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REVIEW

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Comparative efficacy and safety of metformin, anti-obesity agents, and myoinositol in improving IVF/ICSI outcomes and reducing ovarian hyperstimulation syndrome in women with polycystic ovary syndrome: a systematic review and network meta-analysis

Lijun Lin[1,2,3,4†], Ge Chen[1†], Xiaoyong Qiao[1,2,3,4], Yan Chen[1,2,3,4], Hongxia Deng[1,2,3,4] and Liangzhi Xu[1,2,3,4*]

Abstract

Purpose To compare the efficacy and safety of metformin, anti-obesity agents, and inositol with polycystic ovary syndrome (PCOS) undergoing in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI).

Methods A comprehensive search was conducted in PubMed, Web of Science, Embase, Cochrane Library, and ClinicalTrials.gov for studies published in English up to October 26, 2024. Randomized controlled trials (RCTs) evaluating metformin, anti-obesity agents, and inositol were included. A network meta-analysis was performed using frequency statistical methods. Subgroup analyses were conducted based on controlled ovarian stimulation (COS) protocols and body mass index(BMI). The research protocol was registered with PROSPERO (registration code CRD42024502823).

Results 20 RCTs were included with 1,827 patients assessed six different agents. Nineteen trials were rated low risk, with one rated moderate risk. Pairwise meta-analysis showed that metformin did not improve pregnancy outcomes but was associated with a reduced ovarian hyperstimulation syndrome (OHSS) risk (OR = 0.52, 95% CI 0.33–0.83), particularly in agonist protocols, along with lower E2 levels on the trigger day (SMD = -0.56, 95% CI -0.90 to -0.21) and increased side effects (OR = 6.85, 95% CI 4.32–10.86). Network meta-analysis confirmed no significant differences in pregnancy outcomes for these agents compared to controls, though both myoinositol and metformin reduced OHSS risk. Myoinositol was linked to a shorter gonadotropin duration (SMD = -1.21, 95% CI -2.03 to -0.38) and fewer side effects (OR = 0.23, 95% CI 0.06–0.83) compared to controls. Metformin led to lower E2 levels, a higher number

[†]Lijun Lin and Ge Chen contributed equally to this work.

*Correspondence:
Liangzhi Xu
xuliangzhi@scu.edu.cn
Full list of author information is available at the end of the article

of mature oocytes, and increased side effects (SMD = -376.52, 95% CI -610.83 to -142.22; SMD = 2.23, 95% CI 0.36–4.10; OR = 6.85, 95% CI 4.32–10.86) than controls. No studies reported an increased risk of fetal abnormalities.

Conclusion Metformin and myoinositol may reduce OHSS risk in PCOS patients but did not significantly improve pregnancy outcomes. Metformin may lower OHSS risk in agonist protocol, reduce E2 levels on trigger day and increase mature oocytes but cause more side effects, while myoinositol may shorten gonadotropin duration with fewer side effects. Further robust RCTs are needed to confirm these findings.

Keywords Metformin, Anti-obesity agents, Inositol, IVF, ICSI, OHSS, PCOS, Network meta-analysis

Introduction

Polycystic ovary syndrome (PCOS) is now diagnosed based on updated international guidelines, emphasizing an evidence-based approach. Diagnosis in adults requires the presence of two of three criteria: clinical or biochemical hyperandrogenism, ovulatory dysfunction, and polycystic ovaries on ultrasound or elevated anti-Müllerian hormone (AMH) levels, after excluding other potential causes [1]. PCOS can impair reproductive potential through mechanisms such as diminished oocyte quality, altered embryo and endometrial function, and the presence of infertility-related comorbidities. Women with PCOS also face an elevated risk of pregnancy complications, further affecting fertility outcomes [2–5].

Ovulatory dysfunction is the primary cause of infertility in PCOS, and first-line treatments include clomiphene citrate and letrozole for ovulation induction [6]. For those who do not respond to ovulation induction or present other infertility factors (such as tubal or male-related infertility), in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) with controlled ovarian stimulation (COS) is often pursued. However, IVF/ICSI in PCOS patients are challenging, as these patients may experience issues such as exaggerated or poor ovarian response [7–9], high ratios of immature oocytes [10], abnormal fertilization [11, 12], reduced embryo developmental potential [13], low live birth rates [14], and a higher risk of ovarian hyperstimulation syndrome (OHSS) [15].

Metformin, anti-obesity agents, and inositol are recommended by international guidelines for improving metabolic profiles in PCOS [1], yet evidence on their efficacy specifically in enhancing IVF/ICSI outcomes is limited. This uncertainty leaves open the question of which agent offers the best efficacy and safety profile for IVF/ICSI [16–21]. This network meta-analysis aims to systematically evaluate the impact of these agents on IVF/ICSI outcomes, side effect and their role in reducing OHSS risk in women with PCOS, providing clearer guidance for optimizing fertility treatment in this population.

Method and analysis

Search strategy and selection criteria

The present systematic review and network meta-analysis followed the PRISMA guidelines for network meta-analysis [22]. The PubMed, Web of Science, Embase, and Cochrane library databases were searched from database inception to October 26th, 2024, using the following keywords and Medical Subject Heading (MeSH) terms: "PCOS", "metformin", "Anti-obesity medications", "inositol", "liraglutide", "semaglutide", "glucagon-like peptide-1(GLP-1) receptor agonist", "Orlistat", "IVF/ICSI", and "randomized controlled trial". In addition, Clinicaltrials.gov was searched to identify randomized controlled trials (RCTs).

All identified records were screened based on title and abstract by two independent reviewers. Studies were included if they met the inclusion criteria as follows: (1) PCOS patients received only one of the following agents: metformin, anti-obesity agents, or inositol-based medications; (2) Participants underwent IVF/ICSI with embryo transfer (ET) ; (3) RCT study design; and (4) Studies with a low or moderate risk of bias. The exclusion criteria were applied as follows: (1) Studies not reported in English; (2) No parallel controlled design in RCTs; (3) Comparisons within the same category of agents, such as myo-inositol versus D-chiro-inositol; (4) Inclusion of Traditional Chinese medicine treatments; and (5) Absence of primary outcome data. For studies that met the inclusion criteria, full texts were retrieved and assessed in detail. Two reviewers (GC and LJL) independently reviewed the full texts and discussed any discrepancies by consensus. The final selection of studies was documented in a PRISMA flow diagram, detailing the number of studies included and excluded at each stage, along with reasons for exclusion at the full-text stage.

Outcome measures

The primary outcomes included clinical pregnancy, live birth, abortion, and OHSS. Clinical pregnancy was defined as the presence of a gestational sac or fetal heartbeat observed by ultrasound. Live birth was defined as the birth of at least one baby after 24 weeks of gestation.

Abortion was classified as the loss of pregnancy between the fifth and twelfth weeks of gestation. Secondary outcomes included gonadotropin dosage, gonadotropin duration, estrogen (E2) level on trigger day, number of mature oocytes, number of oocytes retrieved, normal fertilization, available embryos on Day 2 or Day 3, and side effects.

Risk of bias assessment

The Cochrane tool was used to assess the risk of bias in each randomized trial [23]. Potential sources of bias included random sequence generation, allocation concealment, blinding of participants, blinding of study staff, blinding of outcome assessors, incomplete outcome data, and selective reporting. Each trial was assigned a score of low, high, or unclear risk of bias for each domain. Two authors (GC and LJL) independently conducted the bias assessment, with any discrepancies resolved by consensus.

Data extraction

Two independent investigators extracted from original reports using specially designed forms that contained information on study country, COS protocol, patients' characteristics, including age and body mass index (BMI), sample size, intervention groups, intervention duration, and primary and secondary outcomes. For different intervention, the control group consisted of untreated patients or patients receiving a placebo.

Data synthesis and statistical analysis

Pairwise meta-analyses using a random effects model were performed when direct data were available. Network meta-analyses were conducted within a frequentist framework using the "mvmeta" and "network" packages in Stata MP 17.0. A multivariate random effects model with restricted maximum likelihood (REML) estimation was used, and network consistency was evaluated using inconsistency tests. For each outcome of interest, the < network meta inconsistency > command was applied to statistically confirm the overall consistency assumption, while the SIDE (Separating Indirect from Direct Evidence) splitting method, using the < network sidesplit all > command, was applied to test for loop inconsistency geometry and node connectivity were visualized for all outcomes [24].

For all treatment comparisons, summary odds ratios (ORs) or standardized mean differences (SMDs) with 95% confidence intervals (CIs), accounting for uncertainty in variance estimates in league tables, are presented. Ranking probabilities and surface under the cumulative ranking curve (SUCRA) values were calculated for each treatment to establish treatment hierarchies. Continuous variables, initially reported as medians with quartiles (or ranges), were converted to means and standard deviations (SDs) when applicable, following established methods [25].

Subgroup analyses were conducted based on COS protocol and BMI separately to examine their associations with primary IVF/ICSI outcomes in PCOS patients, aiming to provide more clinically informative conclusions. To assess potential small study effects, adjusted funnel plots were visually inspected for outcomes with more than ten studies, following recommended practices for detecting publication bias in meta-analyses. The certainty of evidence for the primary outcome was then assessed using the CINeMA (Confidence in Network Meta-Analysis) framework according to Papakonstantinou et al. [26], which categorizes the confidence in results as high, moderate, low, or very low, to support clinical interpretation. The research protocol was registered in PROSPERO (registration code CRD42024502823) : https://www.crd.york.ac.uk/prospero/.

Results

Search results and baseline characteristics

A total of 1,355 studies were initially identified in the database search, with no additional records from other sources. Following duplicate removal (406 studies) and title/abstract screening (451 studies), 498 full-text studies were assessed for eligibility. Based on exclusion criteria, 478 studies were excluded. Ultimately, 20 studies met all criteria and were included in the network meta-analysis [27–46]. A flowchart of the search process is presented in Fig. 1, while Supplementary Fig. 1 shows the risk of bias assessment: 19 trials were low-risk, 1 moderate-risk, and nonhigh-risk. Additional File 1 provides the search strategy, a list of included trials, and excluded trials with reasons.

A total of 1,827 participants with PCOS were randomized to receive one of six agents: metformin, sitagliptin, myoinositol, simvastatin, pioglitazone, or placebo. Sitagliptin, simvastatin, and pioglitazone were included as comparators due to their roles in metabolic regulation, improving insulin sensitivity, and reducing hyperandrogenism. Supplementary Table 1 provided details on the mechanisms and side effects of each agent used in the included studies. No studies reported an increased risk of fetal abnormalities. Most participants (818) received metformin, with smaller groups assigned to pioglitazone (116), simvastatin (52), myoinositol (150), and sitagliptin (15). Participant mean age ranged from 22.8 to 40 years, ovarian stimulation protocols included antagonist (5 studies) and agonist (13 studies), while 2 studies did not specify the protocol. Main characteristics of included studies are summarized in Supplementary Table 2.

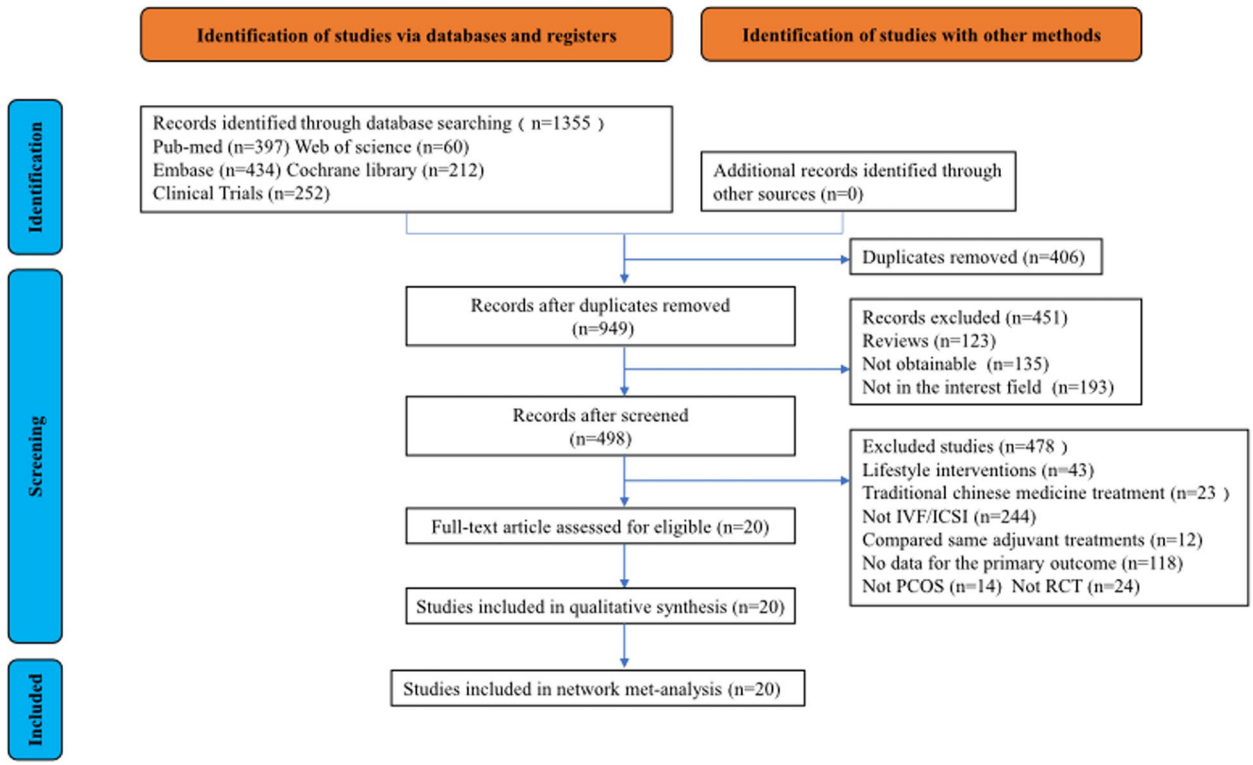

Fig. 1 Flow diagram of the included studies in systematic review and network meta-analysis. *IVF: in vitro fertilization; ICSI: intracytoplasmic sperm injection; PCOS: polycystic ovary syndrome; RCT: randomized controlled trial*

Pairwise meta-analysis

In our analysis, only a limited number of treatments had sufficient literature for direct comparative assessment. Figure 2A-C summarize the pairwise meta-analysis results for pregnancy outcome. Metformin did not demonstrate higher rates of clinical pregnancy, live birth, or abortion compared to controls (OR = 1.08, 95% CI 0.77–1.53; OR = 1.10, 95% CI 0.58–2.10; OR = 1.48, 95% CI 0.63–3.46, respectively). However, the incidence of OHSS was lower in the metformin group than in controls (OR = 0.52, 95% CI 0.33–0.83) (Fig. 2D). In comparisons between metformin and myoinositol, no notable differences were observed in clinical pregnancy or abortion rates (OR = 1.52, 95% CI 0.63–3.66; OR = 1.14, 95% CI 0.46–2.82, respectively) (Fig. 2A and C), with no available data for live birth or OHSS.

For secondary outcomes, metformin showed no differences compared to control in gonadotropin dosage, gonadotropin duration, numbers of mature oocytes, retrieved oocytes, normal fertilization, and available embryos (SMD = 0.32, 95%CI −0.20-0.84; SMD = −0.13, 95%CI −0.39-0.14; SMD = −0.15, 95%CI −0.49-0.19; SMD = 0.73, 95%CI −0.39-1.84; SMD = 0.11, 95%CI −0.54-0.76; SMD = 0.26, 95%CI −0.64-1.16, respectively) (Supplementary Fig. 2A-F). The E2 level on the trigger day was lower in the metformin group than in the control group (SMD = −0.56, 95% CI −0.90 to −0.21), while side effects occurred more frequently with metformin (OR = 6.85, 95% CI 4.32–10.86) (Supplementary Fig. 2G-H). In comparisons between metformin and myoinositol, no differences were observed in the numbers of mature oocytes or oocytes retrieved (SMD = −0.41, 95% CI −1.25-0.43; SMD = −0.24, 95% CI −0.68-0.19) (Supplementary Fig. 2C-D), and no data were available for other secondary outcomes.

Network meta-analysis

The network plots of the primary outcomes are presented in Supplementary Fig. 3A-C. For the primary outcomes, 19 studies were included in the analysis of clinical pregnancy rate, 6 studies for live birth rate, 8 studies for abortion rate, and 13 studies for OHSS risk across all treatments. The most common comparison was metformin versus control, involving 16 RCTs and a total of 1,646 participants.

The netleague analysis results of primary outcomes are shown in Fig. 3. None of the treatments demonstrated differences in clinical pregnancy or abortion compared to the control (Fig. 3A and B), However, myoinositol and metformin were associated with a reduction in OHSS

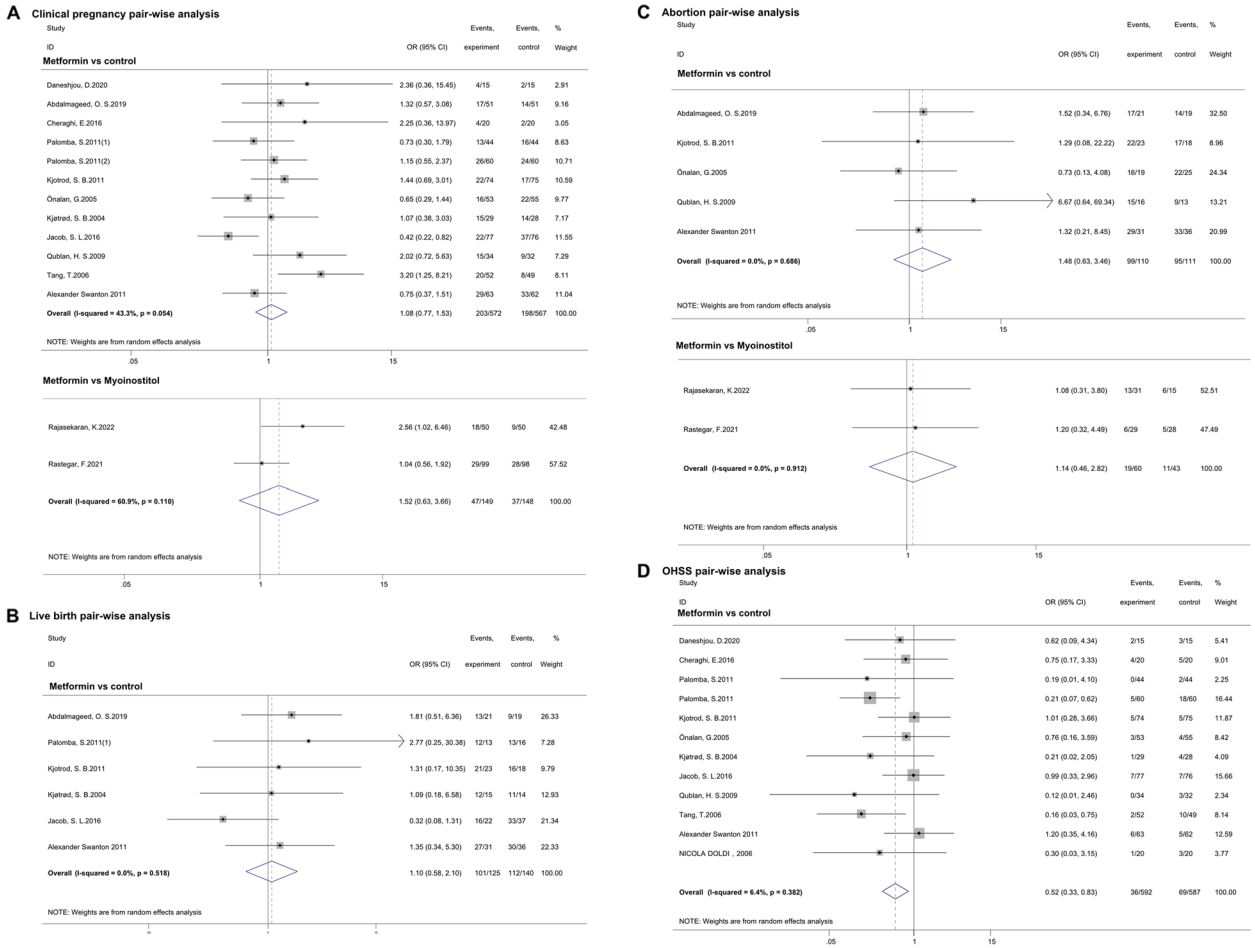

Fig. 2 Pairwise meta-analysis results of the primary outcomes. (**A**) Forest plot of metformin vs. control and metformin vs. myoinositol for clinical pregnancy (**B**) Forest plot of metformin vs. control for the risk of live birth (**C**) Forest plot of metformin vs. control and metformin vs. myoinositol for the risk of abortion (**D**) Forest plot of metformin vs. control for the risk of OHSS. *OHSS: ovarian hyperstimulation syndrome; OR: odds ratio*

risk (OR = 0.18, 95% CI 0.04–0.77; OR = 0.52, 95% CI 0.31–0.86, respectively) (Fig. 3A). Data for live birth rate analysis were not available. According to SUCRA rankings, myoinositol was indicated as having the greatest potential to reduce OHSS occurrence (82%), followed by metformin (48.9%) (Supplementary Fig. 4B).

The network plots of the secondary outcomes are presented in Supplementary Fig. 5. None of the agents altered gonadotropin dosage, number of oocytes retrieved, normal fertilization, or available embryos (Fig. 4A, C and D). However, myoinositol was associated with a reduction in gonadotropin duration compared to metformin, sitagliptin, and control (SMD= −1.00 95% CI −1.72 to −0.28; SMD= −1.13 95% CI −2.06 to −0.21; SMD= −1.21 95% CI −2.03 to −0.38) (Fig. 4A), metformin was associated with lower E2 levels on the trigger day and a higher number of mature oocytes compared to the control (SMD= −376.52 95% CI −610.83 to −142.22; SMD = 2.23 95% CI 0.36–4.10) than control (Fig. 4B-C), Additionally, myoinositol was associated with fewer side effects compared to metformin and the control (OR = 0.03 95% CI 0.01–0.11; OR = 0.23 95% CI 0.06–0.83), while metformin showed a higher incidence of side effects compared to the control (OR = 6.85 95% CI 4.32–10.86) (Fig. 4B). According to the SUCRA values, myoinositol was associated with reduced gonadotropin duration (99.5%) (Supplementary Fig. 6B) and fewer side effects (91.6%) (Supplementary Fig. 6D), metformin was associated with lower E2 levels on the trigger day (56.3%) and an increased number of mature oocytes (76.5%) (Supplementary Fig. 6C, 6G).

Inconsistency

For global inconsistency, no significant inconsistency was found for any outcome except live birth, with $P > 0.05$. For live birth, only studies comparing metformin with the control group were available, with a pairwise meta-analysis showing $P = 0.518$. For local inconsistency, the

A

Clinical Pregnancy					
Myoinositol	0.84 (0.31,2.25)	1.42 (0.74,2.73)	1.31 (0.39,4.34)	1.52 (0.25,9.07)	1.50 (0.75,3.00)
0.59 (0.03,10.00)	**Pioglitazone**	1.70 (0.80,3.63)	1.56 (0.45,5.47)	1.82 (0.29,11.28)	1.80 (0.83,3.89)
0.35 (0.09,1.36)	0.60 (0.05,7.24)	**Metformin**	0.92 (0.33,2.54)	1.06 (0.20,5.66)	1.05 (0.77,1.45)
0.35 (0.00,24.84)	0.60 (0.01,68.85)	1.00 (0.02,56.63)	**Simvastatin**	1.16 (0.17,8.15)	1.15 (0.42,3.18)
0.32 (0.03,3.31)	0.54 (0.02,11.97)	0.91 (0.13,6.12)	0.91 (0.01,78.81)	**Sitagliptin**	0.99 (0.18,5.30)
0.18 (0.04,0.77)	0.31 (0.03,3.56)	**0.52 (0.31,0.86)**	0.52 (0.01,30.27)	0.57 (0.09,3.82)	**Control**
OHSS					

B

Pioglitazone			
0.60 (0.04,8.76)	**Metformin**		
0.49 (0.03,8.57)	0.82 (0.26,2.59)	**Myoinositol**	
0.41 (0.03,5.28)	0.68 (0.30,1.53)	0.83 (0.23,3.00)	**Control**
Abortion			

Fig. 3 Netleague of primary outcomes. (**A**) Netleague of clinical pregnancy and OHSS (**B**) Netleague of abortion. The comparisons of data are odds ratios (95% CI), which should be read from left to right. Odds ratio higher than 1 favor the left treatments, lower than 1 favor the right treatments. Significant results are in bold and underlined. *OHSS: ovarian hyperstimulation syndrome*

Separating Indirect from Direct Evidence (SIDE)-splitting method was applied. All outcomes showed $P > 0.1$. Overall, no evidence of global inconsistency or local inconsistency was detected in the network. All results were tested for loop inconsistency, and no significant differences were observed between direct and indirect evidence (Supplementary Fig. 7A-I), supporting the coherence and reliability of the network's findings.

Subgroup analysis

Subgroup analysis was conducted based on COS protocol and BMI. Based on the subgroup analysis of the agonist protocol, the pairwise meta-analysis results for primary outcomes indicated that metformin did not show higher rates of clinical pregnancy, live birth, or abortion compared to controls (OR = 1.48, 95% CI 0.63–3.46; OR = 1.53, 95% CI 0.66–3.57; OR = 0.68, 95% CI 0.29–1.59, respectively) (Supplementary Fig. 8A-C). However, the incidence of OHSS was lower in the metformin group compared to controls (OR = 0.46, 95% CI 0.25–0.83) (Supplementary Fig. 8D). The netleague plot for the network meta-analysis results of the primary outcomes are shown in Fig. 5. None of the treatments demonstrated differences in clinical pregnancy or abortion rate compared to the control (Fig. 5. A), However, metformin was associated with a reduced risk of OHSS (OR = 0.46 95% CI 0.25–0.86) (Fig. 5. B). Data for live birth rate were unavailable for analysis. According to the SUCRA rankings, metformin showed the highest potential for reducing the occurrence of OHSS (70%) (Supplementary Fig. 9C).

According to the subgroup analysis of the antagonist protocol, the pairwise meta-analysis results for primary outcomes indicated that metformin did not show higher

A

Gonadotropin dosage				
Myoinositol	-139.52 (-1098.01,818.97)	NA	98.90 (-1286.31,1484.12)	8.40 (-1016.90,1033.71)
-1.00 (-1.72,-0.28)	**Metformin**	NA	238.42 (-761.67,1238.51)	147.92 (-216.23,512.07)
-1.13 (-2.06,-0.21)	-0.13 (-0.72,0.45)	**Sitagliptin**	NA	NA
NA	NA	NA	**Pioglitazone**	-90.50 (-1021.93,840.93)
-1.21 (-2.03,-0.38)	-0.21 (-0.61,0.20)	-0.07 (-0.66,0.51)	NA	**Control**
Gonadotropin duration				

B

Side effects			
Pioglitazone	4.31 (0.07,274.75)	0.15 (0.00,7.80)	1.00 (0.02,52.04)
-45.19 (-806.84,716.46)	**Myoinositol**	**0.03 (0.01,0.11)**	**0.23 (0.06,0.83)**
-143.38 (-751.87,465.12)	-98.19 (-646.86,450.49)	**Metformin**	**6.85 (4.32,10.86)**
-519.90 (-1081.48,41.67)	-474.71 (-989.24,39.82)	**-376.52 (-610.83,-142.22)**	**Control**
E2 level on trigger day			

C

The number of retrieved occtyes					
Sitagliptin	0.55 (-5.00,6.11)	-3.39 (-11.61,4.84)	1.28 (-5.09,7.66)	0.11 (-5.44,5.67)	3.71 (-4.41,11.84)
0.88 (-3.78,5.54)	**Metformin**	'-3.94 (-10.25,2.37)	0.73 (-2.55,4.01)	-0.44 (-2.17,1.29)	3.16 (-3.02,9.34)
1.47 (-4.18,7.12)	0.59 (-2.84,4.02)	**Simvastatin**	4.67 (-2.30,11.64)	-3.50 (-9.56,2.56)	7.10 (-1.38,15.58)
2.44 (-2.81,7.68)	1.56 (-1.05,4.17)	0.97 (-3.22,5.15)	**Myoinositol**	-1.17 (-4.61,2.27)	2.43 (-4.42,9.29)
3.11 (-1.57,7.79)	**2.23 (0.36,4.10)**	1.64 (-1.81,5.09)	0.67 (-2.17,3.52)	**Control**	3.60 (-2.33,9.53)
5.41 (-1.16,11.98)	4.53 (-0.45,9.51)	3.94 (-1.82,9.70)	2.97 (-2.45,8.39)	2.30 (-2.31,6.91)	**Pioglitazone**
The number of mature occtyes					

D

Normal fertilization				
Metformin	0.13 (-4.09,4.34)	NA	0.66 (-2.68,4.00)	0.34 (-1.65,2.33)
0.24 (-3.56,4.04)	**Sitagliptin**	NA	0.53 (-4.67,5.74)	0.22 (-4.03,4.46)
0.24 (-3.72,4.20)	0.00 (-5.49,5.49)	**Myoinositol**	NA	NA
0.25 (-2.76,3.26)	0.01 (-4.59,4.61)	0.01 (-4.97,4.98)	**Pioglitazone**	-0.32 (-3.66,3.03)
0.47 (-1.78,2.71)	0.23 (-3.60,4.05)	0.23 (-4.33,4.78)	0.22 (-2.81,3.25)	**Control**
Available embryos				

Fig. 4 Netleague of secondary outcomes. (**A**) Netleague of gonadotropins dosage and duration (**B**) Netleague of side effects and E2 levels on trigger day (**C**) Netleague of the number of retrieved and mature oocytes (**D**) Netleague of normal fertilization and available embryos The comparisons of binary variables are odds ratios (95% CI), which should be read from left to right. Odds ratio higher than 1 favor the left treatments, lower than 1 favor the right treatments. The comparisons of continuous variables are standardized mean differences (SMD), which should be read from left to right. SMD higher than 0 favor the left treatments, lower than 0 favor the right treatments. Significant results are in bold and underlined. *OHSS: ovarian hyperstimulation syndrome*

A **Subgroup analysis of agonist protocol for clinical pregnancy and abortion**

Clinical pregnancy		
Metformin	1.29 (0.12,13.76)	1.48 (0.63,3.46)
0.77 (0.07,8.24)	**Myoinositol**	1.14 (0.13,10.39)
0.68 (0.29,1.59)	0.88 (0.10,7.95)	**Control**
Abortion		

B **Subgroup analysis of agonist protocol for OHSS**

Metformin		
1.00 (0.02,58.80)	**Simvastatin**	
0.46 (0.25,0.86)	0.46 (0.01,28.52)	**Control**
OHSS		

C **Subgroup analysis of antagonist protocol for clinical pregnancy OHSS**

Clinical pregnancy				
Myoinositol	1.90 (0.09,41.08)	2.92 (0.11,79.49)	3.24 (0.20,51.35)	2.56 (0.30,21.76)
1.13 (0.09,15.01)	**Pioglitazone**	1.54 (0.05,43.88)	1.71 (0.10,28.60)	1.35 (0.15,12.31)
0.52 (0.06,4.44)	0.46 (0.02,8.81)	**Sitagliptin**	1.11 (0.10,12.25)	0.88 (0.07,10.90)
0.47 (0.11,1.96)	0.41 (0.03,4.94)	0.89 (0.14,5.63)	**Metformin**	0.79 (0.14,4.55)
0.35 (0.11,1.09)	0.31 (0.03,3.17)	0.67 (0.11,4.11)	0.75 (0.31,1.83)	**Control**
OHSS				

Fig. 5 Netleague of primary outcomes for subgroup analysis (by protocol). (**A**) Netleague of clinical pregnancy and abortion of agonist protocol group (**B**) Netleague of OHSS of agonist protocol group (**C**) Netleague of clinical pregnancy and OHSS of antagonist protocol group. The comparisons of data are odds ratios (95% CI), which should be read from left to right. Odds ratio higher than 1 favor the left treatments, lower than 1 favor the right treatments. Significant results are in bold and underlined. *OHSS: ovarian hyperstimulation syndrome*

rates of clinical pregnancy or OHSS compared to controls (OR = 0.79, 95% CI 0.16–4.03; OR = 0.75, 95% CI 0.31–1.83; respectively). (Supplementary Fig. 10). The network analysis results of primary outcomes are shown in Fig. 5C. None of the treatments showed significant differences in clinical pregnancy rate or OHSS compared to

the control. Data for live birth or abortion rate analysis were not available.

Subgroup analysis based on BMI was limited because most studies reported BMI as mean ± standard deviation, making it difficult to categorize participants into distinct high- and low-BMI groups. However, two studies specifically included non-obese populations, and an analysis was conducted on these studies. Only data on clinical pregnancy and OHSS in the comparison of metformin and control were available for analysis. The results suggested that metformin did not significantly affect clinical pregnancy rates or the incidence of OHSS compared to the control group in non-obese PCOS patient (OR = 1.50 95% CI 0.90–2.50; OR = 0.56 95% CI 0.09–3.56) (Supplementary Fig. 11).

Small study effects and certainty assessment

The adjusted funnel plots showed no significant asymmetry in pairwise and network meta-analyses, suggesting minimal small-study effects (Supplemental Figs. 12–13). Evidence certainty for primary outcomes, assessed via CINeMA [26], ranged from moderate to very low: 1 comparison was rated moderate, 15 low, and 4 very low, with metformin-related comparisons receiving a moderate rating. Detailed CINeMA results are provided in Supplementary Tables 3–5.

Discussion

Principal findings

The optimal management of PCOS patients who receive IVF/ICSI is challenging for clinicians. Metformin, anti-obesity agonists, and inositol are recommended to improve metabolic profiles outcomes in PCOS patients [1]. However, evidence on their efficacy and safety during IVF/ICSI remains limited [15]. This systematic review and network meta-analysis, which included six commonly used medications across 20 studies, found that none of these drugs significantly improved clinical pregnancy rates, live birth rates, or abortion rates in PCOS patients. However, some drugs, such as metformin and myoinositol, showed potential in reducing OHSS risk, and influencing some ovarian response and side effects. No studies reported an increased risk of fetal abnormalities.

In healthy women, the risk of OHSS is approximately 2.2–8.6%, but this risk rises to 11% in women with PCOS symptoms [47]. Few interventions currently can be considered effective for OHSS [48, 49]. Our network analysis suggests that metformin may help mitigate OHSS risk by lowering E2 levels on the trigger day, as elevated serum E2 levels at the end of COS are known to increase the risk of OHSS [50]. Furthermore, by including a range of guideline-recommended medications for metabolic improvement in PCOS [1], our network analysis found that myoinositol may also offer benefits in the IVF/ICSI context, potentially reducing the risk of OHSS.

Our subgroup analysis based on COS protocols revealed that metformin may reduce OHSS risk in PCOS patients undergoing an agonist protocol, supporting guidelines recommending its use before and/or during FSH stimulation [1]. However, no significant benefits were observed for clinical pregnancy or OHSS risk in the antagonist protocol, aligning with ESHRE's recommendation against routine metformin use in antagonist COS protocols [51]. Our findings further reinforce existing guidelines and may inform clinical decision-making for PCOS patients undergoing IVF/ICSI according to different COS protocol.

We also examined the influence of BMI on the response to different medications among PCOS patients. Given that most studies reported BMI as mean ± standard deviation, it was not possible to distinctly categorize participants into high- and low-BMI subgroups. Only two studies exclusively focused on non-obese PCOS patients, allowing us to perform a pairwise meta-analysis with these studies. Results indicated that metformin did not significantly improve clinical pregnancy rates or reduce OHSS incidence compared to control in non-obese PCOS patients.

Comparison with existing literature

In partial contrast to Ara Unanyan's study, which reported that metformin improved clinical pregnancy rate in PCOS patients [52], our network analysis indicated that while metformin increased the number of mature oocytes, it did not significantly improve the clinical pregnancy rate. This discrepancy in pregnancy outcomes may be due to differences in the patient populations: Unanyan's study included PCOS patients who conceived after ovulation induction with clomiphene, letrozole, recombinant follicle-stimulating hormone, or following IVF/ICSI, while our study focused specifically on PCOS patients undergoing IVF/ICSI.

Our study found that myoinositol showed potential in reducing OHSS risk, aligning with the findings of Stefano Palomba et al. [49] from traditional meta-analyses, which relied on direct comparisons and provided robust results. Our network meta-analysis extended these findings by incorporating both direct and indirect evidence, indicating that myoinositol pretreatment may reduce OHSS risk, shorten gonadotropin treatment duration and reduce side effects, offering a broader perspective on treatment rankings. However, caution is needed as network meta-analyses may involve inconsistencies between direct and indirect comparisons and rely on the assumption of transitivity.

The study by Samarasinghe SNS found that insulin sensitizers had limited impact on reproductive outcomes in overweight or obese PCOS patients [53]. In contrast, Magzoub R et al. argued that more well-powered trials are needed before recommending metformin for treating non-obese infertile PCOS women [54]. Our study, focusing on non-obese PCOS patients, also found that metformin did not significantly improve pregnancy outcomes or reduce OHSS incidence. These results suggest that the effects of metformin in non-obese PCOS patients may differ from those in women with higher BMI, underscoring the importance of considering BMI when evaluating treatment efficacy.

Strengths of this meta-analysis

This study conducted a comprehensive and systematic literature search, rigorous screening, and data extraction, ultimately including 20 studies with low or moderate risk of bias. No global or local inconsistencies were observed, and the inconsistency test showed no direct or indirect differences. Additionally, the funnel plot did not suggest publication bias. We performed a quality assessment of the network meta-analysis using CINEMA and conducted subgroup analyses based on factors that may affect outcomes, which enhanced the credibility and persuasiveness of our findings.

Limitations

This study has several limitations. First, the limited number of studies on factors like obesity restricted subgroup analyses, highlighting the need for well-designed RCTs to explore their impact on IVF/ICSI outcomes. The lack of OHSS severity grading in most studies also underscores the need for standardized reporting to assess medication effects more precisely. Second, while no studies reported increased fetal abnormality risks, long-term follow-up is necessary to confirm safety. Third, the low or very low quality of evidence in many CINeMA assessments calls for higher-quality studies to strengthen clinical guidance. Lastly, network meta-analyses, though valuable, are subject to potential inconsistencies and rely on the assumption of transitivity, warranting cautious interpretation. Future research should aim to optimize drug selection and provide robust evidence for individualized treatment strategies.

Conclusion

The present findings suggest that neither metformin, anti-obesity agents, nor inositol significantly improved clinical pregnancy rates, live birth rates, or miscarriage rates in PCOS patients during IVF/ICIS. However, both metformin and myoinositol showed potential in reducing OHSS risk. Specifically, metformin was associated with a lower OHSS risk in agonist protocols, reduced E2 levels on the trigger day, increased mature oocyte numbers, and more side effects. Myoinositol appeared to shorten gonadotropin treatment duration with fewer side effects. Given the limitations of this analysis, further well-designed RCTs focusing on potential risk factors and long-term follow-up are needed to better assess the efficacy and safety of these treatments, clarify optimal drug selection, and provide clearer guidance.

Abbreviations

PCOS	Polycystic ovary syndrome
IVF	In vitro fertilization
ICSI	Intracytoplasmic sperm injection
RCTs	Randomized controlled trials
COS	Controlled ovarian stimulation
OHSS	Ovarian hyperstimulation syndrome
AMH	Anti-Müllerian hormone
MeSH	Medical Subject Heading
GLP-1	Glucagon-like peptide-1
ET	Embryo transfer
E2	Estrogen
BMI	Body mass index
SDs	Standard deviations
ORs	Odds ratios
SMDs	Standardized mean differences
CIs	95% confidence intervals
SUCRA	Surface under the cumulative ranking curve
CINeMA	Confidence in Network Meta-Analysis
SIDE	Separating Indirect from Direct Evidence

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

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Authors' contributions

All authors contributed to the study conception and design. LJL and GC collected and analyzed the data, and drafted the manuscript; LZX contributed to the analysis and interpretation of the data; XYQ and YC contributed to the interpretation of the data; HXD contributed to the data collection; LZX, LJL and GC designed the study and oversaw the data interpretation. All authors revised the manuscript and approved the version to be published.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable, as this research does not involve direct patient or animal contact.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Obstetrics and Gynecology, West China Second University Hospital, Sichuan University, Chengdu 610041, Sichuan, China. [2]Reproductive Endocrinology and Regulation Laboratory, West China Second University Hospital, Sichuan University, Chengdu 610041, Sichuan, China. [3]Key Laboratory of Birth Defects and Related Diseases of Women and Children, West China Second University Hospital, Ministry of Education, Sichuan University, Chengdu 610041, Sichuan, China. [4]The Joint Laboratory for Reproductive Medicine of Sichuan University, The Chinese University of Hong Kong, Chengdu 610041, Sichuan, China.

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