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Weekly fluconazole therapy for recurrent vulvovaginal candidiasis: a systematic review and meta-analysis

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ABSTRACT

Objective: To investigate the efficacy, compared to placebo, of fluconazole 150 mg weekly, given for six months as prophylaxis against recurrent vulvovaginal candidiasis (RVVC).
Study design: A quantitative systematic review was performed, and randomized controlled trials were included. We conducted searches at Medline, EMBASE, Lilacs, Cochrane Library and ICI Web of Science from 1980 to March 2012. We used the odds ratio (OR) with confidence intervals (CI) of 95% using a random effects model of Mantel-Haenszel. The software used was Review Manager version 5.0.
Results: Through the search strategies we identified 249 articles, of which only two were part of the meta-analysis. Fluconazole was more effective than placebo in reducing symptomatic episodes of VVC, immediately after treatment (OR 0.10, 95% CI 0.03–0.34), 3 months after treatment (OR 0.23, 95% CI 0.07–0.74) and 6 months after treatment (OR 0.39, 95% CI 0.24–0.64).
Conclusion: Weekly treatment with fluconazole (150 mg) for six months is effective against RVVC.

1. Introduction

Infection caused by *Candida* spp. affects 70–75% of women at least once during their lives, and 40–50% of them will experience at least one recurrence. About 5–8% of these women will have recurrent vulvovaginal candidosis (RVVC) [1], which is defined as four or more mycologically proven episodes within 12 months [2]. To date, little is known about the pathophysiology of RVVC. Previous reports suggest that vulvovaginal candidiasis (VVC) can be idiopathic or caused by several different mechanisms: familial susceptibility [3], pregnancy [4], oral contraceptives [5], the use of systemic antibiotics [6], diabetes mellitus [7], sexual behavior [8] and immunosuppression, such as taking corticosteroids or with HIV infection [9].

The treatment of women with recurrent infections can be difficult and frustrating. Most cases of RVVC are caused by identical *Candida albicans* strains [10]. Current choices are limited to azole medications, fungistatic drugs that inhibit synthesis of ergosterol, which is a major component of the fungal cell membrane. The most effective approach to treatment, particularly with *C. albicans* infections, seems to be maintenance antifungal therapy. Treatment options which have been studied and shown to be effective include ketoconazole [11], clotrimazole [12] and fluconazole [13].

Fluconazole has a quick pervasion and high concentrations in the vaginal tissue, besides which, it has a high water solubility and low protein binding. Its success also depends on its prolonged half-life in the vagina above the minimum inhibitory concentration (MIC) of most strains of *C. albicans* for a period of 96 h [14].

We carried out a systematic review and meta-analysis of the effectiveness, compared with placebo, of weekly fluconazole therapy for six months for recurrent RVVC, analyzing the clinical recurrence of vulvovaginal candidiasis and positive culture in Sabouraud dextrose agar immediately after the fluconazole treatment, 3 months after treatment and 6 months after treatment.

2. Methods

2.1. Inclusion and exclusion criteria

To be eligible for inclusion in our systematic review, studies had to examine specific treatments with weekly fluconazole therapy for six months for recurrent vulvovaginal candidiasis, compared with placebo. We included only randomized clinical trials with the

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following inclusion criteria: non-pregnant women and over 18 years old. Excluded were women who were pregnant, with diabetes mellitus, were positive for human immunodeficiency virus (HIV), or had received antifungal agents in the past 4 weeks.

2.2. Search strategy

The aim was to locate all relevant trials, irrespective of publication status or language. Electronic databases – Medline, Embase, BIOSIS, LILACS, Scopus, the Cochrane central register of controlled trials, ISI Web of Science, and IBECS – were searched for randomized controlled trials from 1980 to March 2012. The reference lists of identified articles were also screened and experts in the field were contacted.

We used the following terms, both as text words and, as appropriate Medical Subjects Heading (MeSH) or equivalent subject heading/thesaurus terms: "randomized control trial", "vaginal candidiasis", "vagin* candid* recurrent", "vulvovagin* candid*", "candid* chronic", "genital thrush monilia", "fluconaz*" and "prophyl* fluconaz*. This sensitive filter was created by combining three filters for the identification of diagnostic studies via the Boolean operators "OR" and "AND". We manually scanned the reference lists of all identified articles. There were no restrictions placed on the publication language.

2.3. Data extraction

Multiple teams of three reviewers (MIR, BRS and NCS) independently screened the title, abstract, and key words of each reference identified by the search and applied the inclusion and exclusion criteria. Ten papers that were written in other languages besides English were excluded by their titles or abstracts. The same procedure was applied to full text articles and potentially eligible references. Differences in the opinions of the reviewers were resolved by discussion with a third reviewer (FRS). Data on quality, patient characteristics, interventions, and relevant outcomes were independently abstracted by three reviewers (PPS, AP and LRM).

Assessment of the bias risk was based on the adequacy of randomization, allocation concealment, and comparability of women in the different study groups.

2.4. Outcomes of interest

The diagnosis outcome was clinical recurrence of vulvovaginal candidiasis and positive culture in Sabouraud dextrose agar immediately after the fluconazole treatment, 3 months after treatment and 6 months after treatment.

2.5. Assessment of bias risk in included studies

MIR and BRS independently examined the components of each included trial for bias risk using a standard form. This included information on the sequence generation, allocation concealment, blinding (participants, personnel and outcome assessor), and incomplete outcome data. We did not assess selective outcome reporting and other bias sources. No author was contacted. The trials' methodological components were assessed and classified as adequate, inadequate or unclear according to Chapter 8 of the Cochrane Handbook of Systematic Reviews of Interventions [15].

The classification of sequence generation was as follows: (1) adequate: investigators described a random component in the sequence generation process, (2) inadequate: investigators described a non-random component in the sequence generation process, (3) unclear: insufficient information to permit judgment of the sequence generation process.

2.6. Statistical analysis

We measured inter-rater agreement for study inclusion and assessment of methodological quality (weighted κ). Odds ratio (OR) with 95% confidence intervals (CIs) were calculated for the meta-analysis. The random effects model was chosen a priori as it provides a more conservative estimate of the effect size and does not assume homogeneity amongst the trials. Study heterogeneity was carried out using the χ^2 and I^2 provided by the RevMan software. The assumption of homogeneity was considered invalid for $P < 0.05$. The I^2 statistic [$100\% \times (Q - df)/Q$], was computed to quantify inconsistency across studies in which numbers greater than 75% suggest considerable heterogeneity [16].

Meta-analysis was performed using Review Manager version 5.0.17 software [17].

3. Results

Based on the search strategy we identified 249 articles, of which 229 were excluded by three independent researchers after reading the titles and abstracts. Fourteen relevant articles were read and only two were part of the meta-analysis (Fig. 1) [13,18].

Table 1 provides information on design, population and outcomes. The mean age of participants across the studies was 32.8 years (range from 18 to 65). We pooled the data of 407 participants. RVVC was defined in the methods of both included studies as 4 or more mycologically proven episodes within 12 months and recurrences were defined as mycologic recurrences (*C. albicans* positive cultures) at follow-up visits.

The study quality was satisfactory overall and the trials were judged to be at low risk of bias (adequate sequence generation or allocation concealment, double blinding, and clear reporting of withdrawal rates and loss to follow-up). Both trials stated that participants were randomized in a double-blind, placebo-controlled trial. Methods of allocation were not described (Table 1).

Fluconazole was more effective in reducing symptomatic episodes of VVC than placebo in all outcomes: immediately after the end of the treatment (OR 0.10 (95% CI 0.03–0.34), $p = 0.05$, I^2 74%), 3 months after the end of the treatment (OR 0.23 (95% CI 0.07–0.74), $p = 0.06$, $I^2 = 72\%$) and 6 months after the end of the treatment (OR 0.39 (95% CI 0.24–0.64), $p = 0.67$, $I^2 = 0\%$) (Fig. 2).

Immediately after the end of the treatment, 152/173 women (87.9%) in the fluconazole group remained free of clinical recurrence. At 3 months after the end of treatment the proportion of women free of clinical recurrence was 83/129 (64.3%), and at 6 months after the end of treatment 97/158 (61.3%) (Table 2).

There was no substantial heterogeneity between the two included studies in all outcomes. In the microbiologic analysis

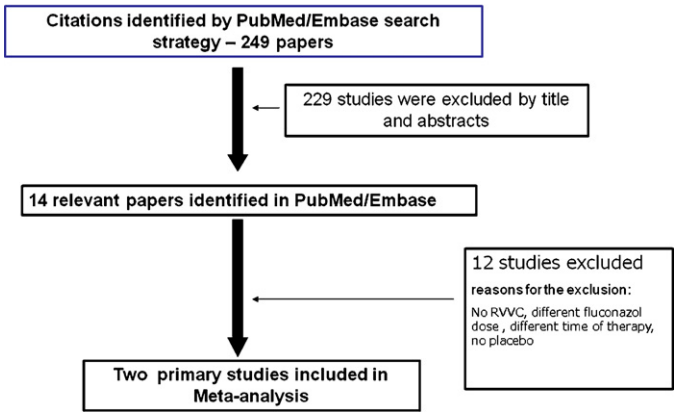

Fig. 1. Study selection process.