Myoinositol vs. Metformin: A Meta-Analytic Approach to Addressing PCOS-Induced Infertility

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ABSTRACT

Background: The condition of Polycystic Ovary Syndrome (PCOS) exists in more than 10% of women globally within their reproductive years and causes hormonal imbalance and insulin resistance together with infertility issues. The medications MET (metformin) and MI (Myoinositol) were found to relieve the symptoms of PCOS and associated challenges of insulin resistance, testosterone levels, and follicle-stimulating hormone (FSH).

Objective: The main goal of this study is to conduct a meta-analysis that evaluates the effects of Metformin and Myoinositol on HOMA-IR, testosterone and FSH markers in PCOS patients.
METHODS: A meta-analysis was conducted in this study to evaluate MET Vs. MI effectiveness on PCOS. The literature search based on PRISMA guidelines was conducted on six electronic databases (MEDLINE, EMBASE, PubMed, Scopus, Google Scholar, and ResearchGate) from 2010 to 2024. A total of thirty randomized clinical comparative studies with a comparison of Metformin and Myoinositol were selected based on exclusion and inclusion criteria. Statistical analysis through standardized mean differences (SMD) under a random-effects model to account for heterogeneity was conducted.

Results: The meta-analysis, including thirty randomized clinical comparative studies, showed that FSH levels between MET and MI were similar because the difference was statistically insignificant (SMD= -0.11, 95% CI: -0.44 to 0.22, I^2= 86%). Testosterone levels also showed no major differences among research studies, resulting in a nonsignificant outcome for MET (SMD= 0.61, 95% CI: -0.98 to 2.21, I^2= 98%). The medium but insignificant effect in HOMA-IR reduction was found when patients received MET (SMD= -0.24, 95% CI: -0.69 to 0.22, I^2= 92%). The wide range of patient characteristics during different treatment periods appeared to cause high heterogeneity across analyzed studies.

Conclusion: Both Metformin and Myoinositol show similar effects on FSH, testosterone, and insulin resistance in PCOS patients. The analysis results demonstrated that MET enhanced insulin sensitivity, although it failed to produce statistically significant data for PCOS patients.

Future research needs to investigate the long-term outcomes together with developing personalized therapeutic methods.
Keywords: *PCOS, Metformin, Myoinositol, Insulin Resistance, Testosterone, FSH, Meta-Analysis*

1. INTRODUCTION

Polycystic ovary syndrome (PCOS) is a hormonal disorder that affects more than 10% of women in the reproductive stage [1]. The medical condition presents with abnormal menstrual periods, increased body hair growth (hirsutism) due to increased testosterone, and several cyst formations in the ovaries. Women with central obesity, along with insulin resistance and PCOS, face an eight-time higher risk of developing type 2 diabetes [2]. PCOS also results in insulin resistance by 50 to 80% [3]. The mental state of affected individuals tends to face negative effects frequently.

Myoinositol (MI) works as an insulin sensitizer in the second messenger system of the follicle-stimulating hormone (FSH) signaling pathway; it exists naturally in citrus fruits and beans [4]. However, insufficient MI levels cause ovulatory problems in women who have PCOS [5]. Insulin sensitizers based on inositol compounds serve as potential treatments for PCOS. This naturally occurring compound, referred to as inositol, exists in nine stereoisomers where Myoinositol alongside D-chiro-inositol is abundant in human tissues [4-5]. Researchers have proven that Myoinositol leads to improved insulin sensitivity while the substance also contributes to producing inositol triphosphate, which serves as a second messenger that controls the activity of FSH hormones. MI stands as a natural food component sourced from sugar, which exists in legumes, nuts, fruits, and whole grains among the nine stereoisomers of inositol [5]. Within cellular structures, glucose 6-phosphate produces MI, while the substance exists in cell membranes bound to phospholipid chains as phosphatidylinositol. Testes and ovaries contain intracellular inositol, primarily as MI, which represents over 99% of this substance [6]. Phospholipid metabolism commences after the structural incorporation of phosphatidyl-MI into cell membranes to synthesize inositol triphosphate, which functions as a secondary signaling molecule that improves hormone signaling for thyroid-stimulating hormone and follicle-stimulating hormone and insulin [4-6]. The past comparative studies showed that the use of MI leads to higher insulin sensitivity, produces better oocyte quality, and reduces both hyperandrogenism and controls menstrual periods and the ovulation process and hirsutism [7]. Patients who are at risk of developing diabetes, together with women suffering from PCOS, experience better lipid profiles and less insulin resistance. These diabetes development risks are also reduced through MI treatment above Myoinositol. Medical research indicates that PCOS women using MI treatment show an improvement in ovulation frequency during their attempts at conception. The therapeutic effects of MI help to enhance fertility because it successfully

enhances insulin sensitivity and lowers triglycerides while normalizing testosterone concentrations [6-7].

Similarly, Metformin (MET) stands as a standard medication for insulin sensitivity problems in PCOS patients since it helps control insulin resistance and regulate menstrual cycles. Metformin mainly contains hydrochloride, represents the major component in the biguanide antidiabetic oral drug, and exists as a white crystalline water-soluble chemical compound. White powder crystals of Metformin have a molecular formula $C_4H_{11}N_5$ and dissolve in water [8]. The kidneys eliminate both substantial amounts of Metformin without transformation due to minimal metabolism processes. This medication works through three main actions diminishing hepatic glucose production while enhancing insulin sensitivity and raising glucose transport in peripheral tissues for its role as a principal treatment in type 2 diabetes. When obese women with PCOS take MET, they experience an average reduction in body mass index (BMI) by 1.25 kg/m^2 [8-9]. Studies have shown that MET co-administered with lifestyle treatments fails to enhance insulin sensitivity further than weight management alone since weight reduction remains the leading method to fight insulin resistance [9]. The improvement of menstrual cycles during MET dosing depends on improved insulin sensitivity, which results in direct modifications to ovarian insulin sensitivity. The gastrointestinal side effects of MET treatment led to frequent discontinuation of the medication [10]. Research studies demonstrate that Metformin helps patients by facilitating weight loss, lowering their insulin and lipid blood levels, decreasing blood pressure, and restoring menstrual cycles and ovulation while decreasing androgen levels [11]. The wide use of Metformin remains limited because of its negative gastrointestinal (GI) effects.

The medical benefits of Myoinositol treatment surpass Metformin by showing positive effects on metabolic and reproductive functions along with exhibiting no recorded adverse effects in women with PCOS [12, 13]. However, research on these subjects is limited, and there is no comprehensive review of Myoinositol compared with traditional insulin sensitization drugs such as Metformin. Studies comparing the clinical effects of MI and MET use in PCOS management have produced inconsistent results across randomized controlled trials (RCTs) that enrolled women who were not attempting pregnancy [13,14]. Research shows that Metformin provides better insulin resistance reduction through the homeostasis model assessment of insulin resistance (HOMA-IR) measurement compared to Myoinositol [14]. Research about other PCOS symptoms and indicators between treatments still lacks sufficient evidence [15]. The evidence for GI side effects shows better tolerance with Metformin vs. MI (Myoinositol). However, there is a lack of comprehensive review of these drugs for treating PCOS symptoms [16]. Past analyses failed to evaluate insulin resistance, testosterone level, and FSH hormone activity simultaneously by the influence of MI and MET. Therefore, this review aims to compare the

influence of Metformin vs. Myoinositol in treating PCOS-induced infertility by focusing on metabolic and clinical aspects.

2. METHODS

2.1 Selection of Studies

Meta-analysis approach has been utilized to assess the impact of Metformin vs. Myoinositol in treating PCOS-induced infertility. The research used databases including MEDLINE, EMBASE, PubMed, Scopus, Google Scholar, and ResearchGate. PRISMA guidelines are used to find the most relevant comparative trials. PRISMA guidelines provide a systematic procedure to extract relevant data [17]. The publication from 2010 to 2024 focused on the review to obtain up-to-date articles. The literature search utilized keywords such as MI, Myoinositol, MET, Metformin, PCOS, Polycystic ovary syndrome, testosterone, HOMA-IR OR Insulin Resistance, FSH, follicle-stimulating hormone, infertility, influence, impact, metabolic profile, and clinical outcomes. The Boolean operators used such as 'AND", "OR, "NOT" to combine the keywords. The Boolean operators help to combine the search terms together and broaden the results to find the most relevant studies [18]. A manual search was also conducted using the reference list of the relevant articles that fulfil eligibility criteria.

2.2 Exclusion and Inclusion Criteria

Only randomized clinical comparative studies were selected to be included in the meta-analysis. The comparative studies meeting the PICO criteria included: Population (P) women with PCOS; Comparator (C) Metformin Vs Myoinositol; Outcome (O) reported by the studies such as testosterone, HOMA-IR index (Insulin Resistance), FSH (follicle-stimulating hormone). Peer-reviewed, free access, complete comparative studies in English included.

The studies excluded which incorporated MI treatment with multiple drug/supplement combinations, duplicate research findings, and studies focused on animal settings. Other than comparative studies, including review protocols, conference papers, case studies, qualitative books, and editorial papers were excluded.

2.3 Data Extraction

A combination of title examination, abstract evaluation, and study design inspection was done to verify the eligibility criteria. This study assessed two key requirements: first, it studied women who had PCOS and second, it analyzed a comparison of Metformin and Myoinositol. The outcome focused were HOMA index evaluation, free testosterone and follicle-stimulating hormone.

The key details from full-text articles included first author names, publication years, countries where research took place, and their sample size. The collected data focused on effects measuring both standard deviation (SD) and mean values.

2.4 Quality Assessment

Cochrane ROB (Risk of Bias Tool) specifically for clinical comparative studies used to assess the quality of the included studies [18]. Cochrane ROB tools provide standard structured domain questions, including blinding of participants, allocation concealment, randomization, and description of selected criteria.

2.5 Data Analysis

The selected studies were analyzed through RStudio software to perform quantitative data assessment. A heterogeneity assessment was performed on the included studies to evaluate data result variations. The forest plot function is used to show the complete pattern of data distribution across studies. The review used standardized mean difference (SMD) calculations to determine the estimated effect size together with a 95% confidence interval.

3. RESULTS

3.1 Literature Search Outcome

Figure 1 shows the meta-analysis PRISMA flow diagram. A total of 2922 relevant articles found from the databases and other source. However, 2520 articles remained after eliminating duplicate studies. Afterwards, 2124 articles were excluded after screening the abstract, and title studies did not match the selection parameters, such as paid and incomplete access. 398 full text articles were assessed for established criteria and were included in the analytical assessment. The available full text studies were excluded for various reasons: (a) lack of focused outcome data or numerical expressions (160), (b) MI treatment with additional substances such as multivitamin complexes (100), (c) research on menopausal women with metabolic syndrome (468), and (d) absence clinical comparative trial design, review and conference paper (108).

A total of thirty studies were included in the meta-analysis. Table 1 depicts the characteristics of studies as eleven studies were conducted in India [19-28], three studies conducted in Iran [30-32], four studies in Italy [33-36], and four studies in Pakistan [37-40]. Other studies conducted in Bangladesh [41], Denmark [42], Egypt [43], Germany [44], Serbia [45], Turkey [46], UAE [47], and Vietnam [48] during 2010 to 2024. Metformin and Myoinositol were administered to PCOS women in all studies. The dose range of MET and MI was 1 to 4 grams for 12 to 24 weeks duration provided to the participants.

Table 2 shows the quality assessment of the included studies. All studies included in the assessment applied randomization procedures to decrease selection bias according to the Cochrane Risk of Bias tool results. The evaluation of the blinding method revealed inconsistent reporting because a single study disclosed blinding methods, but other studies failed to describe blinding practices. The majority of studies mentioned their selection procedures, although allocation concealment received inadequate reporting, which contributed to selection bias.

However, randomization techniques were used consistently, and selection criteria were described in detail, which shows the included studies are reliable.

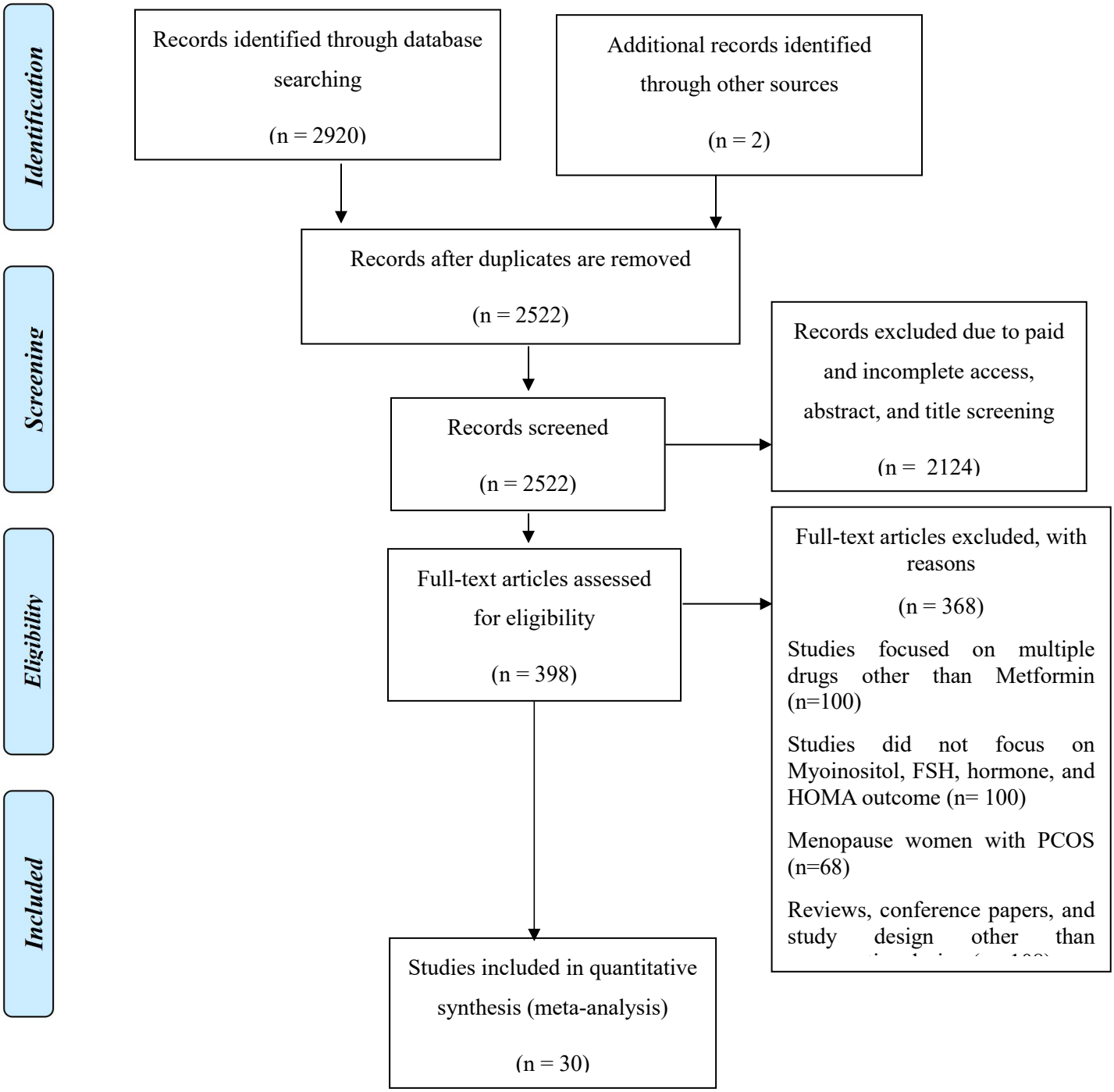

Figure 1: PRISMA flow-diagram shows the study selection

Table 1 shows Study Characteristics

M, the method was mentioned, but there was no detailed description; N, the method was not used in the study; Unclear, no relevant information was found in the study; Y, the method was reported with a detailed description.

Study	Year	Region	Country	Age of Metformin Group (Mean)	Age of Metformin Group (S.D)	Age of Myoinositol (Inofolic) Group (Mean)	Age of Myoinositol (Inofolic) Group (S.D)	Total Participants	no. of Metformin Group	No. of Myoinositol (Inofolic) Group	Pregnancy outcomes	Duration	Doses
Gudović et al.	2024	Belgrade	Serbia	28	4.9	26.3	4.3	60	30	30	follicle-stimulating hormone (FSH) ratios.	6 months	MET (1500 mg) Ml(2000 mg)/day
Fruzzetti et al.	2017	Pisa	Italy	22.3	6	21.6	6.6	46	22	24	follicle-stimulating hormone (FSH) ratios.	6 months	MET (1500 mg) Ml(4 g)/day
Asemi	2018	Arak	Iran	25.9	4.8	27.7	5.2	60	30	30	Free Testerone level	3 months	MET (500 mg) Ml(550 g)/day
Raffone et al.	2010	Messina	Italy	29.7	6	29.1	5.6	120	60	60	follicle-stimulating hormone	3 months	MET (1500 mg) Ml(400

											(FSH) ratios.		ug)/day
Shokrpour et al.	2019	Kashan	Iran	27.7	3.2	28.3	4.9	53	27	26	Insulin Resistance [HOMA-IR]	3 months	MET (500 mg) thrice/day Ml(2mg) twice/day
Tagliaferri et al.	2017	Rome	Italy	25.62	4.7	25.62	4.7	33	16	17	follicle-stimulating hormone (FSH) ratios.	3 months	MET (850 mg) Ml(1000 mg) twice/day
Angik et al.	2015	sawangi	India	23.1	3.51	23.97	3.02	100	50	50	Insulin Resistance [HOMA-IR]	6 months	MET (500 mg) Ml(1 g)/day
Nehra et al.	2017	Haryana	India	23.26	1.03	23.8	0.69	70	35	35	follicle-stimulating hormone (FSH) ratios.	6 months	MET (500 mg) thrice/day Ml(1 g) twice/day
De Leo et al.	2013	Siena	Italy	28.2	1.3	26.2	0.5	60	20	40	follicle-stimulating hormone (FSH) ratios.	6 months	MET (850 mg) Ml(1.5 g) twice/day
Ria et al.	2023	Caira	Egypt	26.8	4.57	26.42	4.61	100	50	50	follicle-stimulating hormone	3 months	MET (500 mg) thrice/day

											(FSH) ratios.		Ml(2mg) twice/day
Ravn et al.	2022	Odense	Denmark	27	0.34	25	0.22	28	12	16	follicle-stimulating hormone (FSH) ratios.	3 months	MET (1500 mg) Ml(1 g)/day
Raj et al.	2024	Tamil Nadu	India	25.11	3.21	24.94	3.88	71	36	35	follicle-stimulating hormone (FSH) ratios.	3 months	MET (1500 mg) Ml(1 g)/day
Chirania et al.	2017	Odisha	India	23.68	4.23	23.92	3.7	52	26	26	follicle-stimulating hormone (FSH) ratios.	12 months	MET (1000 mg) Ml(1 g)/day
Ozay et al.	2016	Izmir	Turkey	22.79	4.13	24.44	4.78	106	54	52	follicle-stimulating hormone (FSH) ratios.	3 months	MET (1000 mg) Ml(1 g)/day
Pourghasem et al.	2019	Heidelberg	Germany	31.06	1.1	31.08	3.31	100	50	50	follicle-stimulating hormone (FSH) ratios.	6 months	MET (1500 mg) Ml(200 mg) twice/day
Prabhakar et	2021	New Dehli	India	28.2	3.41	27.86	3.06	116	57	59	Insulin Resistance	6 months	MET (4g) Ml(4

al.											[HOMA-IR]		g)/day
Nehra et al.	2016	Haryana	India	23.89	0.69	23.26	1.03	60	30	30	Insulin Resistance [HOMA-IR]	6 months	MET (500 g) thrice/day Ml(1 g) twice/day
Le et al.	2023	Hue	Vietnam	28.3	3.5	28.5	3.2	171	113	58	follicle-stimulating hormone (FSH) ratios.	3 months	MET (1700 mg) Ml(2 g) twice/day
Khattak et al.	2024	Rawalpindi	Pakistan	28.61	3.64	28.94	3.77	109	54	55	Insulin Resistance [HOMA-IR]	6 months	MET (500 mg) thrice/day Ml(4g)/day
Thalamati	2019	Andhra Pradesh	India	23	4	24	4	200	100	100	Free Testerone level	5 months	MET (500 mg) thrice/day Ml(550 mg) twice/day
Bahadur et al.	2021	Rishikesh	India	23.78	4.46	21.89	4.23	72	36	36	follicle-stimulating hormone (FSH) ratios.	6 months	MET (500 mg) Ml(550 mg) twice/day
Nabi	2020	New	India	20.2	0.8	24	0.3	70	35	35	Free	4 months	MET

& Guleria		Dehli									Testerone level		(500 mg) twice/day Ml(2 g) twice/day
Rastegar et al.	2021	Tehran	Iran	30.51	5.88	30.9	5.33	140	70	70	Follicle number	6 months	MET (500 mg) thrice/day Ml(2000mg) twice/day
Johra et al.	2023	Dhaka	Bangladesh	25.1	3.56	24.54	3.56	100	50	50	follicle-stimulating hormone (FSH) ratios.	4 months	MET (500 mg) twice/day Ml(1 g) twice/day
Thakur et al.	2020	Uttar Pradesh	India	28.1	3.923	26.6	2.536	72	36	36	Insulin Resistance [HOMA-IR]	6 months	MET (500 mg) Ml(1000 mg) /day
Hamid et al.	2015	Dubai	UAE	27.1	1.6	25.6	1.1	128	66	62	Insulin Resistance [HOMA-IR]	3 months	MET (1500 mg) Ml(200 mg) twice/day
Tauqir et al.	2024	Islamabad	Pakistan	29.7	3.9	28.4	3.1	80	40	40	follicle-stimulating hormone (FSH) ratios.	6 months	MET (500 mg) thrice/day Ml(4g)/day

Nisa et al.	2024	Rawalpindi	Pakistan	28.12	4.84	28.12	4.8	100	50	50	follicle-stimulating hormone (FSH) ratios.	6 months	MET (500 mg) thrice/day Ml(1g)twice/day
Gul et al.	2023	Lahore	Pakistan	27.13	7.82	27.3	7.43	150	75	75	Insulin Resistance [HOMA-IR]	6 months	MET (500 mg) twice/day Ml(2000 mg) twice/day
Agrawal et al.	2019	New Dehli	India	28.12	3.34	28.35	2.74	120	60	60	Insulin Resistance [HOMA-IR]	3 months	MET (500 mg) Ml(600 mg) twice/day

Table 2 shows Quality Assessment using Cochrane Handbook

Study	Randomization	Blinding	Decription of selection criteria	Allocation concealment
Gudović et al., 2024	Y	Unclear	y	N
Fruzzetti et al., 2017	Y	Y	y	N
Asemi, 2018	Y	N	y	N
Raffone et al., 2010	Y	Y	y	N
Shokrpour et al., 2019	Y	N	y	Unclear
Tagliaferri et al., 2017	Y	N	y	N
Angik et al., 2015	Y	N	y	N
Nehra et al. 2017	Y	N	y	N
De Leo et al., 2013	Y	N	y	N
Ria et al., 2023	Y	N	y	N
Ravn et al., 2022	Y	N	y	N
Raj et al., 2024	Y	N	y	N
Chirania et al., 2017	Y	N	y	N
Ozay et al., 2016	Y	N	y	N
Pourghasem et al., 2019	Y	N	y	N
Prabhakar et al., 2021	Y	N	y	N
Nehra et al., 2016	Y	N	y	N
Le et al., 2023	Y	N	y	N
Khattak et al., 2024	Y	N	y	Unclear
Thalamati, 2019	Y	N	y	N
Bahadur et al., 2021	Y	N	y	N
Nabi & Guleria, 2020	Y	N	y	N
Rastegar et al., 2021	Y	N	y	N
Johra et al., 2023	Y	N	y	N
Thakur et al., 2020	Y	N	y	N
Hamid et al., 2015	Y	N	y	Unclear
Tauqir et al., 2024	Y	N	y	N
Nisa et al., 2024	Y	N	y	N
Gul et al., 2023	Y	N	y	N
Agrawal et al., 2019	Y	N	y	N

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M, the method was mentioned, but there was not detailed description; N, the method was not used in the study; Unclear, no relevant information was found in the study; Y, the method was reported with detailed description.

3.2 Meta-analysis

The standardized mean difference in testosterone levels between the metformin and myoinositol treatments for women with PCOS is shown in the forest plot (Figure 2). Random effects modelling was chosen after determining the heterogeneity of studies reached an I^2 value of 50% or higher. The common effect model of testosterone outcome measures reported in three studies [23,28,30] show Metformin and Myoinositol influence on metabolic profile of women with PCOS. Thalamati [28] shows that Myoinositol is more effective compared to Metformin. The common-effects model showed an overall standardized mean difference (SMD) of 0.98 based on a 95% confidence interval [0.72, 1.22], which showed significant difference between treatments and favored treatment (Metformin). However, the random-effects model revealed SMD equals 0.61 (95% CI: -0.98 to 2.21), indicating the overall result is a non-significant effect. It is mainly due to the variations exist in the predicted results which fall within the interval of -19.88 to 21.10. The higher heterogeneity outcomes found among research studies created significant differences in results ($I^2 = 98\%$, $\tau^2 = 1.9373$, $p < 0.01$).

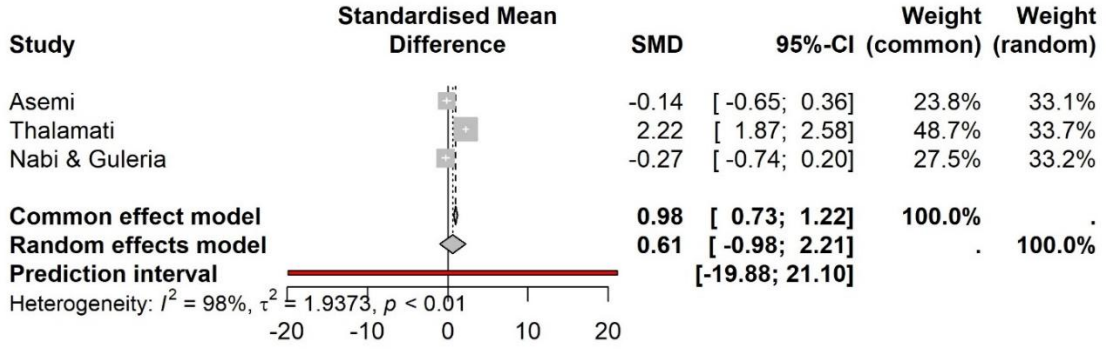

Figure 2: Forest plot explaining the effect size of testosterone in Women in PCOS

The Figure 3 forest plot examines metformin against Myoinositol in women with PCOS by evaluating the standardized mean difference (SMD) effects of follicle-stimulating hormone (FSH) levels. The individual eighteen studies [21, 22, 24, 26, 31, 33,34, 35, 36, 39, 40, 41, 42, 43, 45, 46, 44, 48] demonstrated different effect size levels through precise confidence interval measurements and show Metformin is slightly more effective. The research of Ria et al. [43] favored Metformin demonstrated negative SMD values that demonstrated statistical significance for negative results, yet Nisa et al. [39], Tauqir et al. [40], Pourghasem et al. [44], Chirania et al. [22], Raj et al. [26], De Leo et al. [33] SMD values and CI in Figure 3 indicating significant positive outcomes. The confidence intervals from Nehra et al., Raj et al. [26], and Pourghasem et al. [44] study crossed zero, indicating a nonsignificant statistical impact in their research findings. However, the random-effects model showed an overall standardized mean difference (SMD) of -0.11 based on a 95% confidence interval [-0.44, 0.22], which showed no significant difference

between treatments. The diversity (heterogeneity) between studies reached an extremely high level (I^2 = 86%) according to the results. The individual study outcomes contain substantial variation based on this prediction interval extending from -1.59 to 1.37.

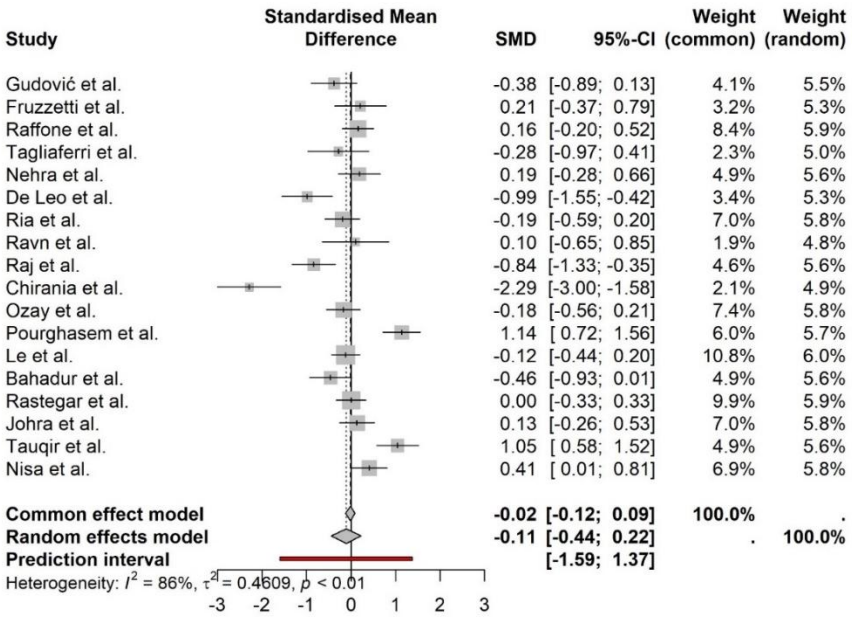

Figure 3: Forest plot explaining effect size of FSH in Women in PCOS

Figure 4 shows the forest plot results of HOMA-IR change analysis between Metformin and Myoinositol therapy in PCOS women as a standardized mean difference (SMD). Nine research investigations [19, 20, 24, 25, 27, 32, 37, 38, 47] monitored the HOMA-IR index in women who participated in metformin or Myoinositol treatments. The common-effects model showed an overall standardized mean difference (SMD) of -0.25 based on a 95% confidence interval [0-0.38, -0.12], which showed significant difference between treatments and favored treatment (Metformin). However, the chosen random-effects model indicates that Metformin has slightly effective effects because their standardized mean difference falls at -0.24. However, the overall SMD results show the results are statistically insignificant (95% CI: -0.69 to 0.22). The prediction interval (-1.90 to 1.42) reflects both extreme and minimal potential results. Further investigation is required to validate clinical implications based on wide-ranging study results (higher heterogeneity) with I^2 = 92% and τ^2 = 0.4390 ($p < 0.01$) (Table 3).

Figure 4 also showed that studies that participated in the analysis demonstrated different findings because of different sample sizes with pooled data. The investigation revealed results supporting the Metformin through negative SMD values with CIs produced by Angik et al. [20], Khattak et al. [38] and Hamid et al. [47]. Research by Nehra et al. [24] and Prabhakar et al. [25] did not show considerable changes since their CIs crossed zero values. The Metformin received strong

support according to the published SMD of -1.87 and its narrow confidence interval as per Gul et al. [37] study. Sample size, along with regional location, needs consideration for the generalization of results and conclusive findings.

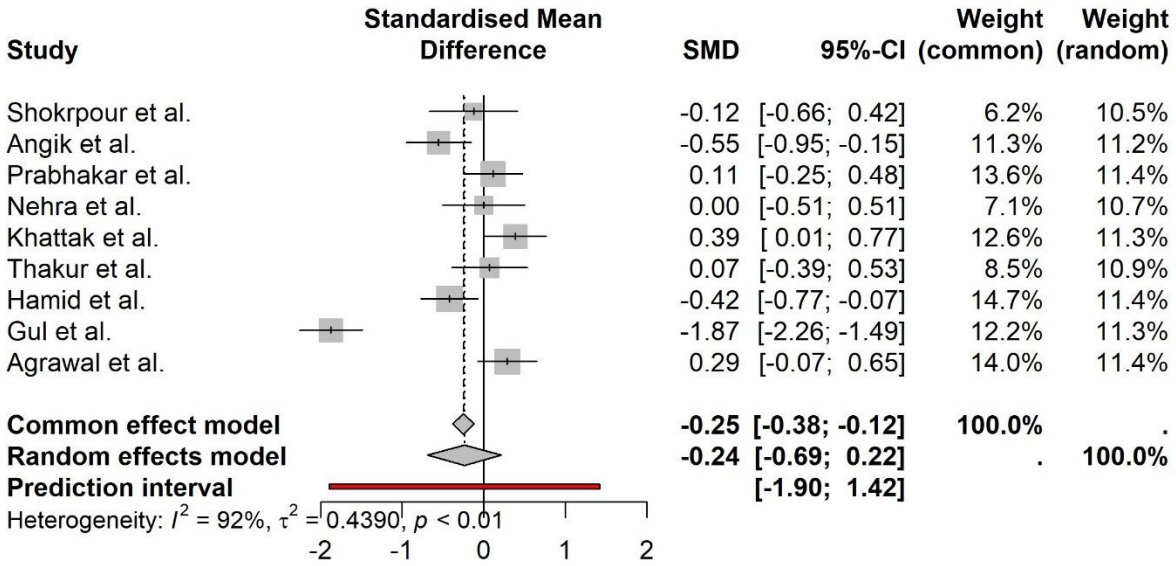

Figure 4: Forest plot explaining effect size of HOMA in Women with PCOS

Table 3 shows Meta-analysis Results

Variables	No. of Studies	SMD (95% CI)	Heterogeneity
FSH	18	-0.1101 [-0.4443; 0.2241]	Q-value = 125.26, Df (Q) = 17, P = 0.0001, I2 = 86.4%
HOMA	9	-0.2370 [-0.6918; 0.2179]	Q-value = 97.68, Df (Q) = 8, P = 0.0001, I2 = 91.8%
Testosterone	3	0.6120 [-0.9841; 2.2081]	Q-value = 93.26, Df (Q) = 2, P = 0.0001, I2 = 97.9%

4. DISCUSSION

The findings of this meta-analysis revealed that MET and MI in PCOS patients, as per the random effect model, demonstrate no substantial distinctions in hormonal and metabolic profiles such as HOMA index and hormone levels (FSH and testosterone) that influence fertility among women. Studies exhibited substantial diversity regarding the measurement of the HOMA index. However, the common effect model showed the significant effect of Metformin compared to Myoinositol. The hormone Testosterone acts as a crucial factor in PCOS development since its level increases among women who have this condition. The condition of hyperandrogenism

results in high testosterone production, thus generating hirsutism, acne, and impairing ovulation [49]. HOMA-IR indicates insulin resistance through the evaluation of fasting insulin and glucose levels. The diagnosis of insulin resistance occurs when HOMA-IR values exceed 2.0–2.5, though thresholds adapt based on population characteristics. HOMA-IR usually exceeds 2.5–3.0 levels in women with PCOS because their glucose metabolism shows signs of deterioration [50]. Follicle-Stimulating Hormone (FSH) dominates reproductive health through its control of gonadal functions. During the female menstrual cycle, FSH causes ovarian follicle expansion as well as estrogenic synthesis, leading to eventual ovulation. Women with PCOS demonstrate normal or slightly low FSH results and elevated LH measurements, which can result in ovulation problems through their disrupted follicle development. The increase in FSH level enables better follicular maturation, yet it signals potential ovarian insufficiency. The LH/FSH ratio exceeding 2:1 disturbs follicular development through its inappropriate proportion, thereby causing anovulation and infertility problems [51]. Therefore, proper balance of FSH is necessary for ovulation and enables hormonal control for PCOS. Although Metformin shows widespread use in previous studies on HOMA-IR and testosterone compared to Myoinositol because it enhances insulin sensitivity to minimize hyperandrogenism itself, no-statistical significance results found between overall results. This analysis identified high heterogeneity, possibly because each person processes drugs differently as well as because their PCOS type, along with treatment lengths, affects results.

As an insulin sensitizer Metformin belongs to the biguanide medication category. The drug halts the production of hepatic gluconeogenesis while raising glucose absorption in skeletal muscle tissue. AMPK acts as the main cellular energy sensor that Metformin activates to achieve its functions [52]. The activation of AMPK through metformin treatment leads to lowered hepatic gluconeogenic gene expression, which reduces the amount of glucose produced by the liver. Through its mechanisms, Metformin strengthens insulin receptor signals that lead to increased insulin sensitivity throughout the cells [20-37,53]. The strong impact of metformin benefits PCOS patients mainly because insulin resistance typically creates the first condition that leads to hyperinsulinemia, which fuels hyperandrogenism. Hyperandrogenism exacerbates clinical features such as hirsutism, acne, and menstrual irregularities in PCOS [51]. Metformin's direct activity on ovarian theca cells leads to the reduction of produced androgens. Metformin treatment leads to reduced circulating LH concentration which adds to the reduction of androgen hormone levels. The combination of these actions establishes Metformin as an effective drug for treating reproductive and metabolic problems in patients who have PCOS [52-53]. However, the meta-analysis result shows that further long-term influence analysis is needed as no significant difference was found between the treatments.

Moreover, MET reduces blood glucose entry and not only decreases hepatic sugar production but also boosts insulin responsiveness through better glucose extraction in tissues beyond pancreas insulin production changes [24-37]. MET functions both independently and with joint treatments to revive proper menstrual cycles. Laboratory research indicates MET reduces the chances of developing ovarian hyperstimulation syndrome in patients undergoing in vitro fertilization but lacks sustained evidence about its effects on achieving live births [54]. Past meta-analysis that focused on Metformin, Myoinositol, d-chiro-inositol, and combination of Metformin with other drugs also showed no significant influence on FSH, insulin resistance, and testosterone [55-56]. MET receives little agreement from updated guidelines since it provides no substantial advantages, and it is not recommended as an initial treatment to solve infertility among PCOS patients [57]. This meta-analysis provided evidence from thirty comparative studies that did not show any substantial HOMA index change when MET was used to treat PCOS.

The patients treated with MET showed a decrease in HOMA-IR score as per common effect model in this meta-analysis. However, the studies had higher heterogeneity among studies. The research findings, along with those from previous clinical trials, showed that Metformin effectively treats the metabolic symptoms of PCOS better than Monotherapy with MI demonstrates in regulating metabolic risk factors [28]. However, use of MET showed side effects as well. Patients taking MI experience tolerable side effects that produce no adverse outcomes, whereas MET needs to be discontinued by many PCOS patients due to its side effect profile, which includes gastrointestinal disturbances [58]. The risk of adverse effects associated with MET treatments relative to MI therapy had a calculated ratio of 5.2, while GI side effects caused MET patients to drop out at a rate of up to 50% [14]. Myoinositol presents itself as a suitable treatment option for women with PCOS and oligomenorrhea who have intolerance issues with MET [28]. Research data demonstrated that the administration of MI results in the most patient discontinuation rates because of its inferior clinical results. Similarly, this meta-analysis presented heterogeneous results because of dissimilarities in the populations studied alongside differences in drug dose in sample sizes. The studies displayed significant differences in participant characteristics because heterogeneity reached above 90% in all three analyses (FSH, testosterone, and HOMA).

The main reason behind no significant association found in this study was PCOS's existence in different forms among women, leading to either severe metabolic problems or mostly reproductive problems. The various ways in which PCOS manifests in people can affect how medications respond to the condition [58, 59]. The length of medication exposure affects the treatment success of metformin and Myoinositol administration. Various research analyses examined changes for a limited period of time or recorded short-term outcomes [56]. The start levels of testosterone, as well as FSH and insulin resistance, play a role in determining individual

reaction to therapy. Differing metformin and Myoinositol dose amounts reported by studies likely contribute to variable results [21-40]. The inconsistent data reveals important conclusions about how Metformin and Myoinositol alter hormone and metabolic levels in PCOS patients. The available evidence fails to definitively determine which method provides better FSH control yet shows potential effects of Metformin on testosterone amounts that present substantial variation. The consistent impact of Metformin on insulin resistance (HOMA) measurement remains apparent, yet the high heterogeneity obliges healthcare providers to approach each patient individually.

4.1 Strength and Weakness

The current analysis serves as the first research effort to establish numerical evaluations between Metformin (MET) and Myoinositol (MI) for polycystic ovary syndrome (PCOS) patients utilizing thirty comparative studies. The analysis performed a thorough search, which aimed to prevent the omission of pertinent studies. The study participants who took part in the analyzed research included people from different ethnic backgrounds, which helped increase the overall applicability of the results. The research included only comparative studies in order to minimize bias. All studies in the research lacked blinding procedures. The researchers could not implement a double-blind method because the drugs required different medication formats (sachets and pills), and variable side effects would affect reliability throughout the study.

Multiple restrictions exist with this meta-analysis, even though it demonstrates strong features. Treatment dose variability specifically for MI was a major contributor to heterogeneity because different trials provided widely different amounts of MI medication [19-48]. The inconsistent treatment protocols presented themselves as a potential source that influenced the research outcomes, which future research should normalize.

The analysis restricts by short follow-up periods because different trials monitored patients between 12 to 24 weeks [19-43]. These time parameters enable the evaluation of immediate effects yet provide inadequate information to establish permanent results and security of these therapeutic techniques. The analysis requires additional comparative studies with extended follow-up times to validate and extend the reported short-term results. Additional research needs to be conducted to build stronger evidence about MET and MI effectiveness in PCOS care.

This meta-analysis holds additional significance for the wider aspects of PCOS management. Therapeutic management of elevated testosterone levels reduces issues such as hirsutism, acne, and alopecia, which influence quality of life [60]. The management of testosterone effectively treats PCOS symptoms and reduces the associated mental stress. Collective care for PCOS patients requires collaborative service between endocrinology professionals, dermatology experts,

and mental health providers. Dietary modifications combined with physical activity continue to be fundamental elements that supplement medical prescriptions for the treatment of PCOS.

Anti-androgens, along with novel insulin sensitizers, have emerging potential as treatment options for PCOS management. Medical androgen blockers implementation as part of standard treatment approaches shows promise to improve clinical responses for patients who still experience poor outcomes despite existing therapy [42-48, 60]. Future studies should also focus on how ethnicity and cultural elements impact both treatment adherence and therapeutic outcomes since PCOS affects women globally.

5. CONCLUSION

This research review examines how metformin treatment affects FSH, testosterone, and HOMA level changes in women suffering from PCOS. The meta-analysis found no substantial variation in how FSH changes, but Myoinositol showed possible effects on testosterone concentrations, which varied considerably. The effect of Metformin on insulin resistance and FSH reduction seems modest but shows no statistical significance even when heterogeneity levels are high. The data suggests how complicated PCOS symptoms are, thus proving the necessity for individualized therapeutic methods. The development of sufficient treatment strategies for PCOS needs further research which will merge information about genetics with metabolic patterns and hormonal balances. Endocrinologists, together with gynaecologists and metabolic researchers, must work in cooperation to refine treatments by making them individualized to patient needs.

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