INPLASY PROTOCOL

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Conflicts of interest:
None declared.

The effectiveness and safety of exenatide in the treatment of polycystic ovary syndrome: A systematic review and meta-analysis

Hu, Y[1]; Guo, YY[2].

Review question / Objective: **The aim of this meta-analysis is to evaluate the efficacy and safety of exenatide/exenatide+ metformin in treating patients with polycystic ovary syndrome (PCOS).Participants: females diagnosed with polycystic ovary syndrome according to Rotterdam criteria; Intervention(s): exenatide single or combined exenatide in the treatment of PCOS; comparison(s): exenatide versus metformin or exenatide combined with metformin versus metformin; outcomes: effectiveness metrics including pregnancy rate, menstrual frequency ratio, sex hormone levels, changes in obesity, metabolic disorders, and parameters of safety evaluated by diarrhea, nausea, headache, vomiting and so on; Study: randomized controlled trials in humans with results published.**

Information sources: **We search studies from electronic databases (PubMed, Embase, Web of Science, Cochrane Library). Randomized controlled trials on humans are conducted from their establishment date to November 2022 employing a strategy combining MeSH words with free words. The employed terms included "Polycystic Ovary Syndrome"[MeSH], Ovary Syndrome, Polycystic [Title/Abstract], Syndrome, Polycystic Ovary [Title/Abstract], "Exenatide"[MeSH], Exendin-4[Title/Abstract], Peptide, Ex4[Title/Abstract], randomized controlled trial [Publication Type], randomized [Title/Abstract]. In addition, we sign up with PubMed to receive automated electronic notifications for any new articles containing the prespecified keywords, and searches will also be re-run prior to the final analysis.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 12 November 2022 and was last updated on 12 November 2022 (registration number INPLASY2022110055).

INTRODUCTION

Review question / Objective: **The aim of this meta-analysis is to evaluate the efficacy and safety of exenatide/exenatide+ metformin in treating patients with polycystic ovary syndrome (PCOS).Participants: females diagnosed with polycystic ovary syndrome according to Rotterdam criteria; Intervention(s):**

exenatide single or combined exenatide in the treatment of PCOS; comparison(s): exenatide versus metformin or exenatide combined with metformin versus metformin; outcomes: effectiveness metrics including pregnancy rate, menstrual frequency ratio, sex hormone levels, changes in obesity, metabolic disorders, and parameters of safety evaluated by diarrhea, nausea, headache, vomiting and so on; Study: randomized controlled trials in humans with results published.

Condition being studied: Polycystic ovary syndrome (PCOS) is the most common endocrine disease among women within reproductive age which is involved in excess androgen levels, oligomenorrhoea or amenorrhea, anovulation/oligo-ovulation, and polycystic morphology of the ovaries, according to the Rotterdam criteria.Although insulin resistance and obesity are not indispensably diagnostic criterion for PCOS, they are integral parts of pathophysiological changes that occur with them. The insulin resistance and obesity alone or combined with sex hormone disorder may substantially lead to reproductive and metabolic abnormalities, and contribute to cardiovascular disease, diabetes mellitus, nonalcoholic fatty liver in the future. Exenatide, a member of the GLP-1 receptor agonist family, has been used to treat diabetes and obesity mainly due to its prominent effects on insulin resistance, weight loss, and metabolic disorders. In addition, clinical randomized controlled trials have proved that exenatide has beneficial effects on pregnancy rate[5, 6], menstrual frequency ratio, insulin resistance, and weight loss in women with PCOS. Metformin was conditionally recommended for obese PCOS females who were combined with metabolic abnormalities in 2018 due to guideline for the assessment and management of PCOS. In this meta-analysis, we aim to evaluate the efficacy and safety of exenatide/exenatide+ metformin in treating patients with polycystic ovary syndrome.

METHODS

Participant or population: Inclusion: females diagnosed with polycystic ovary syndrome according to Rotterdam criteria.Exclusion criteria: women with pregnant, unintentional, liver, or kidney dysfunction.

Intervention: Intervention(s): exenatide single or combined metformin in the treatment of PCOS.

Comparator: Comparison(s):metformin in the treatment of PCOS.

Study designs to be included: Randomized controlled trials in humans with results on Pregnancy rate, Menstrual frequency ratio, sex hormone, metabolic disorders or parameters of safety.

Eligibility criteria: PCOS: women with PCOS diagnosed by Rotterdam criteria.

Information sources: We search studies from electronic databases (PubMed, Embase, Web of Science, Cochrane Library). Randomized controlled trials on humans are conducted from their establishment date to November 2022 employing a strategy combining MeSH words with free words. The employed terms included "Polycystic Ovary Syndrome"[MeSH], Ovary Syndrome, Polycystic [Title/Abstract], Syndrome, Polycystic Ovary [Title/Abstract], "Exenatide"[MeSH], Exendin-4[Title/Abstract], Peptide, Ex4[Title/Abstract], randomized controlled trial [Publication Type], randomized [Title/Abstract]. In addition, we sign up with PubMed to receive automated electronic notifications for any new articles containing the prespecified keywords, and searches will also be re-run prior to the final analysis.

Main outcome(s): Primary outcome: pregnancy rate, Menstrual frequency ratio, and sex hormone levels.

Quality assessment / Risk of bias analysis: The risk of bias for each RCT is evaluated

by the Cochrane Collaboration's tool which held 7 domains related: random sequence generation (selection bias), allocation concealment, blinding (blinding of participants and providers, blinding of outcome assessment), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other bias, described by "low risk", "unclear" and "high risk".

Strategy of data synthesis: Meta analysis and forest plots are performed by using Rev Man 5.4. Continuous variables are expressed as standard mean difference (SMD) or mean difference (MD) with 95% CI based on the consistency of research units. RR with 95% confidence interval (CI) of each original research is collected for meta-analysis using the Mantel/Haenszel model when it comes to dichotomous data. Heterogeneity is assessed by the X^2 test, expressed by I^2 values. $I^2$0.1 indicate little heterogeneity among original studies. Analyses are performed by using fix-effects models. $I^2 \geq 50\%$ indicated great heterogeneity, subgroup analysis or sensitivity analysis will be performed. If no reason for the heterogeneity can be found, and the heterogeneity is within acceptable limits, a random-effects model can be used. P values <0.05 is considered significant statistic of the meta-analysis.

Subgroup analysis: In subgroup analyses, exenatide combined with metformin is compared with metformin.

Sensitivity analysis: If $I^2 \geq 50\%$ indicated great heterogeneity, subgroup analysis or sensitivity analysis will be performed. If no reason for the heterogeneity could be found, and the heterogeneity was within acceptable limits, a random-effects model could be used. We use Revman for sensitivity analysis, and reflect the sensitivity of the article by deleting one of the articles.

Country(ies) involved: China.

Keywords: exenatide, metformin, pregnancy, menstrual frequency ratio, sex hormones, weight loss, insulin resistance.

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