Vulvovaginitis and the treatment of asymptomatic partners: a systematic review and meta-analysis

Vulvovaginite e o tratamento de parceiros assintomáticos: uma revisão sistemática e metanálise

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ABSTRACT

Introduction: Treating sexual partners of women with vaginal candidiasis and bacterial vaginosis is a discussed topic. Despite the recommendations of international guidelines, doctors are still known to treat asymptomatic partners. **Objective:** To evaluate the influence of asymptomatic partner treatment in the cure and recurrence of vulvovaginitis in women. **Methods:** The following databases were searched using Mesh terms: PubMed, Embase, SciELO and CINAHAL. The selection criteria included randomized clinical trials published from 1982 to 2012. **Studies** involving pregnant women were excluded. Methodological quality was assessed using Jadad's scale. Review Manager 5.1 was used for statistical analysis. **Results:** Eight randomized clinical trials were included based on the chosen criteria: 1,088 women were enrolled. For bacterial vaginosis, the relative risk for cure was 1.00 (95%CI 0.95–1.05, p=0.13), and for recurrence 0.84 (95%CI 0.62–1.14, p=0.34). Vaginal candidiasis had a RR of 1.03 (95%CI 0.94–1.14, p=0.48) for cure, and 1.02 (95%CI 0.77–1.33, p=0.91) for recurrence. **Conclusion:** Treatment of asymptomatic sexual partners of women with vaginal candidiasis or bacterial vaginosis does not affect the cure or recurrence rates and may increase the risk of side effects and unnecessary financial costs.

Keywords: vulvovaginitis; vaginosis, bacterial; candidiasis; partner; treatment.

RESUMO

Introdução: O tratamento de parceiros sexuais de mulheres com candidíase vaginal e vaginose bacteriana é um assunto muito abordado. Apesar das recomendações estabelecidas nos manuais internacionais, este tópico ainda é muito questionado por um grande número de médicos que prosseguem desobedecendo estes manuais. **Objetivo**: Avaliar a influência do tratamento de parceiros assintomáticos na cura e recorrência de vulvovaginite em mulheres. **Métodos**: Foi realizada busca com descritores específicos nas seguintes bases de dados: PubMed, Embase, SciELO e CINAHAL. No critério de seleção foram incluídos ensaios clínicos randomizados publicados no período de 1982 a 2012. Estudos envolvendo mulheres grávidas foram excluídos. Na avaliação qualitativa, utilizou-se a Escala de Jadad. A análise dos dados foi realizada por meio do programa estatístico Review Manager 5.1. **Resultados**: Oito ensaios clínicos randomizados foram selecionados: 1.088 mulheres foram escolhidas. Na vaginose bacteriana, o risco relativo para cura foi de 1,00 (IC95% 0,95–1,05, p=0,13) e para recorrência foi de 0,84 (IC95% 0,62–1,14, p=0,34). A candidíase vaginal apresentou risco relativo de 1,03 (IC95% 0,94–1,14, p=0,48) para cura e de 1,02 (IC95% 0,77–1,33, p=0,91) para recorrência. **Conclusão**: O tratamento do parceiro sexual assintomático de mulheres com candidíase vaginal e vaginose bacteriana não afetaria as suas taxas de cura e recorrência, como também poderia causar efeitos colaterais e custos desnecessários.

Palavras-chave: vulvovaginite; vaginose bacteriana; candidíase; parceiro; tratamento.

INTRODUCTION

Vulvovaginitis (VV) is a common complaint and one of the most frequent reasons patients seek gynecologists[1]. Annually, about 10 million doctor appointments are attributed to symptoms and signs of vaginal discharge[2].

Although VV is a very relevant condition to women due to the high personal and financial costs ensued, women and medical community often minimize it. This causes constant incorrect diagnosis and treatment by both women and doctors[1], resulting in exaggerated use of antibiotics and antifungals.

The main causes of VV are well established: bacterial vaginosis (BV), vaginal candidiasis (VVC), and trichomoniasis (VT). However, several questions are debatable, such as best drug to be used, treatment regimen, and the most appropriate route of administration. Since VT has been confirmed as a sexually transmitted disease (STD), the treatment of an asymptomatic partner is uncontested[3-5].

Some studies suggest that the treatment of sexual partners of women with BV could reduce recurrence rates from 5 to 20%. Nevertheless, data evaluating the efficacy of this practice are controversial[6-8]. In a well-designed clinical trial, Mengel et al. found a reduction of recurrence rates in patients with BV whose partners were simultaneously treated[9]. Nonetheless, three other studies found no relationship between oral therapy of the partner and recurrence rates of women[10-12].

VVC cannot be established as a STD since the transmission of the agent does not necessarily cause VV. It is known that the incidence of VVC increases dramatically in the second decade of life, corresponding to the onset of sexual activity, when several factors (tissue trauma, deposition of semen in the vaginal cavity, exaggerated use of soaps and chemicals, hormonal changes) influence the vulvovaginal ecosystem[13]. The sexual transmission of Candida can occur during intercourse, but intercourse frequency and timing could

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influence the development of an acute crisis[14]. The practice of oral sex has also emerged as one of the risk factors[15]. Current studies have associated homosexual practices with an increase in the prevalence of Candida in female genitals[16]. On the other hand, some studies suggest that the role of sexual practice in the establishment of VVC has been amplified[17,18].

A recent study, which proposed to evaluate the transmission of genital candidiasis among heterosexual couples, could not prove sexual acquisition[19]. Such investigation evaluated the Candida species from couples and found that only 25% of men and women had the same species of Candida, differently from previous studies[15]. In other studies that have treated sexual partners of women with VVC, no increase in cure rates, decline, or recurrence was observed[17].

Currently, despite the existing technology for diagnosis and treatment of VV, the role of sexual transmission has yet to be defined. The clarification of this controversy could avoid unnecessary treatment of sexual partners, thus reducing costs, side effects, and conflicts within the couple.

This study proposes to systematically evaluate the influence of treatment of asymptomatic partner in the cure and recurrence of VV.

MATERIAL AND METHODS

This study adhered to the PRISMA guidelines[20].

Inclusion criteria

Randomized controlled trials published in the last 30 years to assess the effectiveness of partner's treatment in the cure and recurrence of VV.

Exclusion criteria

Women under 16 years of age, HIV positive, pregnant, asymptomatic, and sex workers were excluded of the study. These groups represent populations at increased or decreased risk for STDs, wherein the prevalence of disease differs from the general population. This could interfere with the sensitivity and/or specificity of the analysis in this review.

Search and selection of literature

Eligible studies were identified in the following databases: PubMed, Embase, SciELO, CINAHAL, and Google Scholar. The studies were determined in a literature search of databases following medical subject heading terms and/or text words (Mesh Terms): (Treatment*)* AND (Vulvovaginitis) OR (Candidiasis) OR (Moniliasis) OR (Vaginitis, Monilia) OR (Vaginosis) OR (Vaginitis) OR (Trichomonas)) AND (Partners) AND ((randomized controlled trial) OR (clinical trial) OR (follow-up) OR (prospective)) NOT (Pregnant Woman).

The bibliographies of the identified publications were reviewed for additional pertinent studies. No language restrictions were applied.

Two investigators (AKG and HMR) looked up for articles published until May 2012. After search in the databases, 513 potentially relevant papers were identified, 102 of which were excluded after review of titles. Then, the abstracts of the 411 remaining titles were read, removing 313 titles. Of the 98 remaining articles, 8 were duplicated among the databases, which left 90 articles for final reading and qualitative assessment by Jadad's scale[21]. This considers studies to be methodologically adequate when they obtain a score of 3 or more[21]. Thus, studies with three or more points (eight studies) were classified as of high methodological quality, and remained in the systematic review (**Figure 1**).

Data extraction

Several characteristics of the original articles were extracted and included in the systematic review. The data included last name of the first author, year of publication, country, number of subjects, type of VV studied, as well as type of intervention and results.

Analysis

Statistical analysis was done using Review Manager (RevMan) 5.1 to provide a group analysis of the results from the selected clinical trials. The pooled analysis was obtained by analyzing the combined results of the chosen studies using the random effect model, and then testing for heterogeneity using the χ^2 test. Homogeneity of the selected studies was carried out.

RESULTS

Bacterial vaginosis

Four randomized controlled trials were selected:

1. Verjtorp et al.[10] conducted a major double-blind randomized clinical trial with 117 women using 500 mg of metronidazole twice a day for seven days. Half of the partners were randomly treated with the same treatment regimen or placebo. Cure and recurrence rates were similar among women with treated (cure: 51/54 and recurrence: 13/54) or placebo partners (cure: 44/53 and recurrence: 14/53) (**Table 1**).
2. Moi et al.[4], in another double-blind randomized controlled trial with 241 women, treated with 2 g of metronidazole, and repeated two days later. The partners were randomly treated with the same dose of metronidazole. Cure and recurrence rates were similar among women with treated (cure: 115/119 and recurrence: 19/112) or placebo partners (cure: 111/113 and recurrence: 14/106) (**Table 1**).
3. Vutyavanich et al.[11] conducted a randomized clinical trial of 250 Thai women treated with 2 g of tinidazole and a partner randomly treated with placebo or tinidazole. Cure and recurrence rates were similar among women with treated (cure: 111/122 and recurrence: 43/117) or placebo partners (cure: 113/119 and recurrence: 33/126) (**Table 1**).
4. Colli et al.[5] carried out a double-blind randomized study with 131 Italian women who were treated with 2% clindamycin in the form of vaginal cream for seven days. The partners were randomly treated with oral clindamycin or placebo. Cure and recurrence rates were similar among women whose partners treated (cure: 66/69 and recurrence: 5/38) or not treated the cure: 65/69 and recurrence: 9/32) (**Table 1**).

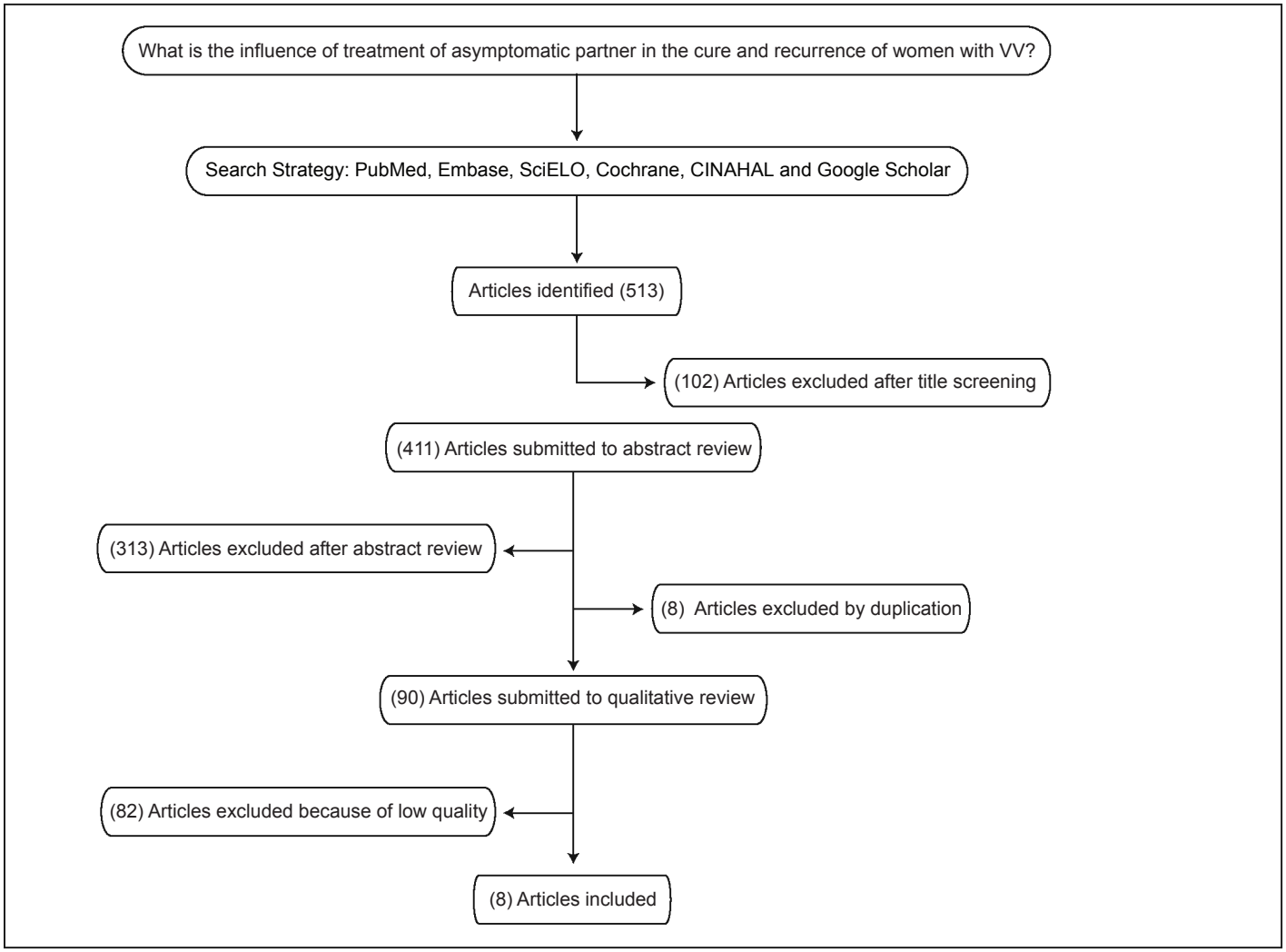

Figure 1 – Study selection.

Table 1 – Characteristics of selected randomized clinical trials for bacterial vaginosis and vulvovaginitis candidiasis.

Study	Country	Subjects	Randomized intervention	Results
Vejtorp et al.[10] (1988)	Denmark	107 non-pregnant women with BV	Women: 500 mg of Metronidazol twice a day/7 days Partners: 50% = same treatment, 50% = placebo	Treated: Cure: 51/54 Recurrence: 13/54 Placebo Cure: 44/53 Recurrence : 14/53
Moi et al.[4] (1989)	Denmark	241 non-pregnant women with BV	Women: 2 g of Metronidazol twice a day Partners: same randomized treatment	Treated: Cure: 115/119 Recurrence: 19/112 Placebo Cure: 111/113 Recurrence: 14/106
Vutyavanich et al.[11] (1993)	Thailand	250 non-pregnant women with BV	Women: 2 g of tinidazol Partners: randomized tinidazol or placebo	Treated: Cure: 111/122 Recurrence: 43/117 Placebo Cure: 113/119 Recurrence: 33/126
Colli et al.[5] (1997)	Italy	131 non-pregnant women with BV	Women: clindamycin 2% vaginal cream/ 7 days Partners: randomized oral clindamycin or placebo	Treated: Cure: 66/69 Recurrence: 5/38 Placebo : Cure:65/69 Recurrence: 9/32
Bishop et al.[2] (1986)	Belgium	117 non-pregnant women with VVC	Women : 200 mg 2 X day ketoconazole for 3 days Partners: randomized ketoconazole or placebo	Treated: Cure: 48/57 Recurrence: 13/48 Placebo Cure: 53/60 Recurrence: 19/53
Calderon-Marquez et al.[23] (1987)	Mexico	44 non-pregnant women with VVC	Women : 200 mg 2 X day ketoconazole for 3 days Partners: randomized ketoconazole or placebo	Treated: Cure:17/20 Recurrence:0/16 Placebo Cure:15/19: Recurrence:2/15
Fong et al.[24] (1992)	Canada	54 non-pregnant women with VVC	Women : 400 mg 2 X day ketoconazole for 7 days Partners: randomized 200 mg de ketoconazole for 5 days	Treated: Cure: 26/28 Recurrence : 8/26 Placebo Cure: 15/19 Recurrence : 9/28
Shihadeh et al.[25] (2000)	Jordan	144 non-pregnant women with VVC	Women : 400 mg 2 X day ketoconazole for 7 days Partners: half received randomized ketoconazole	Treated: Cure: 26/28 Recurrence : 8/26 Placebo Cure: 15/19 Recurrence : 9/28

The total RR for cure and recurrence was similar among women whose partners were treated or not for BV: cure RR=1.00, 95%CI 0.95–1.05, p=0.13; recurrence RR=0.84, 95%CI 0.62–1.14, p=0.34), as seen in **Figure 2**.

Vaginal candidiasis

Bisschop et al.[22] carried out a double-blind randomized clinical trial in Belgium with 117 women treated with 200 mg of ketoconazole twice a day for three days, whose partners were randomly treated with ketoconazole or placebo. Cure and recurrence rates were similar among women with treated (cure: 48/57 and recurrence: 13/48) or placebo partners (cure: 53/60 and recurrence: 19/53), as seen in **Table 1**.

Calderón-Marquez[23] performed a double-blind randomized study that included 44 women who used 50 mg itraconazole twice a day for five days, and their randomly treated partners. Cure and recurrence rates were similar among women with treated (cure: 17/20 and recurrence: 0/16) or placebo partners (cure: 15/19 and recurrence: 2/15), as in **Table 1**.

Fong[24] conducted a randomized clinical trial with 54 Canadian women who received 400 mg of ketoconazole for seven days. Their partners received 200 mg of ketoconazole for five days, or a placebo one. Cure and recurrence rates were similar among women with treated (cure: 26/28 and recurrence: 8/26) or placebo partners (cure: 15/19 and recurrence: 9/28), as in **Table 1**.

Shihadeh and Nawafleh[25] carried out a randomized clinical trial in Jordan with 144 women who received 400 mg of ketoconazole for seven days. Half of their partners received 400 mg ketoconazole for seven days. Cure and recurrence rates were similar among women with treated (cure: 57/72 and recurrence: 35/57) or placebo partners (cure: 53/72 and recurrence: 28/53), as further explained in **Table 1**.

The total RR for cure and recurrence was similar among women whose partners were treated or not for VVC: cure RR=1.03, 95%CI 0.94–1.14, p=0.48; recurrence RR=1.02, 95%CI 0.77–1.33, as in **Figure 3**.

Vaginal trichomoniasis

Interestingly, in the last 30 years no trials were performed to evaluate the treatment indication of partners of women with VT. The only randomized clinical trial was conducted over 30 years ago; however, it was not possible to include such trial in this study. In 1981, Lyng and Christensen[26] conducted a randomized clinical trial with 118 women, which found that the persistence of the infection was significantly higher in the group with no treatment of partners (14/59) compared to the group that did the treatment (3/59) (RR=0.21, 95%CI 0.06–0.71). This difference persisted in the subgroup of women who had sex with untreated partners. More recently, in a study testing the efficacy of intravaginal nonoxynol 9 for VT, Antonelli et al.[27] observed that women whose partners were treated with metronidazole had better cure rates compared to those whose partners were untreated. This study cannot be considered for this meta-analysis since the randomization tracking was not described.

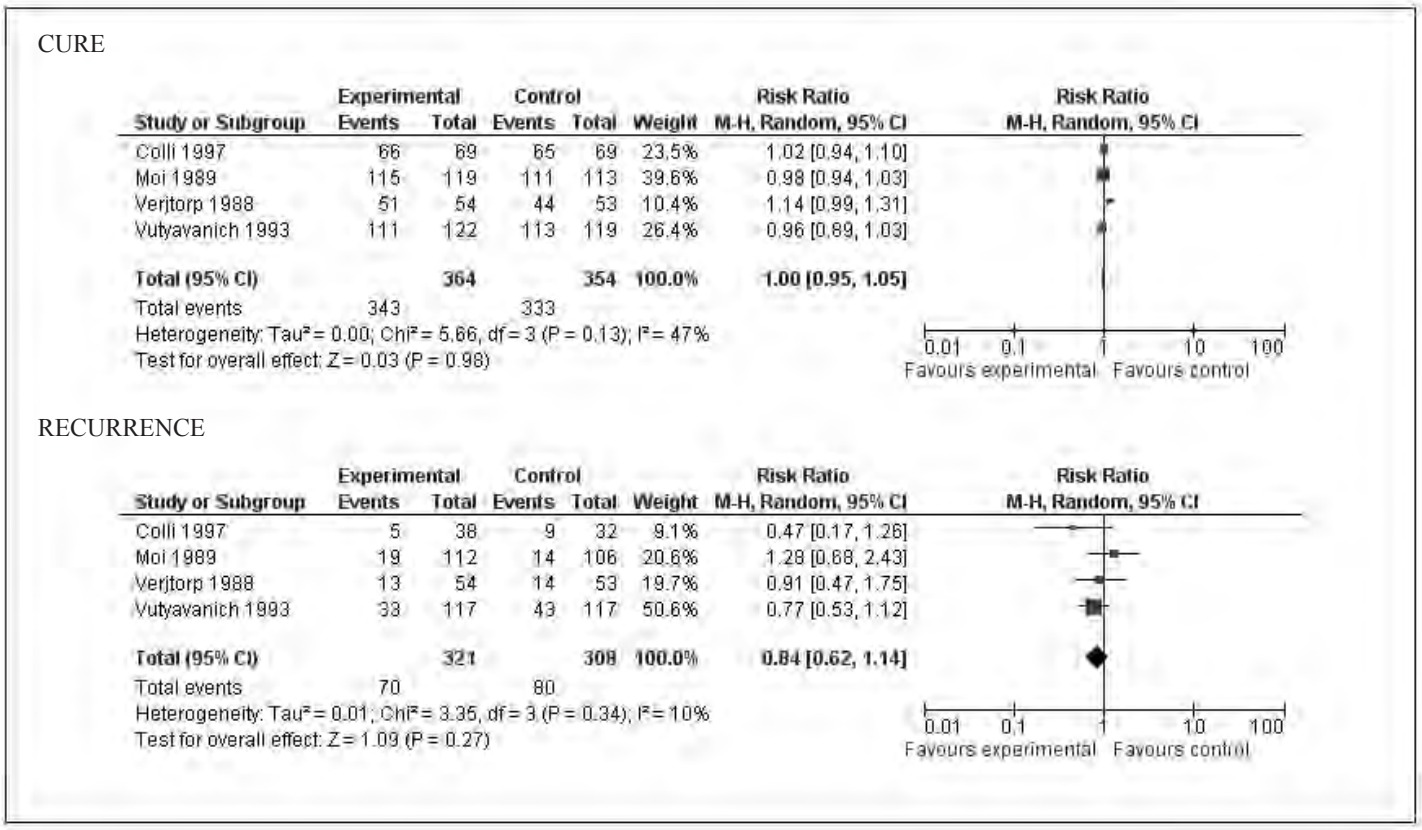

Figure 2 – Pooled analysis of selected bacterial vaginosis studies.

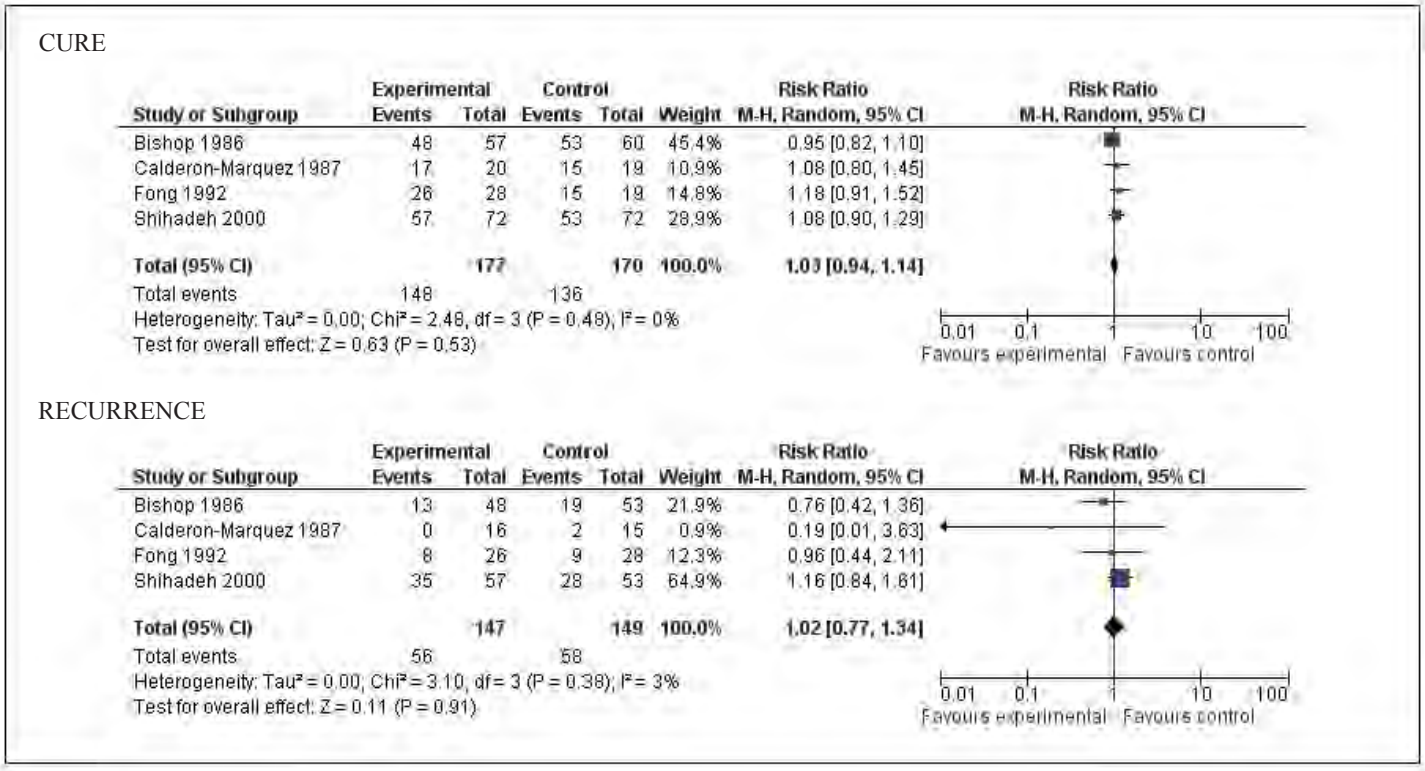

Figure 3 – Pooled analysis of selected vulvovaginitis candidiasis studies.

DISCUSSION

The medical literature and most researchers suggest that sexual partners of women with VV should not be treated[27]. However, some national health programs, including Brazilian health services, treat VV erroneously as a STD and leave treatment to the discretion of gynecologists. Unfortunately, this results in an excess of treatment that increases costs and causes unnecessary physical side effects. There are also serious social and emotional implications that cause conflicts to the couple due to the transmission of a STD. Very few studies consider the latter, or more importantly, the microbial resistance, a result from this practice.

Proponents of partner treatment argue that this practice could reduce recurrences in women, as well as new transmissions. However, our findings do not confirm these VT assertions. VT seems to be the only infectious VV wherein treating the partner increases the chances of cure and reduces recurrence. This being said, the only study that confirms this hypothesis, by Lyng and Christensen[26], was conducted in 1981. Besides this, it is accepted that VT is a protozoan, that cannot be found in the vaginal cavity under normal conditions and is not part of the vaginal flora. It is said that VT must be treated in both parties.

We believe that the ban on placebo use in clinical trials in recent years has impeded randomized trials[28]. Since VT is considered a STD, the consequence of prescribing placebo instead of the treatment is not ethically accepted. In vivo studies in animal models are a solution, even though they are difficult to perform. Even so, it is fundamental to encourage both studies in vitro and in animal models, which are already well-known for VVC, but not yet established for BV.

Contrary to VT, BV and VVC are caused by microorganisms that are part of the normal microflora composition, which sometimes assume the role of pathogens.

The pooled analysis suggested that a slightly lowered risk of recurrence was from the group of women with partners treated for BV-RR 0.84 (95%CI 0.62–1.14), however no statistically significant values were found for cure rates. There was no difference between the group of men who received a placebo and those who were treated with recurrence (1.00, 95%CI 0.95–1.05).

The pooled analysis of studies on VVC suggests that the evidence pointing to asymptomatic partner treatment is much weaker than for VB. The total RR for cure was 1.03 (95%CI 0.94–1.14), and for recurrence was 1.02 (95%CI 0.77–1.33).

Therefore, it is evident from these results that partner treatment does not significantly influence the outcome of cure and/or recurrence rates for BV and VVC.

This evidence can help the general practitioner to treat patients and their partners more adequately, thus avoiding the side effects of overtreatment.

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Received on: 09.13.2014
Approved on: 02.26.2015