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Is it feasible to treat polycystic ovarian syndrome with or without insulin resistance using glucokinase activators as novel hypoglycaemic medications? A protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction A variety of hypoglycaemic drugs are used to treat polycystic ovarian syndrome (PCOS), but their efficacy remains insufficient. Glucokinase activators (GKAs) are a unique class of hypoglycaemic medications with emerging potential, notably in significantly reducing insulin resistance (IR). Nevertheless, the efficacy of GKAs in treating PCOS, particularly in the absence or presence of IR, remains uncertain. The meta-analysis protocol aims to address this knowledge gap, furnish evidence-based data to support potential revisions in PCOS treatment guidelines and promote the utilisation of GKAs in clinical settings.

Methods and analysis A comprehensive search will be conducted across the Cochrane Central Register of Controlled Trials, PubMed, Web of Science, Embase, Medline, Scopus, CNKI, Wanfang and VIP databases to identify randomised controlled trials investigating the use of GKAs in the treatment of PCOS, irrespective of the presence of IR. The search will encompass all available studies without language restrictions and cover the period from the inception of each database to 10 April 2024. Disputes will be resolved by talking with a third expert following the screening of articles and data extraction by two reviewers. The primary outcomes of interest encompass changes in anthropometric parameters, menstrual frequency, sex hormone levels, and glucose metabolism, while secondary objectives include lipid metabolism and adverse events. The methodological quality of each study will be assessed using Version 2 of the Cochrane Collaboration tool for assessing Risk of Bias (RoB 2.0), and the Grade of Recommendations, Assessment, Development and Evaluation (GRADE) technique will be used to assess the quality of evidence and degree of recommendation. The study duration of this study will be from 5 April 2024 to 10 April 2025.

Ethics and dissemination Since this study just analyses data that are readily available to the public and does not directly involve patient participation, ethical approval is not necessary. The findings will be made public by being published in a medical journal that is subject to peer review.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Restricted analytical studies to randomised controlled trials will minimise subjective bias and improve the accuracy and objectivity of the results.
⇒ In this meta-analysis, clinical symptoms, metabolic parameters and adverse events of polycystic ovarian syndrome (PCOS) patients will be used as outcome measures.
⇒ Screening of the PCOS population using the Rotterdam criteria will improve international recognition of the study findings.
⇒ As glucokinase activators are novel hypoglycaemic agents, there are not many studies, and the number of studies that may be included is small.
⇒ The study uses version 2 of the Cochrane collaboration tool for assessing Risk of Bias (RoB 2.0) to assess the quality of the included studies and the Grade of Recommendations, Assessment, Development and Evaluation (GRADE) to assess the quality of evidence and the level of recommendation.

PROSPERO registration number CRD42024535633.

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a prevalent endocrine disorder affecting women of childbearing age, with a prevalence ranging from 10% to 13%.[1] The most common diagnostic criteria for PCOS is the Rotterdam diagnostic criteria,[2] established in 2003 and required the presence of two of the following criteria: irregular menstrual patterns or ovulation failure, clinical or biochemical signs of hyperandrogenism (Ferriman-Gallwey score >5 or testosterone level>2.6 mmol/L), and ovarian ultrasound findings indicative of polycystic ovaries (number of follicles ≥12 with a diameter of 2–9 mm or ovarian

volume >10 cm^3).[1 2] Irregular menstrual patterns include polymenorrhoea (cycles <21 days), oligomenorrhoea (cycles ranging from 35 days to 6 months), amenorrhoea (cycles >6 months) or irregular vaginal bleeding. In addition, it is imperative to conduct an oral glucose tolerance test to rule out secondary diabetes, along with assessments of sex hormone-binding globulin, androgens (such as androstenedione and dehydroepiandrosterone sulfate), 17α-hydroxyprogesterone, cortisol to exclude other diseases leading to hyperandrogenaemia. PCOS should be differentiated from other conditions characterised by persistent anovulation, high androgen and insulin resistance (IR), such as hypothalamic amenorrhoea, hyperprolactinaemia, hypercortisolism, idiopathic hypertrichosis, androgen-secreting tumours and the use of exogenous androgens. PCOS is a multifaceted disorder with an unclear aetiology, often characterised by delayed diagnosis, suboptimal management and various associated complications such as gestational diabetes mellitus,[3] miscarriage[1] and fetal development restriction during pregnancy.[4] Long-term risks associated with PCOS include but are not limited to cardiovascular diseases,[5] type 2 diabetes and non-alcoholic fatty liver disease.[6 7] PCOS is associated with IR,[8] abdominal obesity, as well as disorders of glucose and lipid metabolism. The aetiology of PCOS includes IR, chronic inflammation and an imbalance in sex hormone ratios.[9 10] Some studies have shown that IR will inhibit hepatic synthesis of sex hormone-binding globulin, which will further increase the concentration of free androgens that can reduce the uptake and utilisation of glucose by the cells, in turn decreasing insulin sensitivity.[11 12] Furthermore, IR may influence follicular growth, a factor strongly correlated with adverse pregnancy outcomes in PCOS, such as an increased risk of miscarriage and a decreased incidence of live births. About 75% of patients with PCOS manifest IR as a prevalent characteristic.[1] The pivotal role of IR in the pathophysiology of PCOS is undeniable, causing disturbances in glucose homoeostasis. These disruptions include decreased GLP-1 release, impaired hepatic glycogen synthesis, heightened glucagon production and delayed early phase of insulin secretion, collectively contributing to abnormalities in glucose metabolism.[13] The PI3K/AKT and Mitogen Activated Protein Kinases (MAPK)/Insulin Receptor Substrate (IRS) pathways are involved in IR linked to PCOS.[14 15] Diminished PI3K expression impacts embryo implantation and endometrial alterations in the uterus, while ovarian glucose metabolism disturbances contribute to ovulatory dysfunction locally. Activation of the MAPK/IRS pathway within the uterus suppresses the expression of glucose transporter protein 4. Timely intervention for metabolic irregularities is crucial in the management of PCOS to enhance pregnancy outcomes. There is an increasing demand for robust evidence-based justification to support the revision of PCOS treatment guidelines.

Currently, the predominant hypoglycaemic medications used in the treatment of PCOS comprise thiazolidinediones (TZD), Met, DPP4i, SGLT2i and GLP1RA.[16] TZD increases insulin sensitivity by activating peroxisome proliferator-activated receptor-γ (PPAR-γ), with more adverse effects, including water and sodium retention, weight gain, oedema, osteoporosis, cardiovascular events and a potential increased risk of cancer. Met can inhibit hepatic glycogenolysis and enhance insulin sensitivity in peripheral tissues. DPP4i and GLP1RA both belong to glucagon-like peptide-1 drugs. By inhibiting the release of glucagon, slowing down gastric emptying, and regulating the incretropin system, they contribute to the maintenance of blood glucose homoeostasis, resulting in reductions in body weight and HbA1c levels. Gastrointestinal reactions such as nausea, vomiting and diarrhoea are common adverse reactions associated with Met, DPP4i and GLP1RA.[16 17] SGLT2i functions by inhibiting SGLT 2 in the renal tubules, increasing the urinary glucose excretion to achieve hypoglycaemia, improving IR, reducing body weight and reducing renal damage. However, this mechanism also heightens the susceptibility to genital tract infections and urinary tract infections. Both GLP1RA and SGLT2i are anti-inflammatory, fight oxidative stress and reduce adverse cardiovascular outcomes. The dosage of these hypoglycaemic drugs varies by type, each offering distinct advantages and disadvantages. The prevalence of PCOS is progressively rising in contemporary society, underscoring the growing need for the continuous exploration and development of novel hypoglycaemic agents. Research into new hypoglycaemic medications is imperative to enhance the efficacy of PCOS treatment strategies and address the increasing burden of this condition.

Glucokinase activators (GKAs) are a potentially effective class of hypoglycaemic medications. With compounds such as dorzagliatin and liver-specific activators such as TTP399, GKAs have demonstrated effectiveness in enhancing pancreatic islet function and reestablishing glucose homeostasis with negligible side effects.[18] Dorzagliatin, a fourth-generation GKA, is the inaugural hypoglycaemic medication of its class approved for commercial distribution in China, following the favourable outcomes observed in the SEED and DAWN studies. Dorzagliatin has demonstrated substantial reductions in blood glucose levels in individuals with type 2 diabetes, accompanied by initial enhancements in insulin secretion and pancreatic β-cell function.[19 20] However, it is essential to note that dorzagliatin may exacerbate dyslipidaemia, necessitating careful consideration of this potential side effect prior to its administration, especially for people with genetic hyperlipidemi.[21] Glucose kinase (GK) serves as a pivotal enzyme in cellular glucose metabolism, playing a crucial role in autoregulation to maintain glucose homoeostasis.[22] It uses organ mobilisation in a glucose-concentration-dependent manner to regulate blood glucose levels. Presently, the primary axes through which GK regulates the organism's glucose homoeostasis include the islet-hepatic axis, the intestinal L-cell-islet axis and the neuronal-intestinal cell-islet axis.[23] Elevated blood glucose levels prompt an increase

in GK activity, leading to the stimulation of GLP-1 release from intestinal pancreatic L-cells. This cascade results in heightened insulin secretion from pancreatic β-cells, augmented hepatic glycogen synthesis, reduced hepatic glycogen breakdown and collectively contributes to the reduction of blood glucose levels.[24] Conversely, decreased blood glucose levels lead to a reduction in GK expression, aiding in the maintenance of blood glucose levels within the physiological range. Presently, the use of GKAs for the treatment of PCOS lacks an evidence-based foundation. This meta-analysis aims to systematically evaluate completed or ongoing randomised controlled trials that compare the efficacy and safety outcomes of GKAs alone or in combination with placebo or no intervention in the management of PCOS.

METHODS AND ANALYSIS

This study will be reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guildlines.[25] The PRISMA-P was added in online supplemental material 1, and we have registered this study on the PROSPERO platform (CRD42024535633).

Eligibility criteria

This meta-analysis will include completed or ongoing randomised controlled studies, which will be designed according to the PICOS criteria: (P: population; I: intervention; C: comparisons; O: outcome; S: study type).

The following is the PICOS strategy followed for this meta-analysis protocol:

Population: Women diagnosed with PCOS between the ages of 18 and 45, according to the Rotterdam criteria, with or without IR.[26] There is no restriction on the number of people included.

Interventions: GKAs alone or in combination with other agents.

Comparisons: Placebo or no intervention.

Outcome: Clinical symptoms associated with PCOS, metabolic markers and adverse events are the main outcomes. These include weight, body mass index, waist-to-hip ratio, menstrual frequency changes, luteinising hormone, follicle-stimulating hormone, free testosterone T, anti-Müllerian duct hormone, sex hormone-binding globulin, free androgen index, dehydroepiandrosterone, fasting insulin, blood glucose area under the curve, insulin release test area under the curve, IR index (homeostasis model assessment for insulin resistance (HOMA-IR)), ovarian volume, etc. Secondary outcomes include lipid profiles and other adverse events, such as hypoglycaemia, gastrointestinal distress, hepatic and renal impairment, cardiovascular and cerebrovascular events, and total cholesterol, triglyceride, low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol.[26 27]

Study type

Completed or ongoing randomised controlled clinical trials.

Table 1 PubMed database search formula

	Search strategy
#1	(((((((Polycystic Ovary Syndrome(MeSH Terms)) OR (Stein-Leventhal Syndrome(Title/Abstract))) OR (Stein Leventhal Syndrome(Title/Abstract))) OR (Sclerocystic Ovarian Degeneration(Title/Abstract))) OR (Sclerocystic Ovary Syndrome(Title/Abstract))) OR (Polycystic Ovarian Syndrome(Title/Abstract))) OR (Sclerocystic Ovaries(Title/Abstract))) OR (Sclerocystic Ovary(Title/Abstract))
#2	((((((((((((((((((Glucokinase activators(MeSH Terms)) OR (piragliatin(Title/Abstract))) OR (RO4389620(Title/Abstract))) OR (dorzagliatin(Title/Abstract))) OR (HMS5552(Title/Abstract))) OR (globalagliatin(Title/Abstract))) OR (SY-004(Title/Abstract))) OR (LY2608204(Title/Abstract))) OR (MK-0941(Title/Abstract))) OR (AZD1656(Title/Abstract))) OR (PB-201(Title/Abstract))) OR (PF-04937319(Title/Abstract))) OR (PF-04991532(Title/Abstract))) OR (AMG 151(Title/Abstract))) OR (ARRY-403(Title/Abstract))) OR (TTP399(Title/Abstract))) OR (GKI-399(Title/Abstract))) OR (AZD 6370(Title/Abstract))) OR (TMG123(Title/Abstract))
#3	#1 AND #2

Exclusion criteria

We will exclude case reports, animal studies, theoretical studies, reviews, observational studies, cross-sectional studies, case controls, case series, conference abstracts, book chapters, non-peer-reviewed articles and studies for which relevant data cannot be obtained despite efforts.

Search strategy

We will search the following databases: PubMed, Web of Science, Embase, Medline, the Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, CNKI, Wanfang Data and VIP databases, in accordance with the inclusion and exclusion criteria of this study. We will monitor trial records submitted to ClinicalTrials.gov for more findings on PCOS patients with GKAs trials and incorporate studies published from the time of their inception to 10 April 2024, without language limits. The Mesh phrases “polycystic ovary syndrome” and “glucokinase activators” will be the focal points of the search formula. The comprehensive search approach as demonstrated by PubMed is displayed in table 1. The search strategy for all databases is provided in online supplemental material 2. Three stages will be taken in order to filter the literature for inclusion: A preliminary search will be carried out, followed by a screening of the abstracts and titles. Finally, we will search the entire text if it satisfies the first set of requirements. After importing the retrieved results into EndNote V.X9, duplicate research will be filtered away to produce the final list of included literature.

Study selection

All selection processes for this meta-analysis will be carried out by two independent researchers (GZ and

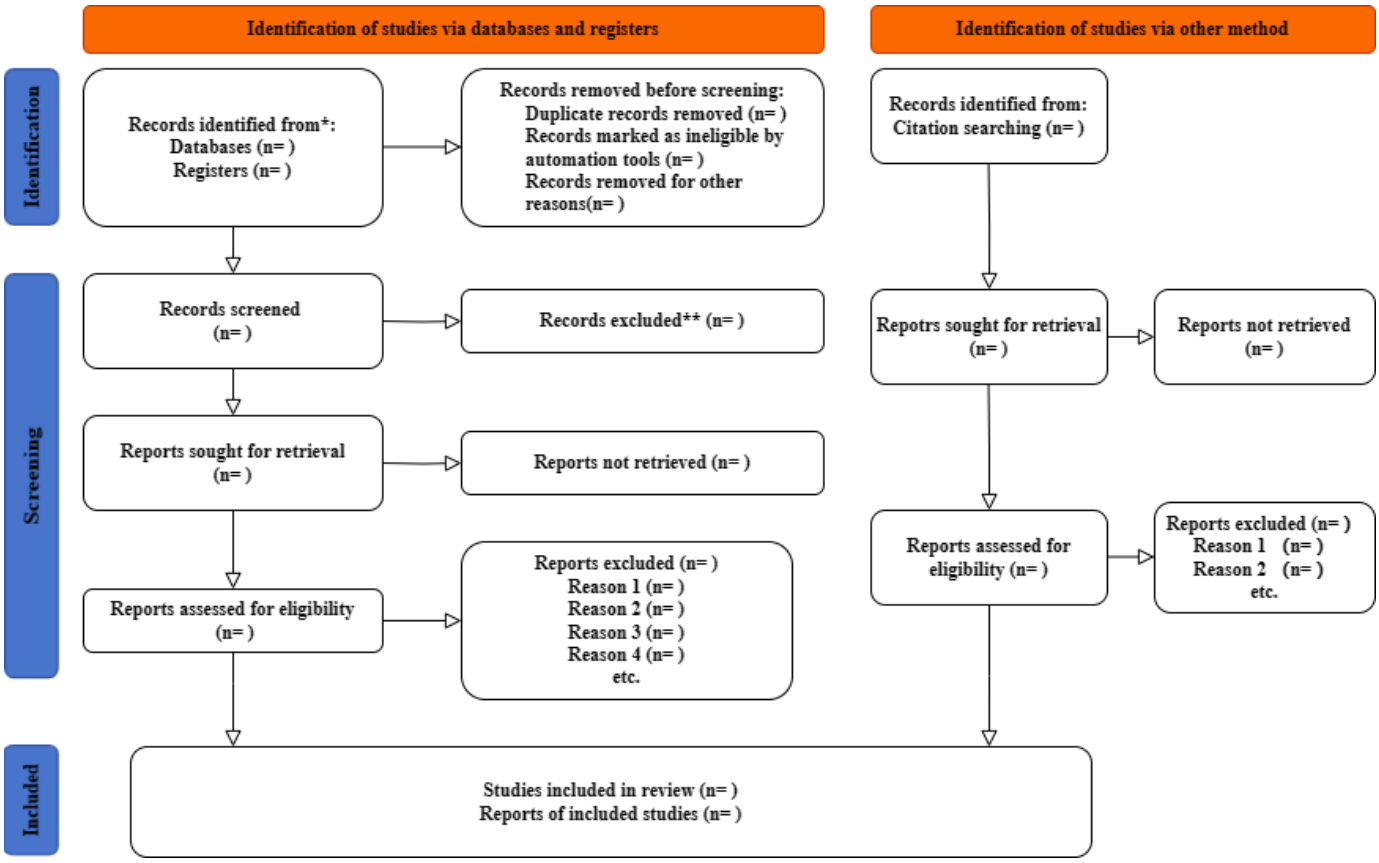

Figure 1 PRISMA flow diagram for systematic review and meta-analysis. *Consider, if feasible to do so, think about reporting the total number of records found in each database or register that was searched (instead of the overall number found in all databases and registers). **The number of records that were eliminated manually and the number that were eliminated using automated techniques, if any. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

YM), and cross-checking will be done at the end of their respective search processes and the reasons for exclusion of excluded studies will be recorded. In case of disagreement, two professionals (LZ and SY) will negotiate a solution or discuss collectively to obtain a final solution to ensure the quality of the included literature. The ultimate included studies will be presented according to the PRISMA statement (figure 1).

Data extraction

After screening the included studies, data extraction will involve two independent researchers (GZ and TZ) extracting relevant study information, including author details, publication date, study characteristics, intervention details, basic demographic measurements of the included population, the number of participants in the trial and control groups, name and dose of the drug, dosage cycle, follow-up duration, and the outcome metrics (including adverse events) that are the focus of this meta-analysis. The various data included in the study will be tallied into an Excel spreadsheet to obtain a database. If there is a discrepancy between the two investigators during the data extraction process, the final database will also be resolved by consultation between the two senior experts (LZ and XLiu).

Missing data

For studies with missing or incomplete data, we will make our best efforts to contact the first or corresponding author by phone or email. If there is no response, we will exclude the study at the stage of analysing the data and will indicate these missing data in the discussion section.

Quality assessment

As the studies contained in the present meta-analysis are randomised controlled trials, we will use version 2 of the Cochrane collaboration tool for assessing Risk of Bias (RoB 2.0) to assess the quality of the included studies.[28] The Grade of Recommendations, Assessment, Development and Evaluation (GRADE)[29] scale assesses the quality of evidence and the level of recommendation. This literature quality assessment tool will be evaluated across six domains: selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias. The risk of bias for each area will be divided into three levels: low risk of bias will be identified as green, potential concerns will be indicated by yellow, and a high risk will be highlighted in red. The assessment tool developed by the Cochrane Collaboration's methodologists, editors and systematic reviewers aims to mitigate researcher bias and enhance the reliability of clinical trials. If the risk of bias across

all domains is low, the overall risk of bias is classified as low; in cases where there are some concerns but no high risk of bias, the final risk of bias is categorised as some concerns; and if there is a high level of bias present, the overall risk of bias is deemed high.

Statistical analyses

Data will be analysed by using Review Manager V.5.4 (RevMan V.5.4) software. Continuous variables will be analysed using mean and SD, while the analysis of categorical variables will be done with risk ratios and 95% CIs. A random effects model is selected when $p<0.10$ and $I^2>50\%$ indicate less heterogeneity, whereas a fixed effects model is used if $p>0.10$ and $I^2<50\%$ indicate more heterogeneity in the study. Whereas 25%–50% denotes mild heterogeneity, 50%–75% denotes substantial heterogeneity and 75%–100% denotes severe heterogeneity, according to an I^2 value of 0%–25% without heterogeneity.[15] To assess publication bias and mitigate bias arising from the meta-analysis process, a funnel plot will be generated if more than ten studies are included. In this plot, the SE value is plotted on the ordinate axis, while the effect size is represented on the abscissa axis.[30] A publication bias is considered minimal when the data points exhibit symmetry and are distributed on both sides of the funnel plot. Egger's test is used to evaluate potential publication bias for each outcome.[31]

Sensitivity analyses

To verify the robustness and reliability of the results, we will conduct sensitivity analysis using Stata V.18 software, strictly according to the exclusion criteria of the studies, and eliminate studies with a high risk of bias. In addition, we will use forest plots to evaluate the effect on the pooled effects of each separate study and conduct a cumulative meta-analysis to assess whether the combined results are stable. If the pooled effect is not significantly changed after excluding a study, it means that the study did not significantly affect the results, and the results of the meta-analysis will be stable. Similarly, if a significant change occurs, then the results are unstable.

Subgroup analyses

It will be conducted based on control group characteristics, the presence of IR in PCOS patients and specific types of GKAs. First, because there are a lot of randomised controlled trials of glucose-lowering drugs for PCOS, in which the control groups are set up differently, including positive control group (effective glucose-lowering drugs) and negative control group (placebo), it is easy to bias the efficacy of the drugs of the GKAs trial. In order to minimise the human element, we will conduct subgroup analyses of the positive and negative control groups. Second, it is unclear whether GKAs efficacy is consistent in PCOS with or without IR, so we will also perform subgroup analyses based on PCOS with or without IR. Third, because of the variety of GKAs types, with the distinction between biphasic and monophasic GKAs and different targets of action, subgroup analyses should also be came true based on the specific types of GKAs in order to identify the type of GKAs that is most likely to be of benefit in PCOS.

Patient and public involvement

It is important to state that there are no patients and the public involved in the question collection and study design.

DISCUSSION

The revision of prevailing medical guidelines represents a crucial aspect of evidence-based medicine. IR is a key pathological characteristic of PCOS, a prevalent endocrine condition in women. IR can increase glucose and lipid metabolism, increase the risk of cardiovascular and cerebrovascular diseases and more pregnancy complications in PCOS.[32] PCOS is a disease that requires long-term chronic management, so patient compliance and confidence in treatment are very important. It is very necessary to provide effective and safe drugs to treat PCOS.[3 33 34] Metformin remains the primary medication prescribed to the majority of patients with PCOS as a first-line medication,[19] and GKAs have emerged as novel hypoglycaemic agents recently.[21 35] These agents exhibit promise in enhancing IR and possess significant clinical research significance.[36] There is evidence that GKAs have the advantages of good efficacy and high safety in the treatment of type 2 diabetes, which can significantly improve IR.[37] Regrettably, there is a dearth of relevant studies investigating the use of GKAs in PCOS treatment. Our meta-analysis protocol aims to address this gap in the literature by assessing the efficacy of GKAs in managing PCOS and examining their impact on IR. GKAs offer a potential alternative for enhancing insulin secretion in the context of PCOS.[38] However, it has been proposed that the long-term negative effects of dorzagliatin should be noted in terms of uric acid, lactic acid, lipid and hepatic and renal function, and cardiovascular parameters.[39] This meta-analysis serves to ascertain whether these adverse events are heightened with the use of dorzagliatin. Further research is warranted to investigate the safety profile of GKAs and their associated adverse effects. Our hypothesis regarding the potential utilisation of GKAs in the treatment of PCOS and in ameliorating IR can be partially explored, providing medical evidence to bolster the refinement of PCOS treatment protocols. This systematic review and meta-analysis will synthesise multiple RCTs results to improve clarity of this topic and directly or indirectly reflect the therapeutic of GKAs. However, it is universally acknowledged that the reliance on a restricted number of RCTs in this study may constrain its capacity to comprehensively address the diversity in patient demographics, treatment approaches, and clinical endpoints linked to the utilisation of GKAs in PCOS. Furthermore, the meta-analysis could be susceptible to potential confounding factors, publication bias and may overlook valuable insights provided by non-randomised

trials. We will include randomised controlled trials. The duration of intervention time, type of GKAs and duration of medication may vary, so we cannot ignore the effects of heterogeneity. Complex sensitivity analysis and subgroup analysis are also challenging. Additionally, our investigation did not delineate the specific mechanisms through which GKAs operate in the treatment of PCOS. Further studies are needed to elaborate on the specific mechanisms by which GKAs improve PCOS endocrine.[1] It is currently unclear whether GKAs will be used to treat PCOS, and more evidence-based medical evidence is needed to provide valuable options for clinicians and patients.

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Contributors GZ conceptualised and designed the study. XLu and PL wrote the original draft. TZ and ZL prepared the initial manuscript and facilitated revisions in consultation with SY and XLiu. YM was responsible for analysing data. LZ developed the statistical analysis methods and provided financial support. All authors have reviewed and authorised the final version of the manuscript. GZ is the guarantor.

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Competing interests None declared.

Patient and public involvement statement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Ethical approval for this study is not required. Because the original data for this meta-analysis are derived from publicly available data, which ensure that no private information about the participants will be disclosed, and the meta-analysis does not require the actual participation of patients. The results will be published in a peer-reviewed medical journal.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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