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Original Research Article

The role of metformin in the management of endometriosis: A systematic review and meta-analysis

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Abstract

Purpose: *To analyze the activity of metformin in endometriosis, with a view to alleviating disease progression.*
Methods: *A search was conducted using electronic databases such as CNKI, VIP, CBM, WANFANG, Embase, PubMed, Cochrane, and Web of Science from January 1980 to January 2022 for randomized trials involving any intrapartum fetal surveillance method. A network meta-analysis was performed within a frequentist framework, and it was assessed for quality and network inconsistency of the trials. A ninety-five percent confidence interval (CI) was used to report the relationship between metformin levels and patients with endometriosis.*
Results: *Eight eligible studies which included 688 patients were evaluated in this meta-analysis. The primary indicators were treatment efficiency and CA-125 level. Metformin significantly increased treatment efficiency (SMD = 3.29, 95 % CI 2.01, 5.40, p < 0.00001). As expected, metformin also reduced the CA-125 level in endometriosis patients as a result (Odds Ratio, OR = -1.20, 95 % CI: -1.40 - 1.00, p < 0.00001).*
Conclusion: *Metformin alleviates pains caused by endometriosis. However, some studies had scanty information about alleviating clinical symptoms other than basic medical research. More randomized controlled trials are needed to confirm treatment efficacy.*

Keywords: *Metformin, Endometriosis, Meta-analysis*

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INTRODUCTION

Endometriosis is a common and debilitating gynecological disease characterized by the presence of endometrial-like tissue outside the uterus. It affects approximately 10% of women of reproductive age and is associated with a range of symptoms, including pelvic pain, dysmenorrhea, dyspareunia, and infertility [1]. Despite advances in surgical and medical management, the optimal treatment strategy for endometriosis remains controversial, and the disease often recurs after treatment. Therefore, new therapies are urgently needed.

One promising candidate is metformin, an oral hypoglycemic agent that has been used for the treatment of type 2 diabetes for decades.

Recently, metformin has been shown to have anti-inflammatory, anti-oxidative, and anti-tumor effects in various diseases, including endometriosis. Preclinical studies have demonstrated that metformin can inhibit the proliferation and invasion of endometrial cells, reduce the formation of endometriotic lesions, and alleviate pain in animal models of endometriosis [2].

Although several clinical trials have investigated the efficacy of metformin in the treatment of endometriosis, the results have been inconsistent, and the optimal dosing regimen and duration of treatment remain unclear. Therefore, a comprehensive meta-analysis of the available evidence is needed to determine the efficacy and safety of metformin for the treatment of endometriosis.

The purpose of this study is to conduct a meta-analysis of randomized controlled trials to evaluate the clinical efficacy of metformin in the treatment of endometriosis. The primary outcomes are treatment efficiency and CA-125 level. The findings of this study will provide clinicians with valuable insights into the potential benefits and limitations of using metformin as a treatment option for endometriosis patients.

METHODS

Search strategy

Two independent reviewers performed a literature search in 3 electronic databases (PubMed, EMbase, and Cochrane Library), and strictly followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2009 Checklist Protocol [3].

Studies published before May 31, 2020, were retrieved using the following keywords: “Metformin” (Mesh) or Dimethylbiguanidine or Dimethylguanylguanidine or Glucophage or Metformin hydrochloride or Hydrochloride, Metformin or Metformin HCl or HCl, Metformin and (“Endometriosis” (Mesh) or Endometrioses or Endometrioma or Endometriomas). Preselected results were limited to English-language publications. Manual searches were also conducted to acquire potentially eligible articles that might have been missed during computer-based searches [4].

Study selection

Two investigators reviewed the titles and abstracts of all studies identified by the search strategy to generate a list of relevant articles, and the full texts were searched and read by other two reviewers. Any disagreement was resolved by discussion or based on the judgment of a third expert until a consensus was reached.

Eligibility criteria

Participants who met the Diagnostic Criteria for Endometriosis: Dysmenorrhea, chronic pelvic pain, painful intercourse, and infertility. Gynecological pelvic examination, imaging, or laparoscopy revealed the focus of the endometriosis.

Those excluded were breastfeeding or pregnant women, patients with severe liver and kidney diseases, patients with endometriosis surgery, and patients with previous aromatase inhibition therapy.

Efficacy criteria

Significantly effective: Clinical symptoms such as dysmenorrhea and chronic pelvic pain disappeared after treatment, and no pelvic mass was found by imaging examination; Effective: The relevant clinical manifestations were improved but did not disappear after treatment, and the pelvic mass reduced or disappeared by imaging examination; Invalid: The symptoms have not improved or even worsened after treatment, and the masses did not reduce or even enlarge on imaging inspection.

Statistical analysis

The meta-analysis was conducted using Cochrane Review Manager software (RevMan 5.3). Continuous outcomes were measured with Standard mean differences (SMDs) and dichotomous outcomes with risk ratios (RRs), both at 95 % confidence intervals (CIs). Heterogeneity measurement was performed with forest plots as well as calculating I^2 (> 50 % was considered extensive heterogeneity). A fixed-effect model was used to combine study results if heterogeneity was minimal; otherwise, a random-effect model was used. Potential publication bias was also examined qualitatively with Funnel plots using RevMan software when the distribution of CI deviated significantly.

RESULTS

Heterogeneity test

Eight trials in this study were tested for heterogeneity, I^2 = 68 % > 50 %, and Q test p < 0.1, suggesting that there was heterogeneity among the trials selected in this study and

random effects were selected for meta-analysis. The reasons for heterogeneity was also determined. Based on the data obtained, it was highly suspected that the source of heterogeneity was that the two groups have different therapeutic effects. Subgroup analysis was carried out according to treatment efficacy. Fixed effects were selected for 8 trials for meta-analysis, and the results were as follows.

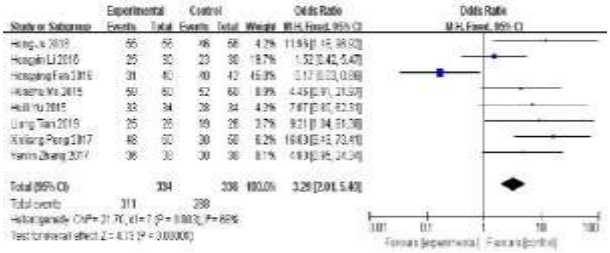

Figure 1: Forest plot of treatment efficacy

Results of meta-analysis given by the fixed effects showed that therapeutic effect of experimental group was 3.29 higher than that of control group, and degree of increase was statistically significant, $p < 0.05$ (Figure 1).

Sensitivity analysis

Results of the sensitivity analysis of 8 trials are as follows.

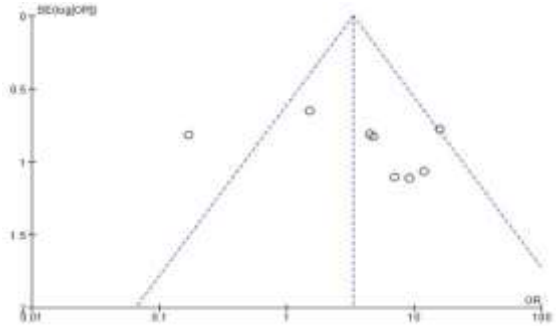

Figure 2: Funnel plot of treatment efficacy

Figure 2 revealed two groupings based on different efficacy judgments, and the trial showed different sensitivities. Therefore, it was highly suspected that different efficacy groups were responsible for heterogeneity.

Meta-regression analysis of heterogeneity

Based on a high suspicion of heterogeneity caused by different sources of blood samples, the random effect size was used as dependent variable, while the blood sample source was grouped as an independent variable, and meta-regression was performed.

Subgroup analysis

Based on the subgroup analysis, there was no obvious heterogeneity between the two groups, which means that the choice of therapeutic effect group would greatly affect the results of meta-analysis. Results showed that two groups of patients have no significant heterogeneity, and the effect size reached 1.44 ($z = 4.67$; $p < 0.05$), in getting a large effect size, which means that metformin group is significantly better than effective level of efficacy control group. Secondly, in the effective category, although effect size reached 1.34 and was not significant ($z = 1.80$, $p > 0.05$). Effective level of metformin used in the treatment group was not significantly different from control group in terms of efficacy. Invalid categories were not included in subgroup analysis (Figure 3 and Figure 4).

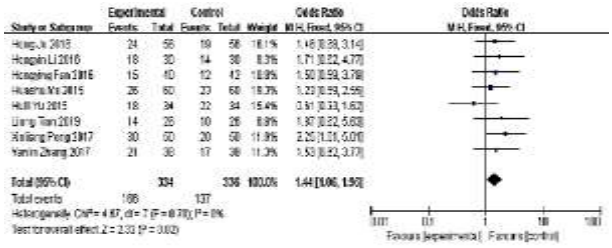

Figure 3: Forest plot of excellent rate

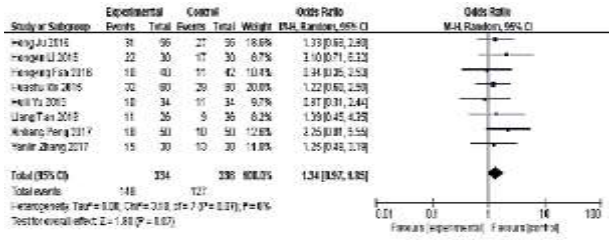

Figure 4: Forest plot of invalid rate

Subgroup bias test

It can be seen from Figure 4 that the funnel chart of this study was symmetrical, so it can be judged that there was no publication bias in the literature of this study (Figure 5 and Figure 6).

CA-125 level subgroup analysis

Based on the CA-125 subgroup analysis, there was no significant heterogeneity between the two groups of CA-125 patients, and effect size gets -1.20, and it was significant ($z = 11.82$ $p < 0.05$), which means that CA-125 detection level of metformin group was significantly lower than that of the control group (Figure 7 and Figure 8).

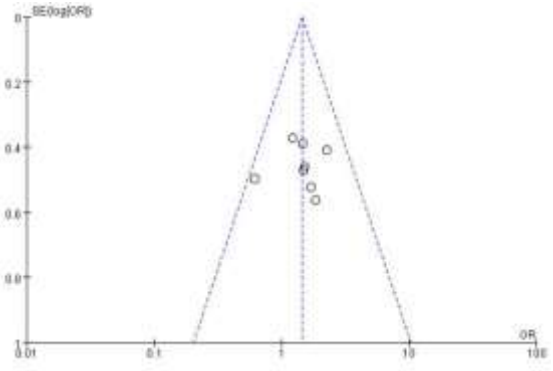

Figure 5. Funnel plot of significant effect

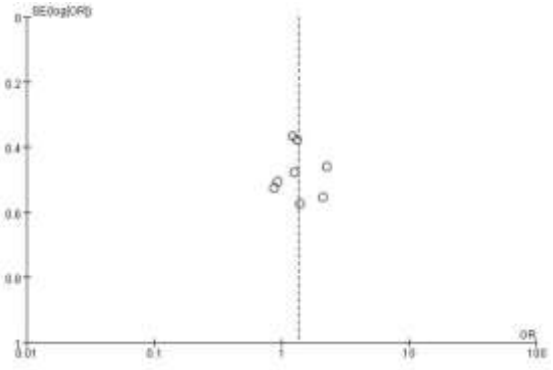

Figure 6: Funnel plot of invalid

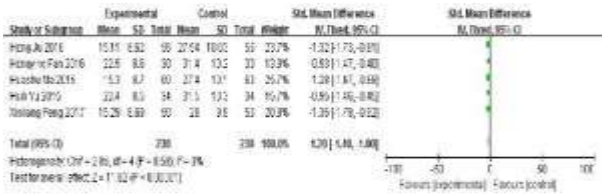

Figure 7: Forest plot of CA-125 level in subgroup

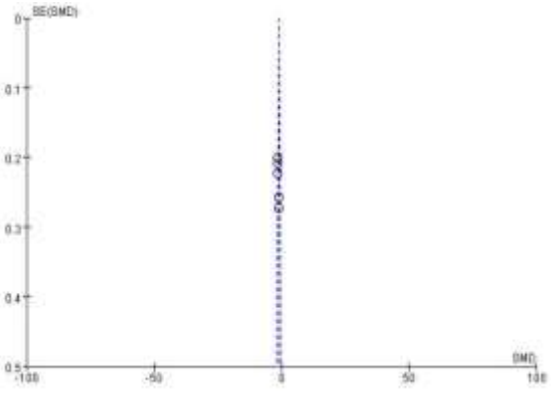

Figure 8: Funnel plot of CA-125 level in subgroup

DISCUSSION

Endometriosis is an estrogen-dependent disease [5]. The incidence of endometriosis in women of childbearing age is 6 - 10 %, and about 30 - 60 % of infertile women suffer from this disease. In recent years, the incidence of endometriosis had shown a younger trend, which seriously affects the physical and mental health of patients, and family and social harmony. Conservative treatment of endometriosis with drugs has the characteristics of convenience of use, high safety, non-invasiveness, and painlessness. It is more conducive for women of childbearing age to tolerate than surgical procedures [6].

Letrozole is a synthetically obtained drug that is effective for the treatment of endometriosis. It belongs to a non-steroidal aromatase inhibitor (3rd generation) [7]. Studies have shown that the main causes of endometriosis are excessive secretion of estrogen, overexpression of aromatase (in the endometrial tissue), and the abnormal proliferation of endometrial cells [8]. Letrozole effectively inhibits the pituitary gonadotropin and hormones that are related to the process of estrogen synthesis [9]. It achieves the purpose of disease treatment by reducing the levels of estrone and estradiol [10]. Furthermore, Letrozole effectively inhibits the expression of aromatase messenger ribonucleic acid in the lesion to prevent the lesion from synthesizing estrogen. The growth state of intimal implant was hindered to a certain extent. Studies have shown that administration of letrozole only hinders the estrogen synthesis process, but did not have a corresponding impact on the biosynthesis process of other steroid hormones [11]. Therefore, the effectiveness and safety of medication were relatively ideal [12]. However, it should be noted that due to individual differences, some patients with endometriosis may not achieve satisfactory results with triazoles alone, suggesting that other adjuvant therapies need to be added to actual clinical conditions [13].

Metformin is currently a commonly used hypoglycemic drug in clinical practice [14]. After administration, it significantly increases patients' insulin sensitivity [15]. Studies have found that they also have a significant inhibitory effect on the proliferation of a variety of tumor cells [16]. At this stage, with gradual deepening of clinical understanding of metformin, more and more studies have reported that metformin may inhibit the uterus by blocking eutopic endometrial cell cycle and activating the adenosine monophosphate-activated protein kinase (AMPK) signal channel [17]. Therefore, it was suggested that if metformin was added based on letrozole to treat the endometrium, the two can achieve complementary medication purposes [18]. They treat endometriosis through different mechanisms, thereby effectively avoiding

individual differences and allowing patients to obtain better treatment outcomes [19].

This study has also confirmed through grouping studies that the total effectiveness and pain improvement effect of study group after combined treatment with letrozole and metformin are better than those of control group given triazole alone [20]. During the treatment period, there were no statistically significant differences in the occurrence of drug-related adverse reactions between the two groups of patients with endometriosis. This suggests that the combination of letrozole and metformin in the treatment of endometriosis is both effective and safe [21]. These findings are consistent with previously reported studies [22].

CONCLUSION

The use of metformin in combination with letrozole in treatment of endometriosis is beneficial to guarantee a better quality of life with enhanced physical and mental health of patients and is worth further investigating for referencing purposes in practical cases in the future.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them. Heling Zhang and Fang Liu contributed equally to this work and are co-first authors.

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