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Review article

Tamoxifen versus clomiphene citrate for ovulation induction in infertile women

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ABSTRACT

This systematic review aimed to compare the clinical efficacy of tamoxifen with that of clomiphene citrate (CC) in anovulatory patients. The PubMed, EMBASE, and CNKI databases were searched up to October 2016 for literature comparing tamoxifen with CC in anovulatory women. The pooled risk ratios (RR) or standardized mean differences (SMD) with 95% confidence intervals (CIs) were subjected to statistical analysis. Twelve studies involving 1302 patients with 2030 ovulation-induction cycles were summarized. There were no statistically significant differences for the ovulation and pregnancy rates in the tamoxifen comparing to the CC group in the pooled analysis. However, in the subgroup of case-control studies, tamoxifen was identified to be associated with higher ovulation (RR = 1.28, 95% *CI*: 1.07, 1.54, I^2 = 0.0%) and pregnancy rates (RR = 1.82, 95% *CI*: 1.09, 3.06, I^2 = 0.0%) than CC. However, no differences were detected in the subgroup of RCTs, even after sensitivity analyses. In addition, no significant differences were found in endometrial thickness and miscarriage rate. Our study showed that there might be some distinctions in the efficacy of TMX and CC for ovulation and pregnancy rates. However, the exact efficacy was needed to be confirmed further.

Contents

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Introduction

Ovulatory disorders are the most common causes of infertility, accounting for 20%–25% of all cases of infertility in women. Approximately 80% of cases of anovulatory infertility are caused by polycystic ovary syndrome (PCOS) [1,2]. PCOS is characterized by the presence of typical ultrasound features of polycystic ovaries, hyperandrogenism, and irregular menses or chronic anovulation in women in whom other causes of hyperandrogenism have been excluded [3]. PCOS was explored a few decades ago as the most common cause of hyperandrogenic anovulatory infertility. However, the pathogenesis and underlying cause are still unclear [4].

For infertile women with anovulation, ovulation induction is considered the treatment of choice. Clomiphene citrate (CC) has been widely used as the first-line drug for ovulation induction [5]. Ovulation can be induced in 70%–80% of anovulatory women by administering clomiphene, but only 30%–40% of such women became pregnant [6]. As an estrogen receptor antagonist, CC can increase the availability of FSH to promote follicular growth and create an LH surge to stimulate ovulation by interfering with negative feedback on the estrogen-signaling pathway [7]. Simultaneously, its antiestrogenic effects on the endometrium and the cervical mucus result in disparate outcomes: a high ovulation rate but a low pregnancy rate. After a long period of treatment, a proportion of anovulatory women still do not become pregnant, although some patients benefit from these conventional treatments. While gonadotropin is commonly used as a second-line intervention to induce ovulation following failure of CC treatment [8,9], these patients may suffer from ovary hyperstimulation and multiple pregnancies; therefore, more caution should be taken, and treatment should be more closely supervised.

With a structure similar to that of CC, tamoxifen citrate (TMX) is another anti-estrogen used for ovulation induction. It has been recommended as an alternative to CC for ovulation induction in anovulatory women concerned about the anti-estrogenic effects of CC on the endometrium and the cervical mucus [10]. It is reported that ovulation can be induced in 50%–90% of anovulatory women, and 30%–50% of such women become pregnant following administration of TMX [11,12]. TMX has also been proven effective in women after failure of CC therapy [11]. TMX achieves better therapeutic efficacy of ovulation and pregnancy rates, is inexpensive, and does not lead to ovary hyperstimulation and multiple pregnancies. These results may be associated with a higher cervical mucus score and better functioning of the corpus luteum [11,12]. In contrast, several studies have suggested that CC is more successful than TMX as a first-line therapy for ovulation induction in anovulatory women [13,14]. In order to compare the effectiveness of TMX to that of CC for the induction of ovulation, Steiner et al. [15] conducted a meta-analysis including only four trials, which suggested that the use of TMX and CC resulted in similar ovulation rates. In 2009, Brown et al. [9] carried out a review that suggested no evidence of a difference in effect between TMX and CC for ovulation induction. However, these conclusions require further verification because of the small numbers of participants they included.

In order to address this controversial problem, a large number of randomized controlled trials (RCTs) focusing on the efficacy of induction of ovulation with TMX versus CC were conducted in the last three decades. Through examination of the literature and identification of the results of RCTs and case-control studies, the purpose of the present systematic review and meta-analysis was to reevaluate the efficacy of induction of ovulation and pregnancy outcomes comparing the use of TMX to that of CC in anovulatory women.

Materials and methods

Types of studies and search strategy

In this systematic review and meta-analysis, randomized controlled trials and case-control studies that compared TMX and CC for ovulation induction in anovulatory patients were considered. Women with PCOS and those with isolated anovulatory non-PCOS with infertility were included in anovulatory patients.

The PubMed, EMBASE, and Chinese National Knowledge Infrastructure (CNKI) databases were searched exhaustively until October 2016. Additional studies were identified through the references of the included articles, and no restriction was placed on the language. The combined keywords were ‘tamoxifen’,’ clomiphene’, ‘anovulation’, ‘polycystic ovary syndrome’, ‘ART’, and ‘assisted reproductive technology’.

Eligibility and exclusion criteria

Studies were selected for eligibility using the following inclusion criteria: (i) RCTs or case-control studies focused on the comparison of TMX and CC for ovulation induction in anovulatory patients; (ii) studies on infertile patients with PCOS or those with isolated anovulation; (iii) studies assessing at least one of the following outcomes: endometrial thickness at the day of human chorionic gonadotrophin (HCG), ovulation rate, pregnancy rate, and miscarriage rate. Two of the following three features were required: oligo- or anovulation, clinical and/or biochemical signs of hyperandrogenism and polycystic ovaries as seen on ultrasound scanning, with exclusion of other etiologies.

The exclusion criteria were strict: (i) studies that were not RCTs or case-control trials; (ii) the patients with normal ovulation; (iii) studies reporting only other clinical outcomes; (iv) raw data and adequate details of study results not accessible; (v) review articles, commentaries, and case reports.

Quality assessment

According to the recommended approach in the Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 [16], the quality of the included RCT studies was assessed independently by two co-authors. Six specific domains were summarized: adequate sequence generation, allocation concealment, blinding, incomplete outcome data addressed, free of selective reporting, and other issues. In addition, the quality of the case-control studies was assessed by using the criteria identified according to the published research [17].

Clinical outcomes and subgroup analysis

For this systematic review, the primary outcomes were ovulation rate and pregnancy rate per cycle. Endometrial thickness, human chorionic gonadotropin levels, and miscarriage rates were also assessed. Few studies reported on ovary hyperstimulation or multiple pregnancies. According to the different types of study design, including the RCT and case-control group, the subgroups of endometrial thickness, ovulation rate, pregnancy rate, and miscarriage rate were analyzed in detail. In addition, the subgroups of infertile patients with PCOS and isolated anovulatory non-PCOS women were also summarized.

Statistical analysis

The fixed-effects and random-effects models with the pooled risk ratios (RRs) and 95% confidence intervals (CIs) or the