanic/Latino: 2/35 (6%) ○ Mixed Race: 1/35 (3%) 	<p>Cohort 1: 35 women with PCOS-related infertility received Letrozole (2.5mg) on cycle days 3-7 for one treatment cycle</p> <p>Cohort 2: 35 women with PCOS-related infertility received Letrozole (2.5mg) + Clomiphene (50mg) on cycle days 3-7 for one treatment cycle</p>	<p>Primary Outcome: Ovulation, defined as mid-luteal progesterone level of >3 ng/mL</p> <p>Secondary Outcomes:</p> <ul style="list-style-type: none"> ● Conception ● Clinical Pregnancy ● Live Birth Rates ● Singleton Birth ● Pregnancy Loss ● Size and number of developing follicles on cycle days 12-14 ultrasound ● Endometrial thickness on cycles days 12-14 ultrasound ● Adverse events related to the study medications

<p>Stadtmauer et al. (2011).³⁸</p>	<p>The Impact of a Gonadotropin-Releasing Hormone Antagonist on Gonadotropin Ovulation Induction Cycles in Women with Polycystic Ovary Syndrome: A Prospective Randomized Study</p>	<p>Prospective, randomized control study</p>	<p>Eastern Virginia Medical School in Norfolk, Virginia</p>	<p>98 anovulatory women with PCOS who underwent 154 gonadotropin ovulation induction cycles randomly allocated to 3 treatment groups:</p>	<p>Age Range:</p> <ul style="list-style-type: none"> ● Group 1 (Follistim): 29.9 ± 4.2 ● Group 2 (Follistim + Ganirelix if FS≥13mm): 30.8 ± 3.9 ● Group 3 (Follistim + Ganirelix): 30.5 ± 4.4 <p>BMI:</p> <ul style="list-style-type: none"> ● Group 1 (Follistim): 32.2 ± 8.5 ● Group 2 (Follistim + Ganirelix if FS≥13mm): 29.9 ± 7.5 ● Group 3 (Follistim + Ganirelix): 29.0 ± 7.2 <p>Race/Ethnicity: Not reported</p>	<p>Primary Intervention: Gonadotropin medication regimen used for ovulation induction:</p> <ul style="list-style-type: none"> ● Group 1: n = 50 randomized to Follistim treatment group ● Group 2: n = 51 randomized to Follistim + Ganirelix if FS≥13mm ● Group 3: n = 41 randomized to Follistim + Ganirelix 	<p>Primary Outcomes:</p> <ul style="list-style-type: none"> ● Per cycle clinical pregnancy rate (CPR) ● Live birth rate (LBR) <p>Secondary Outcomes:</p> <ul style="list-style-type: none"> ● Total gonadotropin dose ● Days of stimulation ● Serum LH ● Peak E₂ ● Premature luteinization rate
<p>Vandermolen et al. (2001).³⁹</p>	<p>Metformin Increases the Ovulatory Rate and Pregnancy Rate From Clomiphene Citrate in Patients with Polycystic Ovary Syndrome who are Resistant to Clomiphene Citrate Alone</p>	<p>Randomized, double-blind, placebo controlled trial</p>	<p>Multi-center study across three academic institutions in Virginia and Missouri</p>	<p>26 anovulatory women with PCOS who were resistant to Clomiphene (n = 11 randomized to Metformin treatment group, n = 14 randomized to Placebo treatment group)</p>	<p>Age Range:</p> <ul style="list-style-type: none"> ● Metformin Group: 29 ± 1.2 ● Placebo Group: 30 ± 1.0 <p>BMI:</p> <ul style="list-style-type: none"> ● Metformin Group: 37.6 ± 4.3 ● Placebo Group: 38.4 ± 2.2 <p>Race/Ethnicity: Not reported</p>	<p>Cohort 1: 11 anovulatory women with PCOS were randomized to receive Metformin treatment (500mg three times daily for 7 weeks)</p> <p>Cohort 2: 14 anovulatory women with PCOS were randomized to receive placebo, instructed to take three times daily for 7 weeks</p>	<p>Ovulation and Pregnancy Rates</p>

Risk of Bias Assessment

In order to assess the risk of bias in the included eight studies, this meta research project leveraged the Cochrane Risk of Bias Tool for Randomized Trials (RoB 2).⁴⁰ RoB 2 is the preferred and recommended tool to assess risk of bias in RCTs and clinical trials due to the streamlined and fixed set of assessment domains used to determine whether studies present a high, medium, or low risk of bias. The Cochrane website lists seven domains by which to assess bias, which includes: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential biases.⁴¹ A risk of bias table as outlined below in *Table 2* highlights each of the eight studies and the risk of potential biases across each of the seven domains. Studies found to have a low risk of bias are represented by green circles. Meanwhile, studies with a high risk of bias are represented by red circles, and studies whose methodology presents unclear conclusions on risk of bias are represented by yellow circles. It is important to note that by performing this risk of bias assessment as a solo researcher, this presents some significant limitations, as I do not have the capability to confer or collaborate with a team of researchers and colleagues to validate these assertions. However, by following a systematic process of assessing bias in studies, this meta research project aims to maintain the validity and quality of this review process. Given that the primary objective of this meta research project is to assess patient demographic representation in these clinical trials, studies with domains that presented a potential risk for bias were still included in the final inclusion criteria but will be critiqued further relative to secondary

outcomes and how they may influence factors such as ovulation, pregnancy rates, and fertility.

Table 2: Risk of Bias Summary Assessment Table

	Random sequence generation (Selection Bias)	Allocation concealment (Selection Bias)	Blinding of participants (Performance Bias)	Blinding of outcome assessment (Detection Bias)	Incomplete outcome data (Attrition Bias)	Selective reporting (Reporting Bias)	Other Bias
Aubuchon et al. (2009)							
Cataldo et al. (2008)							
Khorrarn et al. (2006)							
Legro et al. (2007)							
Legro et al. (2014)							
Mejia et al. (2019)							
Stadtmauer et al. (2011)							
Vandermolen et al. (2001)							
Legend:  = Low risk of bias  = Unclear risk of bias  = High risk of bias							

RESULTS

A total of 8 randomized controlled trials and clinical trials published between the years of 1999 - 2021 were included in this final meta research analysis. These 8 studies, their statistical analyses and study findings are reported below in *Table 3*. Across the 8 studies, 2,027 women with PCOS-related infertility were recruited, randomized, treated, and assessed for outcomes such as rates of ovulation, pregnancy, and live birth rates. All 8 studies were conducted within either clinical research centers or academic medical centers across the U.S. in locations such as New York, California, Pennsylvania, Virginia, and Missouri. Findings from these eight studies are subsequently stratified based on the following outcomes:

Participant Demographics

Of the eight assessed studies, three studies (Cataldo et al., Stadtmauer et al., and Vandermolen et al.) did not report the race or ethnicity of the enrolled participants. First, while the Cataldo et al. study did provide a table for baseline characteristics of the two treatment groups (Clomiphene-only versus Clomiphene plus Metformin), the baseline characteristics only included information about participants' age, BMI, insulin/glucose levels, and various metrics on infertility such as previous history of infertility, conception, live birth rates, etc. Similarly, the Stadtmauer et al. study also provided a table for patient demographics, yet provided no information about participant race or ethnicity. Their demographic characteristics simply included participants' age, BMI, and baseline FSH, LH, and E₂ levels. Finally, the Vandermolen et al. study provided a table for patient

characteristics both before and after treatment, but similarly to the previous two studies, only included characteristics about the participants' age, weight, BMI, insulin/glucose levels, and various hormone levels.

While the remaining five studies did report on patient demographic information for each of their study subjects, the degree of racial/ethnic representation varied significantly. Three studies (Legro et al. (2007), Legro et al. (2014), and Mejia et al.) had an overwhelmingly white population base. First, while the Legro et al. (2007) study ensured that the baseline characteristics and demographic representation across the three treatment groups were as similar as possible, all three groups had a disproportionate representation of white women (70.7%, 67.6%, and 71.2% white in each cohort group, respectively). Hispanic or Latino women had the next highest representation, but at much lower percentages (25.4%, 29.3%, and 23.9% in each cohort group, respectively), followed by Blacks (17.8%, 19.3%, and 15.4%, respectively), American Indian or Alaska Native (10.1%, 13.0%, and 11.5%, respectively), Asian (2.4%, 2.4%, 3.4%, respectively), and Native Hawaiian or Pacific Islander (0.5%, 0%, and 0%, respectively).¹ Next, the Legro et al. (2014) study also had a disproportionate race/ethnicity ratio. Across the two comparison groups (Clomiphene group versus Letrozole group), the majority of patients identified as white (80.3% and 77.0%, respectively), followed by Hispanic/Latinos (18.1% and 16%, respectively), Blacks (11.7% and 15%, respectively), Asian (3.2% and 3.2%, respectively), and mixed race (3.2% and 4%, respectively).¹ Finally, the Mejia et al. study had perhaps the most disproportionate racial/demographic representation among the recruited participants. Across the two

¹ Summed percentages across all racial and ethnic groups may sum to greater than 100% because participants were allowed to choose more than one racial category

comparison groups (Letrozole versus Letrozole + Clomiphene), an overwhelming majority of participants identified as White (83% and 86%, respectively), followed by Hispanic or Latino (6% and 6%, respectively), Blacks (6% and 3%, respectively), Asians (3% and 3%, respectively), and mixed race (3% and 3%, respectively).

On the contrary, were two studies whose participant demographics involved predominantly women of color. First, the Aubuchon et al. study included 5 Black participants, 2 white participants, and 1 Southeast Asian participant. Finally, the Khorram et al. study recruited participants that all identified as women of color. Across the two comparison groups (Metformin group versus Clomiphene group), the majority of participants identified as Hispanic/Latino (94% and 93%, respectively), followed by one person who identified as white in the Metformin group (6%), and one person who identified as Black in the Clomiphene group (7%).

Ovulation Outcomes Compared Across Race/Ethnicity

Six of the eight studies focused on rates of ovulation as either their primary or secondary outcomes. Of these six studies, four studies assessed whether additive drug treatments taken in combination are more efficacious than single drug treatments in improving rates of ovulation among women diagnosed with PCOS. First, the Cataldo et al. study assessed whether a combination of Clomiphene Citrate in combination with Metformin ER could 1) improve ovulation induction, and 2) lower the threshold dose of clomiphene needed to induce ovulation. The study found that 83% of participants who received the combination therapy ovulated, while 75% of participants who received just Clomiphene Citrate plus a

placebo ovulated ($p = 0.04$). However, the study also found that The frequency distribution of the lowest clomiphene dose (50, 100, or 150 mg daily) resulting in ovulation was indistinguishable between the two treatment groups (Ovulation in 52.2% in intervention vs. 45.5% in control for 50mg dose, ovulation in 20.6% in intervention vs. 18.1% in control for 100mg dose, ovulation in 5.7% in intervention vs. 8.1% in control for 150mg dose; $p = 0.47$). Mirroring a similar study design, the Khorram et al. study assessed whether participants who received a combination of Metformin plus Clomiphene Citrate experienced distinguishable rates of ovulation in comparison with patients who were prescribed Clomiphene Citrate alone. The findings illustrated that 44% of patients who received the combination drug treatments ovulated, while only 6.7% of participants who received Clomiphene Citrate alone ovulated ($p = 0.037$). The Legro et al. (2007) study involved a triple-armed randomized controlled trial, whereby patients either received Clomiphene alone, Metformin alone, or a combination of the two drug treatments at the same time. The findings from this study illustrated that participants in the Clomiphene only group ovulated an average of 2.22 times during the study cycle ± 1.87 , while participants in the Metformin-only group ovulated an average of 1.43 times ± 1.72 , and the combination drug therapy group ovulated an average of 2.80 times ± 2.04 ; $p < 0.001$ for all three groups. Finally, the Mejia et al. study assessed whether Letrozole alone or in combination with Clomiphene Citrate would increase ovulation rates. They found that 42.9% of individuals randomized to Letrozole treatment alone ovulated, while 77.1% of individuals randomized to the Letrozole + Clomiphene Citrate treatment group ovulated ($p = 0.007$). In all four of these studies, the researchers were able to assert that combination drug treatments were

statistically significantly more efficacious than single-drug treatments in improving ovulation rates among women with PCOS. Across these four studies that assessed additive drug treatments, none of the studies stratified their findings across race or ethnicity groups.

Two additional studies also assessed ovulation outcomes, but compared solo drug treatments - either against a different drug treatment, or against a placebo. First, the Legro et al. (2014) study assessed whether Letrozole or Clomiphene was more efficacious in improving ovulation rates among women with PCOS. The study concluded that 76.6% of women who were randomized to the Clomiphene group ovulated, while 88.5% of women who were randomized to the Letrozole group ovulated ($p < 0.001$). Additionally, the Vandermolen et al. study assessed whether Metformin could improve the ovulatory rate of women with Clomiphene Citrate-resistant PCOS compared to a placebo treatment. The study found that 75% of women who received the Metformin treatment ovulated, while 27% of the women who received the placebo treatment ovulated ($p = 0.02$). It is clear that neither of these two studies stratified their results across race or ethnicity.

Conception Outcomes Compared Across Race/Ethnicity

Four out of the eight studies assessed rates of conception among patients who ovulated. Of these four studies, the Mejia et al.'s findings were found to not be statistically significant ($p = 0,709$). Of the three remaining studies, two studies assessed whether additive drug treatments taken in combination were more efficacious than single drug treatments in improving conception rates among these women with PCOS. First, the Khorram et al. study

found that five study subjects in the combination Clomiphene plus Metformin group conceived, while none of the study subjects in the Clomiphene group alone conceived ($p = 0.043$). Additionally, the Legro et al. (2007) study found that 39.5% of study subjects who received Clomiphene treatment ovulated ($p = 0.002$), compared to 21.7% who were randomized to the Metformin treatment group ($p = 0.002$), and 46% randomized to the combination therapy group of both Clomiphene plus Metformin ($p < 0.001$). Neither of these studies stratified their results across race or ethnicity groups.

The Legro et al. (2014) study assessed conception rates among study subjects who ovulated between solo-drug treatment comparison groups. They found that 35.8% of study subjects who received Clomiphene alone ovulated, while 46.5% of study subjects who received Letrozole alone ovulated ($p = 0.007$). Similar to the Khorram et al. and Legro et al. (2007) studies above, the Legro et al. (2014) study did not stratify their results across race or ethnicity groups.

Pregnancy Outcomes Compared Across Race/Ethnicity

Five of the eight studies assessed pregnancy outcomes across the various treatment groups. Among these five studies, both the Mejia et al. and the Stadtmauer et al. studies produced pregnancy outcomes that were not statistically significant ($p = 0.356$ and $p = 0.16$, respectively). Of the remaining three studies, the Legro et al. (2007) study was the only trial to assess pregnancy outcomes across single versus additive drug treatments. They found that 23.9% of women who were randomized to the Clomiphene treatment group became

pregnant, compared to 8.7% for those randomized to Metformin, and 31.1% randomized to the combination therapy group of both Clomiphene plus Metformin ($p < 0.001$). Meanwhile, the Legro et al (2014) study compared Clomiphene versus Letrozole in assessing pregnancy outcomes. This study found that 21.5% of women randomized to the Clomiphene treatment group became pregnant, compared to the 31.3% randomized to the Letrozole treatment group ($p = 0.003$). Finally, the Vandermolen et al. study assessed pregnancy rates across the Metformin versus placebo intervention groups. They concluded that 55% of individuals randomized to the Metformin treatment group became pregnant, compared to 7% who were randomized to the placebo group ($p = 0.02$). Thorough analysis of these articles found that none of the above studies reported or stratified findings across race or ethnicity metrics.

Live Birth Rate Outcomes Compared Across Race/Ethnicity

Four of the eight studies assessed live birth rate outcomes among women who became pregnant. Among these four studies, the Mejia et al. and the Stadtmauer et al. studies produced findings that were not statistically significant ($p = 1.00$ and $p = 0.08$, respectively). The Legro et al. (2007) study assessed live birth rate outcomes across single versus additive drug treatments and found that 22.5% of individuals randomized to receiving Clomiphene treatment successfully had a live birth, yet this finding was found to be statistically insignificant ($p = 0.31$). However, 7.2% of individuals randomized to the Metformin group had a successful live birth, and 26.8% randomized to the combination therapy group experienced a live birth; $p < 0.001$ for both groups. Finally, the Legro et al. (2014) study compared Clomiphene versus Letrozole treatments in assessing live birth rates. This study

found that 19.1% of individuals randomized to Clomiphene-only experienced live birth, while 27.5% of individuals randomized to Letrozole-only experienced live birth, $p = 0.007$. None of the four above studies that assessed live birth rate outcomes stratified findings across race or ethnicity metrics.

Table 3: Statistical Findings, Study Results, and Study Conclusions of Reviewed Studies

Author & Year	Title	Statistical Findings & Study Results	Study Conclusions & Racial Stratification of Findings
Aubuchon et al. (2009)	Metformin Does Not Improve the Reproductive or Metabolic Profile in Women with Polycystic Ovary Syndrome (PCOS)	<p>Urinary FSH levels (4.3 ± 1.4 versus 4.7 ± 1.68 U/g, $p = 0.48$), and LH levels (7.1 ± 5.2 versus 7.5 ± 3.6 U/g, $p = 0.26$), and Pdg (0.92 ± 0.69 versus 1.1 ± 1.0 $\mu\text{g}/\text{mg}$, $p = 0.40$) did not differ significantly between the metformin and the placebo groups</p> <p>Two participants ovulated on both placebo and metformin treatments</p> <p>Urinary gonadotropins were not statistically significantly different before and after metformin, whether or not the participants who ovulated were included</p> <p>Serum sex steroid response to metformin and placebo were not statistically significant ($p > 0.16$ for all secondary outcomes).</p> <p>BMI-normalized biomarkers were not statistically significant between metformin and placebo groups</p>	<p>Short-term, high-dose metformin has minimal effects on metabolic markers and reproductive hormones in a small sample of obese women with PCOS</p> <p>The study hypothesis that metformin (via increased insulin sensitivity and SHBG), reduces free sex steroids and induces a compensatory FSH rise</p> <p>There was minimal effectiveness of metformin in promoting insulin sensitivity</p> <p>Study results were not stratified by racial/ethnic group</p>
Cataldo et al. (2008)	Extended-Release Metformin Does Not Reduce the Clomiphene Citrate Dose Required to Induce Ovulation in Polycystic Ovary Syndrome	<p>At least one ovulation occurred in 174/209 subjects (83%) in the clomiphene plus metformin group, and at least one ovulation occurred in 157/209 subjects (75%) in the clomiphene-only group ($p = 0.04$).</p> <p>The frequency distribution of the lowest clomiphene dose (50, 100, or 150 mg daily) resulting in ovulation was indistinguishable between the two treatment groups (Ovulation in 52.2% in intervention vs. 45.5% in control for 50mg dose, ovulation in 20.6% in intervention vs. 18.1% in control for 100mg dose, ovulation in 5.7% in intervention vs. 8.1% in control for 150mg dose; $p = 0.47$).</p>	<p>Patients who received the combination drug treatment of Clomiphene plus Metformin had a greater rate of ovulation than patients who received Clomiphene-only plus the placebo treatment.</p> <p>Metformin XR does not reduce the lowest dose of clomiphene that induces ovulation in women with PCOS</p> <p>Study results were not stratified by racial/ethnic group</p>

<p>Khorram et al. (2006)</p>	<p>Two Weeks of Metformin Improves Clomiphene Citrate-Induced Ovulation and Metabolic Profiles in Women with Polycystic Ovary Syndrome</p>	<p>Both groups found a significant increase in the sex hormone-binding globulin (SHBG) levels after treatment on day 21 of the cycle, but the increment in SHBG in the CC+Met group was significantly higher ($p < 0.05$) than in the CC-only group.</p> <p>There was a significant decrease in fasting insulin ($p < 0.025$) and ratio of glucose to insulin ($p < 0.05$) in the CC+Met group, but not in the CC-only group.</p> <p>On day 21, Serum P levels was significantly elevated in the CC+Met group in contrast to the CC-only group ($p = 0.015$)</p> <p>In the CC+Met group, 7/16 subjects (44%) ovulated, whereas only 1/15 subjects (6.7%) ovulated in the CC-only group ($p = 0.037$)</p> <p>In the CC+Met group, 5 subjects conceived, whereas no subjects in the CC-only treatment conceived ($p = 0.043$).</p>	<p>In obese patients with PCOS, two weeks of Metformin treatment significantly reduces serum insulin and insulin resistance and increases SHBG levels, resulting in an improved response to Clomiphene Citrate</p> <p>Study results were not stratified by racial/ethnic group</p>
<p>Legro et al. (2007)</p>	<p>Clomiphene, Metformin, or Both for Infertility in the Polycystic Ovary Syndrome</p>	<p>Live birth rates:</p> <ul style="list-style-type: none"> ● Clomiphene Group: 47/209 (22.5%); $p = 0.31$ ● Metformin Group: 15/208 (7.2%); $p < 0.001$ ● Combination Therapy Group: 56/209 (26.8%); $p < 0.001$ <p>Number of ovulations (Mean \pm SD):</p> <ul style="list-style-type: none"> ● Clomiphene Group: 2.22 ± 1.87; $p < 0.001$ ● Metformin Group: 1.43 ± 1.72; $p < 0.001$ ● Combination Therapy Group: 2.80 ± 2.04; $p < 0.001$ <p>Pregnancy:</p> <ul style="list-style-type: none"> ● Clomiphene Group: 50/209 (23.9%); $p < 0.001$ ● Metformin Group: 18/208 (8.7%); $p < 0.001$ ● Combination Therapy Group: 65/209 (31.1%); $p < 0.001$ 	<p>Live birth rates were significantly lower in the Metformin group than in either the Clomiphene or Combination Therapy Group. Ovulation rates were significantly higher in the combination group than in either the Clomiphene or Metformin groups alone, however this did not translate into an increase in live-birth rates among subjects who received the combination therapy treatments. Rates of conception and pregnancy were significantly higher in the Clomiphene and Combined Therapy Group than in the Metformin group. These findings show that Clomiphene is superior to metformin in achieving live birth in women with PCOS-related infertility</p> <p>Study results were not stratified by racial/ethnic group</p>

		<p>Conception rates among subjects who ovulated:</p> <ul style="list-style-type: none"> ● Clomiphene Group: 62/157 (39.5%); p = 0.002 ● Metformin Group: 25/115 (21.7%); p = 0.002 ● Combination Therapy Group: 80/174 (46.0%); p<0.001 	
Legro et al. (2014)	Letrozole Versus Clomiphene for Infertility in the Polycystic Ovary Syndrome	<p>Live birth rates:</p> <ul style="list-style-type: none"> ● Clomiphene Group: 72/376 (19.1%); p = 0.007 ● Letrozole Group: 103/374 (27.5%); p = 0.007 <p>Ovulation Rates:</p> <ul style="list-style-type: none"> ● Clomiphene Group: 288/376 (76.6%); p<0.001 ● Letrozole Group: 331/374 (88.5%); p<0.001 <p>Pregnancy Rates:</p> <ul style="list-style-type: none"> ● Clomiphene Group: 81/376 (21.5%); p = 0.003 ● Letrozole Group: 117/374 (31.3%); p = 0.003 <p>Pregnancy Loss Among Women Who Conceived:</p> <ul style="list-style-type: none"> ● Clomiphene Group: 30/103 (29.1%); p = 0.65 ● Letrozole Group: 49/154 (31.8%); p = 0.65 <p>Conception rates among subjects who ovulated:</p> <ul style="list-style-type: none"> ● Clomiphene Group: 103/288 (35.8%); p = 0.007 ● Letrozole Group: 154/331 (46.5%); p = 0.007 <p>Congenital Anomalies:</p> <ul style="list-style-type: none"> ● Clomiphene Group: 1/66 (1.5%); p = 0.65 ● Letrozole Group: 4/102 (3.9%); p = 0.65 	<p>Women who received Letrozole had more cumulative live births than those who received Clomiphene Citrate. The cumulative ovulation rates were higher in those who received Letrozole treatment than Clomiphene. There were no significant between-group differences in pregnancy loss between the two treatment groups. Conception rates among subjects who ovulated were 10% higher in the Letrozole group than the Clomiphene group.</p> <p>Study findings/results stratified by race/ethnicity were not reported</p>

<p>Mejia et al. (2019)</p>	<p>A Randomized Controlled Trial of Combination Letrozole and Clomiphene Citrate or Letrozole Alone for Ovulation Induction in Women with Polycystic Ovary Syndrome</p>	<p>Rates of Ovulation:</p> <ul style="list-style-type: none"> ● Letrozole Group: 15/35 (42.9%); p = 0.007 ● Letrozole + Clomiphene Group: 27/35 (77.1%); p = 0.007 <p>Conception Rates:</p> <ul style="list-style-type: none"> ● Letrozole Group: 3/35 (8.8%); p = 0.709 ● Letrozole + Clomiphene Group: 4/35 (12.1%); p = 0.709 <p>Clinical Pregnancy:</p> <ul style="list-style-type: none"> ● Letrozole Group: 1/35 (2.9%); p = 0.356 ● Letrozole + Clomiphene Group: 3/35 (9.1%); p = 0.356 <p>Fecundity among those who ovulated:</p> <ul style="list-style-type: none"> ● Letrozole Group: 3/14 (21%); p = 0.686 ● Letrozole + Clomiphene Group: 4/25 (16%); p = 0.686 <p>Live Birth Rates:</p> <ul style="list-style-type: none"> ● Letrozole Group: 1/14 (7%); p = 1.00 ● Letrozole + Clomiphene Group: 3/25 (12%); p = 1.00 <p>There were no significant adverse events related to the treatments during the course of the study</p>	<p>Women who received the combination treatment of Letrozole and Clomiphene had a statistically significantly higher rate of ovulation compared to individuals who received the letrozole treatment alone.</p> <p>There were no statistically significant differences in conception, pregnancy, and fecundity rates between the two treatment groups. Significant adverse events related to the treatments did not occur during the study. Participants in both groups reported similar acceptability of side-effects</p> <p>Study results were not stratified by racial/ethnic group</p>
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<p>Stadtmauer et al. (2011)</p>	<p>The Impact of a Gonadotropin-Releasing Hormone Antagonist on Gonadotropin Ovulation Induction Cycles in Women with Polycystic Ovary Syndrome: A Prospective Randomized Study</p>	<p>Primary Outcomes:</p> <ul style="list-style-type: none"> ● Per cycle clinical pregnancy rate (CPR); p = 0.16: <ul style="list-style-type: none"> ○ Group 1 (Follistim): 12/50 (24%) ○ Group 2 (Follistim + Ganirelix if FS\geq13mm): 19/51 (37%) ○ Group 3 (Follistim + Ganirelix): 9/41 (22%) ● Live birth rate (LBR); p = 0.08: <ul style="list-style-type: none"> ○ Group 1 (Follistim): 10/50 (20%) ○ Group 2 (Follistim + Ganirelix if FS\geq13mm): 18/51 (35%) ○ Group 3 (Follistim + Ganirelix): 7/41 (18%) <p>Secondary Outcomes:</p> <p>Premature luteinization was highest in group 1 (21% vs. 1.8% in group 2 and 2.1% in Group 3). Group 3 had the highest cancellation rate and cost without improving CPR and LBR. No differences were noted in peak serum E2, total gonadotropin dose, or days of stimulation</p>	<p>While clinical pregnancy rates were the greatest in Group 2 compared to groups 1 and 3, the results were not statistically significant. Similarly, live birth rates were highest in Group 2 compared to groups 1 and 3, but results were just out of margins of statistical significance</p> <p>Adding Ganirelix in a flexible protocol to gonadotropin OI cycles in women with PCOS may be beneficial by decreasing premature luteinization</p> <p>Study results were not stratified by racial/ethnic group</p>
<p>Vandermolen et al. (2001)</p>	<p>Metformin Increases the Ovulatory Rate and Pregnancy Rate From Clomiphene Citrate in Patients with Polycystic Ovary Syndrome who are Resistant to Clomiphene Citrate Alone</p>	<p>Rates of Ovulation:</p> <ul style="list-style-type: none"> ● Metformin Group: 9/12 (75%); p = 0.02 ● Placebo Group: 4/15 (27%); p = 0.02 <p>Pregnancy Rates:</p> <ul style="list-style-type: none"> ● Metformin Group: 6/11 (55%); p = 0.02 ● Placebo Group: 1/14 (7%); p = 0.02 	<p>In anovulatory women with PCOS who are resistant to Clomiphene Citrate, Metformin was found to significantly increase ovulation rates and pregnancy rates. These results provide a rationale and justification for the use of Metformin and Clomiphene Citrate treatment for obese Clomiphene Citrate resistant women with PCOS before proceeding to ovulation induction with gonadotropins or to in-vitro fertilization/embryo transfer (IVF/ET). Furthermore, it is clear that Metformin treatment is less expensive compared to gonadotropins and IVF/ET.</p> <p>Study results were not stratified by racial/ethnic group</p>

DISCUSSION

With knowledge that Polycystic Ovary Syndrome is a condition that tends to disproportionately affect minority women of color, the primary objective of this meta research project was to critically assess racial representation in the methodology and recruitment in randomized controlled trials and clinical trials for studies on PCOS-related infertility. Across the eight studies that were identified in the final search criteria, three studies (37.5%) failed to report the race or ethnicity of the enrolled participants. Meanwhile, while five studies (62.5%) did provide information about the patients' racial and demographic characteristics, three of the studies (37.5%) involved an overwhelming majority of white women, with women of color comprising a very small proportion of the overall study population. While there were two studies (25%) whose study recruitment involved predominantly women of color, these studies had a very small sample size. The Khorram et al. study contained a total sample size of 31 participants, while the Aubuchon et al. study had a total sample of 8 participants. While both of these studies recruited predominantly women of color, it is unclear whether this was due to chance alone, or whether the diversity of these individuals were intentionally recruited.

In assessing all eight of the included studies, none of the authors outlined the recruitment methodology procedures nor sampling techniques leveraged when selecting participants for these clinical trials. For the five studies who reported on patient demographics, the only information provided was a baseline characteristics table, which outlined the facets such as the average age, BMI, and race/ethnicity of the study subjects. However, the methods section for these individual studies failed to provide an adequate explanation about the sampling techniques they deployed,

or the rationale behind who they included in their sampling framework. Despite the fact that five of the eight studies included information about patient demographics, none of these studies stratified the primary or secondary results based on these racial or ethnic categories. As such, when assessing the various outcome measures (such as ovulation rates, conception, and fertility outcomes), it was impossible to discern whether these findings were representative of all patients, or whether there were disparate outcomes across various patient demographic groups.

Despite efforts to ensure a high degree of evidence synthesis for this meta research project, this study had some limitations. As a solo researcher, I had to contend with the challenges of independently determining the best and optimal design for my study inclusion methodology, including selecting which academic databases to leverage, outlining my search strategy with consistency across all sites, and determining which studies to filter and screen during the inclusion and exclusion phase. Traditionally, these types of review processes would be best executed alongside a robust team of academic researchers, statisticians, database research scientists, and subject matter experts - all of whom can work together to cross-validate decisions. Additionally, this study was significantly limited by the fact that only 8 final studies survived the inclusion/exclusion criteria to be included in the final assessment. As I navigated the process of filtering through studies based on the defined inclusion and exclusion criteria, I realized that a significant majority of the published studies across the five databases were conducted in international contexts, such as China, India, Iran, Finland, and Saudi Arabia. While many of these international studies did assess the four major pharmacotherapy drug treatments of interest among women with PCOS-related infertility, it is clear that the racial and ethnic demographics of individuals in the aforementioned countries are largely homogeneous. With the U.S. serving as a

melting pot of different cultures and ethnicities, including these homogeneous population groups from international settings would not only be out of scope of this research question, but would detract from our understanding of whether clinical trial recruitment strategies in the U.S. are representative of the true population affected by PCOS-related infertility. Consequently, when these international studies were filtered out, this left a very small final sample of studies to be assessed in this meta research paper, which made generalizing findings rather difficult.

Another significant limitation that I encountered during this process was the fact that each of the eight studies had different intervention and outcome measures. Given that my final inclusion criteria included any combination of the pharmacotherapy drug treatments of Clomiphene, Letrozole, Metformin, or Gonadotropins, there were no two studies that had the same study methodology or design. For example, some studies assessed the role of additive versus singular drug treatments on fertility-related outcomes (such as Clomiphene + Metformin vs. Clomiphene alone), while other studies assessed a single drug treatment against a placebo. Therefore, comparing results across these eight studies was difficult to accomplish.

It is clear that clinical trials and academic research studies in the U.S. are all required to follow a strict set of protocols and procedures in order to ensure safety to study subjects, maintain strong ethical procedures, and minimize sources of error and biases. Through metrics such as Cochrane's Risk of Bias Tool for Randomized Trial (RoB 2) or the Joanna Brigg's Institute (JBI) Checklist for Critical Appraisal in RCTs and Clinical Trials, clear and guided procedures have been developed in order to ensure the methodological quality of these various studies. However, it is evident that these checklists and toolkits fail to include metrics that require these clinical trials and RCTs to include diverse sampling procedures in their methodology. The United States

is a nation full of rich racial and ethnic diversity. Over the years, the racial representation of the U.S. has taken a shift, with people of color slowly surpassing white individuals as the emerging majority population group. With knowledge of our nation's deeply rooted history of oppression perpetuated against minority people of color, it is clear that these facets of structural inequities and racism have played a pervasive role in generating social disadvantage and health disparities among people of color. As such, it is clear that the future directions of academic studies and clinical trials must take into account the racial and ethnic diversity of the U.S. population in order to determine whether these populations are disproportionately affected by certain disease outcomes.

By failing to include racial and ethnic representation in clinical trial studies, there continues to be a significant gap in our understanding of the various factors that may contribute to inequitable and disproportionate burdens of health among minority populations. It is clear that the eight studies included in this meta research project, as well as all other studies could be strengthened by robust metrics that ensure diverse representation, such as the inclusion of an axis of diversity sampling matrix by which demographic characteristics can be operationalized. Additionally, organizations or programs that involve the critical review or appraisal of academic studies and clinical trials must incorporate diverse frameworks and checklists to ensure sound representation across various population demographic factors. By re-prioritizing the way we approach the methodology and recruitment strategies of clinical trials, we can help to make promising strides in our path towards population health equity in healthcare and medicine.

APPENDICES

Appendix A: Search Strategy for Ovid MEDLINE:

Ovid MEDLINE(R) Search Strategy		
	Keyword Search	Number of Studies Yielded
1	exp Polycystic Ovary Syndrome/	16526
2	Polycystic Ovary Syndrome.tw.	14536
3	Polycystic Ovar\$.tw.	19195
4	PCOS.tw.	13347
5	PCOD.tw.	305
6	Stein-Leventhal Syndrome.tw.	566
7	Clomiphene.tw.	5258
8	exp Clomiphene/	5389
9	Letrozole.tw.	3333
10	exp Letrozole/	2326
11	Metformin.tw.	24358
12	exp Metformin/	16221
13	Gonadotropins.tw.	11282
14	exp Gonadotropins/	128948
15	exp Ovulation Induction/	14314
16	exp Ovulation/	26452
17	exp Fertility/	44401
18	exp Infertility/	70960
19	Randomized Controlled Trial.pt.	565060
20	Controlled Clinical Trial.pt.	94818
21	Randomized.ab.	557686
22	Randomised.ab.	110840
23	Clinical Trials as topic.sh.	199700
24	exp Animals/ not humans.sh.	4993841
25	((1 or 2 or 3 or 4 or 5 or 6) and (7 or 8 or 9 or 10 or 11 or 12 or 13 or 14) and (15 or 16 or 17 or 18) and (19 or 20 or 21 or 22 or 23)) not 24	541
26	limit 25 to (english language and yr="1999 - 2021" and (clinical study or clinical trial, all or clinical trial or controlled clinical trial or randomized controlled trial))	303

Appendix B: Search Strategy for PubMed:

PubMed Search Strategy		
	Keyword Search	Number of Studies Yielded
1	"Polycystic Ovary Syndrome" [MeSH Terms]	16526
2	"Polycystic Ovary Syndrome [Title/Abstract]	14783
3	Polycystic Ovar* [Title/Abstract]	19387
4	"PCOS" [Title/Abstract]	13539
5	"PCOD" [Title/Abstract]	320
6	"Stein-Leventhal Syndrome" [Title/Abstract]	750
7	"Clomiphene" [Title/Abstract]	5329
8	Clomiphene [MeSH Terms]	5389
9	"Letrozole" [Title/Abstract]	3385
10	Letrozole [MeSH Terms]	2327
11	"Metformin" [Title/Abstract]	24761
12	Metformin [MeSH Terms]	16224
13	"Gonadotropins" [Title/Abstract]	15533
14	Gonadotropins [MeSH Terms]	128949
15	Ovulation Induction [MeSH Terms]	14313
16	Ovulation [MeSH Terms]	26450
17	Fertility [MeSH Terms]	44397
18	Infertility [MeSH Terms]	70960
19	(Animals [MeSH Terms]) NOT (Humans [MeSH Terms])	4993555
20	((#1 OR #2 OR #3 OR #4 OR #5 OR #6) AND (#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14) AND (#15 OR #16 OR #17 OR #18) NOT (#19))	2144
21	((#1 OR #2 OR #3 OR #4 OR #5 OR #6) AND (#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14) AND (#15 OR #16 OR #17 OR #18) NOT (#19)) Filters: Clinical Trial, Randomized Controlled Trial, from 1999 - 2021	386
<p>Final Search Strategy: (((("Polycystic Ovary Syndrome"[MeSH Terms] OR "Polycystic Ovary Syndrome"[Title/Abstract] OR "polycystic ovar*"[Title/Abstract] OR "PCOS"[Title/Abstract] OR "PCOD"[Title/Abstract] OR "Stein-Leventhal Syndrome"[Title/Abstract]) AND ("Clomiphene"[Title/Abstract] OR "Clomiphene"[MeSH Terms] OR "Letrozole"[Title/Abstract] OR "Letrozole"[MeSH Terms] OR "Metformin"[Title/Abstract] OR "Metformin"[MeSH Terms] OR "Gonadotropins"[Title/Abstract] OR "Gonadotropins"[MeSH Terms]) AND ("ovulation induction"[MeSH Terms] OR "ovulation"[MeSH Terms] OR "fertility"[MeSH Terms] OR "infertility"[MeSH Terms])) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])) AND ((clinicaltrial[Filter] OR randomizedcontrolledtrial[Filter]) AND (1999:2021[pdat]))</p>		

Appendix C: Search Strategy for Scopus:

Scopus Search Strategy			
	Keyword Search	Search Within	Number of Studies Yielded
1	{Polycystic Ovary Syndrome}	Title/Abstract/Keyword	22008
2	"Polycystic Ovar*"	Title/Abstract/Keyword	25793
3	{PCOS}	Title/Abstract/Keyword	16309
4	{PCOD}	Title/Abstract/Keyword	458
5	"Stein Leventhal"	Title/Abstract/Keyword	1140
6	#1 OR #2 OR #3 OR #4 OR #5		27308
7	Clomiphene	Title/Abstract/Keyword	8037
8	Clomifene	Title/Abstract/Keyword	12540
9	Letrozole	Title/Abstract/Keyword	11639
10	Metformin	Title/Abstract/Keyword	65473
11	Gonadotropin*	Title/Abstract/Keyword	129969
12	#7 OR #8 OR #9 OR #10 OR #11		210390
13	{Ovulation Induction}	All Fields	30569
14	Ovulation	All Fields	144907
15	Fertility	All Fields	980361
16	Infertility	All Fields	270945
17	13 OR #14 OR #15 OR #16		11391716
18	Randomi?ed Control* Trial	Title/Abstract/Keyword	959708
19	{RCT}	Title/Abstract/Keyword	35831
20	Randomi?ed	Title/Abstract/Keyword	1219516
21	Clinical Trial*	Title/Abstract/Keyword	2012380
22	Controlled Clinical Trial*	Title/Abstract/Keyword	1138787
23	#18 OR #19 OR #20 OR #21 OR #22		2422607
24	#6 AND #12 AND #17 AND #23		2180
25	Filter by Date: 1999 - 2021		1980
26	Limit to English		1876
27	Limit to Final Publication Stage		1866

FINAL SEARCH STRATEGY: ((TITLE-ABS-KEY ({polycystic ovary syndrome})) OR (TITLE-ABS-KEY ("polycystic ovar*")) OR (TITLE-ABS-KEY ({pcos})) OR (TITLE-ABS-KEY ({pcod})) OR (TITLE-ABS-KEY ("stein leventhal"))) AND ((TITLE-ABS-KEY (clomiphene)) OR (TITLE-ABS-KEY (clomifene)) OR (TITLE-ABS-KEY (letrozole)) OR (TITLE-ABS-KEY (metformin)) OR (

TITLE-ABS-KEY (gonadotropin*)) AND ((ALL ({ovulation induction})) OR (ALL (ovulation)) OR (ALL (fertility)) OR (ALL (infertility))) AND ((TITLE-ABS-KEY (randomi?ed AND control* AND trial)) OR (TITLE-ABS-KEY ({rct})) OR (TITLE-ABS-KEY (randomi?ed)) OR (TITLE-ABS-KEY (clinical AND trial*)) OR (TITLE-ABS-KEY (controlled AND clinical AND trial*))) AND (LIMIT-TO (PUBSTAGE , "final")) AND (LIMIT-TO (PUBYEAR , 2021) OR LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2019) OR LIMIT-TO (PUBYEAR , 2018) OR LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2013) OR LIMIT-TO (PUBYEAR , 2012) OR LIMIT-TO (PUBYEAR , 2011) OR LIMIT-TO (PUBYEAR , 2010) OR LIMIT-TO (PUBYEAR , 2009) OR LIMIT-TO (PUBYEAR , 2008) OR LIMIT-TO (PUBYEAR , 2007) OR LIMIT-TO (PUBYEAR , 2006) OR LIMIT-TO (PUBYEAR , 2005) OR LIMIT-TO (PUBYEAR , 2004) OR LIMIT-TO (PUBYEAR , 2003) OR LIMIT-TO (PUBYEAR , 2002) OR LIMIT-TO (PUBYEAR , 2001) OR LIMIT-TO (PUBYEAR , 2000) OR LIMIT-TO (PUBYEAR , 1999)) AND (LIMIT-TO (LANGUAGE , "english"))

Appendix D: Search Strategy for Ovid Embase:

Ovid Embase Search Strategy		
	Keyword Search	Number of Studies Yielded
1	exp ovary polycystic disease/	31479
2	exp ovary cyst/	44127
3	Polycystic Ovary Syndrome.tw.	19984
4	Polycystic Ovar\$.tw.	26886
5	PCOS.tw.	20167
6	PCOD.tw.	442
7	Stein-Leventhal Syndrome.tw.	230
8	Clomiphene.tw.	6672
9	exp Clomifene/	6341
10	Letrozole.tw.	6355
11	Metformin.tw.	41399
12	Gonadotropin*.tw.	60097
13	exp Gonadotropin/	27748
14	exp Superovulation/	3179
15	exp Ovulation Induction/	17085
16	exp Hormonal Therapy/	303910
17	exp Ovulation/	25947
18	Fertility.tw.	109319
19	Infertility.tw.	82880
20	"Clinical Trial*".tw.	619296
21	exp Clinical Trial/	1689749
22	Randomi?ed Controlled Trial\$.tw.	283084
23	exp Randomized Controlled Trial/	706430
24	Rct.tw.	46392
25	Randomized.tw.	870359
26	Randomised.tw.	174360
27	((1 or 2 or 3 or 4 or 5 or 6 or 7) and (8 or 9 or 10 or 11 or 12 or 13) and (14 or 15 or 16 or 17 or 18 or 19) and (20 or 21 or 22 or 23 or 24 or 25 or 26))	1529
28	limit 27 to (ovid full text available and full text and human and english language and "remove preprint records" and yr="1999 - 2021")	47

Appendix E: Search Strategy for Web of Science:

Web of Science Search Strategy			
	Keyword Search	Search Within	Number of Studies Yielded
1	Polycystic Ovary Syndrome	Topic	20946
2	"Polycystic Ovar*"	Topic	24918
3	PCOS	Topic	14542
4	PCOD	Topic	257
5	Stein-Leventhal Syndrome	Topic	252
6	Clomiphene	Topic	5447
7	Letrozole	Topic	5903
8	Metformin	Topic	36664
9	Gonadotropins	Topic	11884
10	Ovulation Induction	All Fields	8776
11	Ovulation	All Fields	37994
12	Fertility	All Fields	228136
13	Infertility	All Fields	70209
14	Randomized Control* Trial	Topic	474045
15	RCT	Topic	30243
16	Randomized	Topic	968036
17	Randomised	Topic	963698
18	Clinical Trial*	Topic	760585
19	Controlled Clinical Trial*	Topic	303704
20	((#1 OR #2 OR #3 OR #4 OR #5) AND (#6 OR #7 OR #8 OR #9) AND (#10 OR #11 OR #12 OR #13) AND (#14 OR #15 OR #16 OR #17 OR #18 OR #19))		767
21	Refine by Publication Years: 1999-2021, Open Access only, English Language		281

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