REVIEW ARTICLE

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Antifungal (oral and vaginal) therapy for recurrent vulvovaginal candidiasis: a systematic review and meta-analysis

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INTRODUCTION

Recurrent vulvovaginal candidiasis (RVVC) affects about 138 million women annually worldwide, with a global annual prevalence of 3,871 per 100,000 women[1]. Vulvovaginal candidiasis (VVC) is a common fungal infection caused by *Candida* species, predominantly *Candida albicans*. However, RVVC significantly compromises women's quality of life, causing severe symptoms of itching, pain, dyspareunia, dysuria, and leucorrhea. For this reason, the control of this recurrent infection remains a challenge for patients and experienced gynecologists[2-4]. RVVC is a condition arbitrarily defined as three episodes or more of VVC in the previous 12 months. However, some investigators demand yet another additional event, i.e., four attacks[2,3]. The etiopathogenesis of RVVC is still unclear. It is known that different elements are involved in this condition, such as immune mechanisms, genetic mutations, and behavioral patterns. However, the etiological factor remains unknown, hindering the clinical management of women with RVVC[5-7].

A significant number of topical and oral imidazole agents are available in various formulations with clinical and cure rates ranging from 80 to 90%[2-4]. Fluconazole has been the most used, and it is an inexpensive and well-tolerated antifungal drug that is easily administered orally. Meta-analyses realized about the theme demonstrate that fluconazole effectively reduces the recurrence of vaginal candidiasis up to 6 months after treatment[8,9]. However, in the last decade, fluconazole resistance has been reported in women with RVVC, consequence, in most cases, of the widespread availability of over-the-counter antifungal agent. Earlier epidemiological studies found that almost all women diagnosed with fluconazole-resistant *C. albicans* had experienced previous exposure to fluconazole[10]. While effective control of RVVC is achievable through using fluconazole maintenance suppressive therapy, the cure of RVVC remains elusive, especially in this era of fluconazole drug resistance. Ketoconazole and itraconazole are options of treatment found, as long as the cross-resistance is not determined[4].

Accordingly, our systematic review and meta-analysis aimed to assess antifungal treatment effectiveness for RVVC and provided an evidence-based protocol treatment for clinical use.

METHODS

This systematic review study with meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) guidelines[11]. The protocol of this systematic review is available in a previous publication[12].

Literature search and screening

PubMed, Embase, Scopus, Web of Science, SciELO, the Cochrane Central Registry of Controlled Trials (CENTRAL), CINAHL, and clinical trial databases, until July 2021, were used. Gray literature was searched using OpenGrey. No language restrictions were applied. The medical subject heading terms included: "candidosis," "vaginitis," "candida," "antifungal," "clotrimazole," "econazole," "butoconazole," "fenticonazole," "isoconazole," "miconazole," "omoconazole," "oxiconazole," "terconazole," "tioconazole," "sertaconazole," "natamycin," "amphotericin," "fluconazole," "ketoconazole," "itraconazole,"

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"posaconazole," "voriconazole," "nystatin" and were combined with Boolean "OR" and "AND" operators.

Eligibility criteria

Three researchers (JL, ACAS, and APFC) independently reviewed each article based on its title and abstract. The relevant data were collected by JL, RNC, and AKG. The inclusion criteria were as follows: randomized, blind, published clinical trials that analyzed women who had at least three episodes of vaginal candidiasis confirmed by the presence of signs and symptoms plus a positive vaginal culture for fungus, who had signs and symptoms plus positive vaginal microscopy compatible with vaginal candidiasis, and who had been treated with antifungal drugs administered intravaginally or orally. Studies with women immunosuppressive conditions or users of immunosuppressive drugs were excluded.

Data extraction

The clinical and mycological recurrence rate at 12 months, time to the first recurrence, and cure rate at 30 days were analyzed as the primary outcomes. The secondary outcomes were the proportion of participants with at least one recurrence during treatment and follow-up period, and complications/side effects.

A standardized data extraction form was used to collect the following data: authors, year of publication, country, the follow-up, mean age, the number of participants, interventions, and primary outcomes. The duplicate or secondary publications were excluded.

Quality evaluation

To assess the risk of bias, the Cochrane Collaboration bias risk tool was applied[13]. The studies were classified into "low risk of bias," "high risk of bias," or "unclear risk of bias." Two authors (JL and ACAS) assessed each original study and then qualified, and disagreements were resolved by consulting a third author (RNC).

Statistical analyses

The Review Manager software 5.3.3 was used to perform the meta-analysis. To evaluate the effectiveness of the proposed treatments, the dichotomous data were extracted from each study and inserted in a 2x2 contingency table. Then, we calculated the odds ratio (OR) for dichotomous data and mean weight difference (MD) for continuous data with a 95% confidence interval (95%CI) to obtain a global estimate summary. Heterogeneity was assessed by the I^2 statistic: (<25%, without heterogeneity; 25–50%, moderate heterogeneity; and >50%, strong heterogeneity). The fixed-effect model was chosen due to the low heterogeneity observed between studies. We used Egger's funnel plot to assess possible publication bias. A linear regression approach was used to assess the asymmetry of the funnel plot. Moreover, the outcomes that assessed the certainty of evidence were evaluated according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool[14].

RESULTS

A total of 18,965 potential records were initially identified. Later, 118 additional records were identified. After review of the title and abstract, 78 full-text papers were reviewed, 13 studies met inclusion criteria, and 9 studies were included in the meta-analysis. A flowchart of the study selection process is shown in Figure 1.

This systematic review included 13 papers representing 1,552 women, with a mean age of 30.92 years. The study included seven studies from the United States, two from England, and one each from Sweden, Spain, Italy, and Iran. The general characteristics of all included studies were summarized and are shown in Table 1.

Four meta-analyses were performed as follows:

1. Mycological recurrence (seven studies)[15-17,20-22,26];
2. Second clinical recurrence (six studies)[15,17,20-22,26];
3. Average recurrence time (two studies)[26,27];
4. Effectiveness of clotrimazole with other antifungals (two studies)[23,24].

The meta-analysis for mycological recurrence at 12 months showed that the OR for people treated with fluconazole, ketoconazole, clotrimazole, and oteseconazole was 0.36 (95%CI: 0.24–0.55) when compared with untreated people. For clinical recurrence at 12 months, the OR for women treated with fluconazole, ketoconazole, and clotrimazole was of 0.36 (95%CI: 0.24–0.54) risk of clinical recurrence when compared with the control group. Meta-analysis showed that there is no difference of effectiveness when comparing clotrimazole with other drugs (fluconazole and ketoconazole) (OR: 0.76, 95%CI: 0.41–1.41). The women treated with fluconazole and itraconazole had an average recurrence time of 0.364 months (10.92 days) longer than untreated people. Presenting adverse effects were considered mild; for this reason, antifungal protocols were considered safe.

It was impossible to analyze subgroups between different classes of antifungals and topical and vaginal routes due to the diversity of outcomes, which would allow comparisons with a maximum of two studies each.

All studies were randomized; eight were double-blind, placebo-controlled trials[15,16,18,20,22,25-27]; only three trials described a good random sequence generation process and the methods used for allocation concealment[18,20,27]. The risk of bias for each included study is shown in Table 2.

According to the GRADE system, the studies provided strong and moderate evidence for all results. In general, the quality of evidence was strong due to the characteristics of the study design. The quality of evidence was downgraded one level because of the imprecision of the results (Table 1).

DISCUSSION

This study shows that clotrimazole, fluconazole, ketoconazole, and oteseconazole at different levels reduced the recurrence of VVC and decreased the fungal count in culture after 12 months

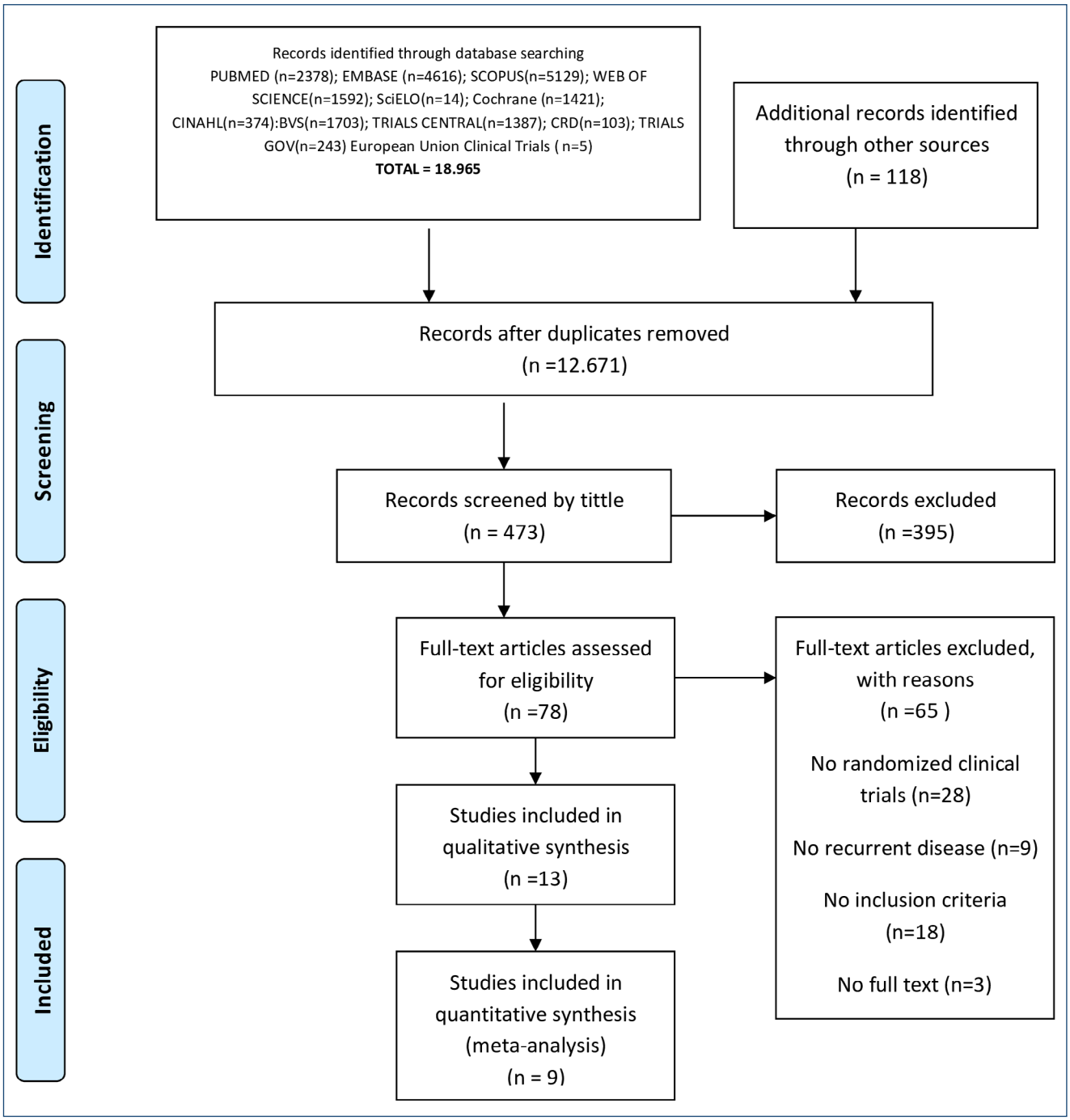

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

of treatment compared with placebo. Several studies evaluate the effectiveness of fluconazole in treating vaginal candidiasis; a minority refers to its use in treating CVVR. Donder's study evaluated the effectiveness and safety of an individualized, degressive, and prophylactic regimen in 136 women with RVVC. It was observed that individualized, degressive, and prophylactic maintenance therapy with oral fluconazole is an effective treatment regimen to prevent clinical relapses in women with RVVC[28]. The meta-analysis conducted by Rosa et al.[8] also suggests that fluconazole appeared to be the best drug. However, the latter highlights only the effectiveness of the drug in reducing symptoms. Two of the clinical trials included

Table 1. Characteristics of the studies included in the systematic review.

Author/year	Country	Interventions	N	Mean age	Follow-up	Outcomes	Certainty
Bolouri et al., 2009[15]	Iran	Weekly oral fluconazole´placebo	97	31.9 years (18–45)	12 months	Clinical recurrence and mycological recurrence	⊕⊕⊕⊕ HIGH
Brand et al., 2018[16]	EUA	Different dose-ranging of oteseconazole´placebo	215	34.6 years (18–64)	48 weeks	Proportion individuals with 1 or more episodes of CVV (culture) at week 48	⊕⊕⊕⊕ HIGH
Bushell et al., 1988[17]	England	Monthly clotrimazole vaginal tablet´placebo	41	27.8 years (18–41)	12 months	Clinical and mycological recurrence	⊕⊕OO LOW
Davidson et al., 1978[18]	England	Monthly vaginal clotrimazole´placebo	40	25.5 years (19–43)	10 months	Severity of symptoms during treatment; time to symptoms; time to reappearance of yeasts	⊕⊕⊕⊕ HIGH
López-Olmos et al., 2000[19]	Spain	Oral fluconazole´clotrimazole vaginal tablet´oral itraconazole	45	36.8 years (15-–53)	12 months	Clinical cure, mycological cure; recurrence	⊕⊕⊕O MODERATE
Roth et al., 1990[20]	Sweden	Monthly clotrimazole vaginal tablet´placebo	64	28.1 years	12 months	Clinical recurrence, mycological recurrence	⊕⊕⊕O MODERATE
Sobel et al., 1986[21]	EUA	Oral ketoconazole´placebo	63	32 years (19–47)	12 months	Clinical and mycological recurrence rate; time to clinical recurrence; adverse effects; disease-free patients	⊕⊕⊕⊕ HIGH
Sobel et al., 1989[22]	EUA	Monthly clotrimazole vaginal suppository´placebo	27	34.4 years (21–50)	12 months	Clinical and mycological recurrence rate; cure rate; mean time to symptom recurrence	⊕⊕⊕⊕ HIGH
Sobel et al., 1994[23]	EUA	Oral ketoconazole´vaginal clotrimazole	151	27.15 years (18–42)	2 months	Clinical cure and mycological cure; clinical recurrence; mycological recurrence; side effects	⊕⊕⊕O MODERATE
Sobel et al., 1995[24]	EUA	Oral fluconazole´clotrimazole vaginal tablet	432 (93 RVVC)	28.5 years (17–64)	35 days	Clinical cure and mycological cure; therapeutic response (clinical and mycological cure); recurrence rate; improvement of symptoms	⊕⊕⊕O MODERATE
Sobel et al., 2001[25]	EUA	Oral fluconazole one dose plus placebo´oral fluconazole 2 doses	556 (215 RVVC)	31 years (18–65)	35 days	Clinical cure and mycological cure	⊕⊕⊕⊕ HIGH
Sobel et al., 2004[26]	EUA	Weekly oral fluconazole´placebo	387	33.8 years (18–65)	12 months	Proportion of women in clinical remission at the end of the maintenance period (6 months) with definite cure	⊕⊕⊕O MODERATE
Spinillo et al., 1997[27]	Italy	Itraconazole vaginal tablet´placebo	114	30.5 years (18–50)	12 months	Clinical and mycological recurrence rate; proportion of patients free of symptomatic recurrence at 6 months and 12 months; mean time to symptom recurrence	⊕⊕⊕O MODERATE

Evaluated using the Grading of Recommendations Assessment, Development and Evaluation system: Very low ⊕OOO, Low ⊕⊕OO, Middle O⊕⊕⊕, High ⊕⊕⊕⊕[14].

in this review[15,25] did not demonstrate the effectiveness of fluconazole in clinical remission and the long-term mycological recurrence rate. A possible explanation for this ineffectiveness may be the presence of azole-resistant *Candida* species such as *Candida glabrata* and much less commonly *Candida krusei.*

The meta-analysis did not demonstrate the effectiveness of clotrimazole, itraconazole, and ketoconazole in the clinical remission of symptoms in women with RVVC. In their meta-analysis, Qin et al.[9] demonstrated the greater effectiveness of these drugs, including fluconazole. However, this study did not consider patients with RVVC, only patients with VVC. The difference of results can be justified because the randomized clinical trials (RCTs) that evaluated clotrimazole and ketoconazole included few patients, which may have influenced the absence of a significant difference, and we need to point the resistance azoles again.

An RCT with high-quality evidence, Brand et al.[16] showed that oteseconazole could be a promising new drug, decreasing the recurrence of symptoms and the reappearance of yeasts in the vagina. In addition, this new antifungal may be the most effective drug in *Candida* species resistant to other azoles[29]. The latter RCT was not included in the studies by Rosa et al.[8] and Qin et al.[9].

Regarding the proportion of participants with at least one recurrence during treatment and follow-up period, Sobel et al.[26] and Spinillo et al.[27] observed a higher rate of recurrences in the placebo groups. Fluconazole and itraconazole increased the time of occurrence of the first episode[26,27]. Clotrimazole, ketoconazole, itraconazole, and oteseconazole in the studies of moderate evidence are antifungal drugs with effectiveness for RVVC treatment. Fluconazole could reduce the rate of recurrence of symptomatic VCC. However, a long-term cure remains a challenge to achieve[16,22,23,26,27].

Table 2. Quality assessment of the included studies using the Cochrane risk of bias tool.

Study/year reference	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Bolouri et al., 2009[15]	?	?	?	?	?	+	?
Brand et al., 2018[16]	?	?	?	?	+	+	+
Bushell et al., 1988[17]	?	?	?	?	+	?	?
Davidson et al., 1978[18]	+	+	+	+	+	+	+
López-Olmos et al., 2000[19]	−	−	−	−	?	+	?
Roth et al., 1990[20]	?	+	+	+	+	?	+
Sobel et al., 1986[21]	?	?	?	?	+	+	?
Sobel et al., 1989[22]	?	?	?	?	+	?	?
Sobel et al., 1994[23]	+	?	?	?	+	+	+
Sobel et al., 1995[24]	?	?	?	+	+	+	?
Sobel et al., 2001[25]	?	?	?	?	+	+	+
Sobel et al., 2004[26]	?	?	?	+	+	?	?
Spinillo et al., 1997[27]	+	+	+	+	+	?	?

Key: − High risk of bias; ? unclear risk of bias; + low risk of bias[13].

The limitations of our study are based on potential missing data, biases, and heterogeneity in treatment protocols. However, this study included studies with new antifungals that professionals do not commonly use. Despite the immense diversity of treatment modalities, this study can illuminate potential targets for the treatment of RVVC, assuming that most of the randomized trials were evaluated with an unclear risk of bias.

CONCLUSIONS

This study provides moderate and high evidence that antifungal protocols using fluconazole, ketoconazole, and clotrimazole presented effectiveness for mycological and clinical recurrence rates when compared with placebo. The protocols using fluconazole, clotrimazole, ketoconazole, itraconazole, and oteseconazole were effective in the short-term treatment of RVVC. However, there was no difference in effectiveness between the drugs. In the long term, oteseconazole appears as a new effective drug compared with a placebo.

AUTHORS' CONTRIBUTIONS

JL, AKG: Conceptualization, Investigation. **JL, ACS, APFC:** Data curation, Writing – original draft, Formal analysis. **JL, PCG, AKG:** Methodology, Project administration. **JL, HS, RNC:** Software. **AKG:** Supervision. **RNC, HS:** Validation. **JL, ACS, AKG:** Visualization. **AKG, PCG, HS, RNC:** Writing – review & editing.

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