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EFICÁCIA DOS PROTOCOLOS DE TRATAMENTOS ANTIFÚNGICOS EM MULHERES COM CANDIDÍASE VULVOVAGINAL RECORRENTE: REVISÃO SISTEMÁTICA DE ENSAIOS CLÍNICOS RANDOMIZADOS E METANÁLISE

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Dissertação apresentada ao Programa de Pós-Graduação em Tocoginecologia da Faculdade de Ciências Médicas da Universidade Estadual de Campinas como parte dos requisitos exigidos para a obtenção do título de Mestra em Ciências da Saúde, na área de Fisiopatologia Ginecológica.

Dissertation submitted to the Post Graduate Programme on Obstetrics and Gynecology from the School of Medical Sciences of the State University of Campinas as part of the requirements for obtaining the title of Master's Degree in Health Sciences, in the area of Gynecological Physiopathology.

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RESUMO

Introdução: O tratamento eficaz da candidíase vulvovaginal recorrente (CVVR) com controle adequado dos sintomas e erradicação do fungo, representa um desafio na prática clínica. Recentemente, grande variedade de drogas e formulações vem sendo disponibilizadas e muitos são os esquemas antifúngicos utilizados para tratamento, alguns com efeitos adversos que reduzem a aderência das mulheres ao tratamento. A falta de critérios claros específicos para indicação dos antifúngicos disponíveis e seu uso abusivo tem contribuído para a crescente resistência antifúngica verificada em alguns ensaios clínicos. **Objetivo**: avaliar a eficácia de diferentes protocolos antifúngicos habitualmente utilizadas por via oral e vaginal, no tratamento da candidíase vulvovaginal recorrente. **Material e Métodos**: revisão sistemática em bases de dados, sem restrição de data ou idioma, de ensaios clínicos randomizados com drogas antifúngicas administradas por via oral e vaginal com a finalidade de tratar a doença. O desfecho primário foi a taxa de recorrência clínica e micológica. Três revisores selecionaram de forma independente os ensaios clínicos e extraíram dados das publicações originais. O risco de "viés" foi avaliado pela ferramenta "Cochrane Risk of Bias". Utilizamos o sistema Grade para avaliar a qualidade dos estudos incluídos. Dados quantitativos foram avaliados por metanálise com o software RevMan 5.3. **Resultados**: Treze estudos foram incluídos na revisão sistemática, envolvendo 1.552 mulheres. Nove estudos foram avaliados em 4 metanálises. Para o desfecho taxa de recorrência micológica em 12 meses, 7 estudos avaliando Fluconazol (2), Clotrimazol (3), Cetoconazol (1) e Oteseconazol (1) mostraram que essas drogas são eficazes em relação ao placebo, reduzindo o risco de recorrência em 36% (OR 0,36; $p<0.001$). Para o desfecho taxa de recorrência clínica em 12 meses, 6 estudos avaliando fluconazol (2), clotrimazol (3) e Cetoconazol (1) evidenciaram resultados semelhantes, com 36% de redução no risco de recorrência clínica com os antifúngicos em relação ao placebo (OR 0,36; $p<0.001$). Em relação ao tempo para a primeira recorrência, 2 estudos avaliando fluconazol e itraconazol observaram tempo de recorrência médio 0,364 meses (10,92 dias) maior nos grupos placebo, o que indica eficácia ($p<0.001$). Para a avaliação da eficácia dos protocolos, a metanálise avaliou as taxas de cura clínica em 2 estudos comparando Clotrimazol com outros tratamentos (cetoconazol e fluconazol). Não houve diferença de eficácia ao se comparar Clotrimazol com os demais medicamentos. Efeitos adversos foram raros, associados principalmente ao uso de cetoconazol e

fluconazol, sendo a cefaleia a mais comum. Nenhum protocolo relatou complicações. **Limitações**: Não foi possível realizar a metanálise para todos os estudos e desfechos. **Conclusões**: Para taxas de recorrência micológica e clínica, os antifúngicos mostram eficácia em relação ao placebo. O tempo para a recorrência foi menor nos grupos tratamento e não houve diferença de eficácia entre os antifúngicos na cura da CVVR. Os protocolos de clotrimazol, cetoconazol, itraconazol e oteseconazol foram eficazes no tratamento de curto prazo da CVVR. No entanto, a longo prazo, oteseconazol foi o único antifúngico eficaz na recorrência da candidíase vulvovaginal em comparação com o placebo. Efeitos adversos foram raros, sendo a cefaleia a mais relatada. Todos os protocolos são considerados seguros.

ABSTRACT

Introduction: The effective treatment of recurrent vulvovaginal candidiasis (RVVC) with adequate control of symptoms and eradication of the fungus, represents a challenge in clinical practice. Recently, a wide variety of drugs and formulations have been made available and many antifungal regimens are used for treatment, some with adverse effects that reduce women's adherence to treatment. The lack of specific clear criteria for indicating the available antifungals and their abuse has contributed to the growing antifungal resistance seen in some clinical trials. **Objective**: to evaluate the efficacy of different antifungal protocols commonly used orally and vaginally, in the treatment of recurrent vulvovaginal candidiasis. **Material and Methods**: systematic review in databases, without date or language restriction, of randomized clinical trials with antifungal drugs administered orally and vaginally in order to treat the disease. The primary end point was the rate of clinical and mycological recurrence. Three reviewers independently selected clinical trials and extracted data from original publications. The risk of “bias” was assessed by the “Cochrane Risk of Bias” tool. We used the Grade system to assess the quality of the included studies. Quantitative data were assessed by meta-analysis. **Results**: Thirteen studies were included in the systematic review, involving 1,552 women. Nine studies were evaluated in 4 meta-analyzes. For the outcome rate of mycological recurrence in 12 months, 7 studies evaluating Fluconazole (2), Clotrimazole (3), Ketoconazole (1) and Oteseconazole (1) showed that these drugs are effective in relation to placebo, reducing the risk of recurrence in 36% (OR 0.36; $p < 0.001$). For the outcome clinical recurrence rate at 12 months, 6 studies evaluating fluconazole (2), clotrimazole (3) and ketoconazole (1) showed similar results, with a 36% reduction in the risk of clinical recurrence with antifungals compared to placebo (OR 0.36; $p < 0.001$). Regarding the time to the first recurrence, 2 studies evaluating fluconazole and itraconazole observed an average recurrence time of 0.364 months (10.92 days) longer in the placebo groups, which indicates a certain effectiveness ($p < 0.001$). To assess the effectiveness of the protocols, the meta-analysis evaluated the rates of clinical cure in 2 studies comparing Clotrimazole with other treatments (ketoconazole and fluconazole). There was no difference in effectiveness when comparing Clotrimazole with other drugs. Adverse effects were rare, mainly associated with the use of ketoconazole and fluconazole, with headache being the most common. No protocol reported complications. **Limitations**: It was not possible to

perform the meta-analysis for all studies and outcomes. **Conclusions**: For rates of mycological and clinical recurrence, antifungals show efficacy compared to placebo. The time to recurrence was shorter in the treatment groups and there was no difference in effectiveness between antifungals in curing CVVR. The protocols of clotrimazole, ketoconazole, itraconazole and oteseconazole were effective in the short-term treatment of CVVR. However, in the long run, oteseconazole was the only antifungal effective in the recurrence of vulvovaginal candidiasis compared to placebo. Adverse effects were rare, with headache being the most reported. All protocols are considered safe.

LISTA DE TABELAS E FIGURAS

LISTA DE ABREVIATURAS E SIGLAS

CVVR – CANDIDÍASE VULVOVAGINAL RECORRENTE

CVV – CANDIDÍASE VULVOVAGINAL

SUMÁRIO

1. INTRODUÇÃO

A maioria das mulheres apresentará ao longo da vida episódios de corrimentos vaginais, muitas vezes causados por vulvovaginites. A Candidíase vaginal aparece como a 2ª causa mais frequente de vulvovaginites (25%), estando atrás da vaginose bacteriana (1). É caracterizada por um processo de descamação e transudação do epitélio vaginal, associado à inflamação local de intensidade variável, decorrente da colonização vaginal por Cândida, pré-requisito para que a doença ocorra. Cerca de 20 a 25% das mulheres assintomáticas apresentam culturas vaginais positivas para *Candida sp* (2).

Estima-se que nos EUA, ocorram cerca de 10 milhões de consultas ginecológicas por ano atribuídas a casos de candidíase vulvovaginal, que na verdade tem outras causas não fúngicas (3). O diagnóstico incorreto implica em um grande número de mulheres tratadas muitas vezes erroneamente, sugerindo equivocadamente a candidíase vulvovaginal recorrente (CVVR).

A infecção causada pela *Candida sp* afeta entre 70 a 75% das mulheres, pelo menos uma vez durante suas vidas, principalmente mulheres jovens no menacme. O pico de incidência ocorre em média aos 20 anos de idade. Cerca de 40 a 50% das mulheres vão apresentar recorrência e 5 a 8% das adultas terão candidíase vulvovaginal recorrente, definida arbitrariamente como 3 ou mais episódios ao ano (2).

A Cândida, espécie *albicans* responde por 85-90% dos casos, acompanhada pelas espécies *C. glabrata (*5-10%), *C.tropicalis (*até 5%), C. krusei, e *C. parapsilopis.* Estudos mostram a presença de outra espécie de Cândida relacionada à CVVR, a *C. duobushaemulonii,* com baixa sensibilidade ao fluconazol (4) e um aumento de resistência aos azóis pelas espécies já descritas (5,6).

A candidíase vulvovaginal não é classificada como infecção sexualmente transmissível. Cerca de 35 a 40% das mulheres com candidíase apresentam coinfecção com vaginose bacteriana. As espécies de Cândida podem ser organismos comensais ou transformar uma colonização sem sintomas em uma infecção.

Classicamente, os mecanismos de transformação da colonização em infecção são multifatoriais e relacionam-se a diabetes mellitus tipo 1, uso de antibióticos, de corticosteroides e imunossupressores, imunodeficiências, doenças da tireoide, stress, alterações hormonais, gravidez, obesidade, uso de anticoncepcionais orais com alta dose de estrogênios, uso de espermicidas, diafragma e DIUs, hábitos de vida, higiene, vestuário,

dieta rica em açúcar, vida sexual (sexo oral e sexo anal), entre outros (3). Apesar disso, a maioria das mulheres com CVVR não apresentam essas condições (7).

Por outro lado, a ocorrência de CVVR parece ser primariamente devida a diferentes suscetibilidades dos fatores do hospedeiro e não à maior frequência de colonização ou à presença de cepas mais virulentas de *Candida sp* (3). Foi verificada forte associação entre atopia e CVVR, sendo possível que um aumento da resposta das células T e a diminuição da alergia possam ser usadas como ferramentas no tratamento de CVVR (8).

Embora tenham sido publicadas evidências que sugerem que a susceptibilidade para o desenvolvimento de CVVR é associada a diversos fatores como resposta alérgica vaginal localizada, deficiência na imunidade mediada por células Cândida-específicas, resposta neutrofílica hiperativa, presença de polimorfismo funcional nos genes que codificam a proteína, a lecitina de ligação à manose ou à citocina anti-inflamatória interleucina-4, as causas da CVVR na maioria dos pacientes permanecem inexplicadas (9,10). A resposta imune do tipo celular (células T CD4) é predominante na resistência das mucosas do hospedeiro às infecções por cândida. Por outro lado, a susceptibilidade à infecção está associada à resposta do tipo humoral (células B) (7).

Atribui-se à resistência terapêutica muitos casos de candidíase vulvovaginal, porém outra hipótese é que a CVV primária é uma reação alérgica causada por imunoglobulina E cândida específico (IgE). Mulheres com candidíase vaginal recorrente costumam ter maior concentração de eosinófilos no sangue periférico que as assintomáticas (11,12).

A *Candida albicans* pode agir como patógeno comensal ou agressor, dependendo da interação com seu hospedeiro e as possíveis modificações do meio vaginal. Assim, os sintomas apresentados podem ser devidos, em certos casos, majoritariamente por uma resposta alérgica da mucosa sensibilizada do que propriamente pela ação direta do fungo (10).

Os sintomas da candidíase vulvovaginal (CVV) incluem prurido vulvovaginal, irritação, queimação, dor, dispareunia e corrimento vaginal. A disúria no final da micção também pode ocorrer. Os sinais clínicos incluem eritema da vulva, edema, escoriação e formação de fissuras, juntamente com eritema e edema do introito e da mucosa vaginal e colpite difusa. O fluxo vaginal pode mostrar conteúdo branco, inodoro, flocular, pastoso, eventualmente esverdeado, aderente à mucosa, com aspecto de “leite coalhado”. Uma descarga branca não-nodosa é sugestiva de CVV, mas é extremamente inespecífica (13).

A inflamação crônica da mucosa vaginal e as fissuras vulvares podem predispor a mulher a infecções virais, como HPV, herpes, HIV e hepatites.

O diagnóstico da CVV pode ser realizado em testes de consultório, incluindo medida do pH vaginal, que encontra-se quase sempre abaixo de 4,5 mas é considerado inespecífico e pela avaliação do corrimento com solução salina e hidróxido de potássio a 10% (KOH), importantes para fazer um diagnóstico diferencial com outras causas de vulvovaginites. A utilização de KOH a 10% permite melhor visualização fungica por levar ao rompimento celular. O exame direto por microscopia ótica, a fresco e por coloração Gram, deve buscar evidenciar pseudohifas e/ou blastosporos. Em pacientes com sintomas sugestivos, mas microscopia negativa, uma cultura para fungos em meios específicos (Sabouraud e Nikersen) é útil, já que as hifas ou blastosporos são identificados apenas com microscopia em cerca de 50% dos casos (14). Além disso, a cultura de levedura positiva permite a especiação do organismo causador, o que, por sua vez, pode ter implicações importantes para a terapia antifúngica.

Embora a cultura também permita o acesso ao organismo para o teste de susceptibilidade antifúngica, esse teste é raramente utilizado na prática clínica, a menos que os pacientes experimentem falha clínica ou micológica repetida. Estudos têm observado que o diagnóstico por PCR é mais sensível que a cultura na detecção de espécies de Cândida na vagina (10,15).

O Center for Disease Control (CDC) classifica a candidíase vulvovaginal em complicada e não complicada. A doença também pode ser sintomática ou assintomática e apresentar diversos graus de gravidade - leve, moderada ou grave/severa, cada grau recebe as pontuações 1, 2 ou 3, respectivamente. O grau de gravidade será definido pela gravidade dos achados como eritema vulvar ou vaginal, prurido, edema, presença de fissuras ou escoriações da vulva e/ou da vagina. Escores menores ou igual a 4 classificam a doença em leve, entre 4 e 7 em moderada e acima de 7 em grave (16).

As opções atuais de tratamento para candidíase vulvovaginal incluem agentes antifúngicos vendidos sem prescrição médica, para uso por via oral ou intravaginal. O fluconazol tem sido usado extensivamente com um impacto desconhecido na suscetibilidade fúngica.

O conjunto antifúngico atual compreende cinco diferentes classes de drogas antifúngicas: azóis, polienos, equinocandinas, alilaminas e flucitosina. Para o tratamento da

candidíase vulvovaginal utiliza-se habitualmente antifúngicos azólicos e polienos, disponíveis para uso oral, local e intravenoso.

Os antifúngicos azólicos são comumente utilizados para prevenir e tratar infecções fúngicas invasivas. Os azólicos bloqueiam a síntese de ergosterol, o esterol mais importante da membrana celular fúngica, interferindo na ação do produto gênico de ERG11: citocromo P450 lanosterol 14-alfademetilase, que é inibinda. Subdividem-se em imidazólicos, que possuem 2 átomos de nitrogênio no anel azólico e incluem Cetoconazol, Butoconazol; Clotrimazol; Econazol; Fenticonazol; Isoconazol; Miconazol; Omoconazol; Oxiconazol; Tioconazol e Sertaconazol e em triazólicos, que possuem 3 átomos de nitrogênio no anel azólico e incluem Fluconazol; Itraconazol; Posaconazol; Voriconazol e Terconazol (17,18).

Apresentam baixa toxicidade, sendo considerados seguros e bem tolerados. Possíveis efeitos adversos ocorrem por bloqueio da biossíntese das enzimas do complexo P450, que produzem o colesterol nas células hepáticas. As reações adversas mais comuns ocorrem no uso oral e consistem em distúrbios gastrointestinais como náuseas, vômitos, diarreia, distensão e dor abdominal além de cefaleia e exantema. Cetoconazol e fluconazol estão relacionados a elevação transitória de bilirrubinas e transaminases, raramente associada a hepatite clínica. Os azólicos de uso local podem raramente estar associados a irritação e queimação vaginal e podem diminuir a resistência de preservativos e diafragma. Azólicos não são recomendados para uso em gestantes e lactantes por serem excretados no leite materno e apresentarem possibilidade de efeitos teratogênicos e embriotóxicos (17,18).

Os antifúngicos polienos são compostos de moléculas com diversas ligações duplas conjugadas, que agem ligando-se ao ergosterol, de forma a afetar a permeabilidade da membrana celular, o que leva a perda de íons (Ca^{++}, K^{+} e Na^{+}) e de proteínas e incluem Nistatina, Natamicina e Anfotericina. A anfotericina está relacionada aos maiores efeitos adversos como toxicidade renal, hipocalemia, hipomagnesemia, anemia, distúrbio hepático, calafrios, febre, vômitos, cefaleia e tromboflebite local. Nistatina pode apresentar irritação local no uso vaginal (17,18).

Ensaios clínicos demonstram taxas comparáveis de cura entre as vias tópica e oral (acima de 90% de cura), com uma pequena diminuição nas taxas de cura com tratamentos de curta duração (70 a 80%) em relação aos de longa duração (19,20). Entretanto, até o presente momento, não existe evidência de maior eficácia ou superioridade de algum

protocolo antifúngico ou esquema terapêutico no tratamento da candidíase vulvovaginal não complicada.

Recomenda-se que na doença não complicada de intensidade leve a moderada e nos episódios únicos isolados e não recorrentes, seja indicado tratamentos de curta duração (em até 7 dias) e em dose única. Nos casos de doença complicada grave/severa ou recorrente, deve-se evitar o tratamento em dose única e preferir tratamentos mais longos. Nestas pacientes, pode-se usar fluconazol 150mg, via oral, em duas doses, com intervalo de 72 horas, atingindo cerca de 85% de cura (19,20). Para pacientes com sintomas locais irritativos de grande intensidade pode-se associar o uso de corticosteroides tópicos de baixa potência para alívio sintomático.

Nas pacientes gestantes está contraindicado o uso de antifúngicos durante toda a gestação, devendo-se optar por tratamento tópico com azólicos já estudados e considerados seguros como miconazol e isoconazol ou com polienos como a nistatina por 7 a 14 dias (19,20).

Pacientes HIV positivas costumam apresentar episódios mais frequentes e graves de candidíase vulvovaginal quando apresentam o nível de CD4 menor que 100 células por mm^3. O tratamento deve ser feito de forma semelhante as pacientes não imunossuprimidas. Recomenda-se terapia supressiva com fluconazol 150mg via oral semanal continuamente para as que apresentam baixos níveis de CD4 (16,19,20).

O tratamento eficaz da CVVR, com controle adequado dos sintomas e erradicação do fungo, representa um desafio na prática clínica diária. Muitos são os esquemas antifúngicos disponíveis para tratamento, alguns deles com efeitos adversos que acabam reduzindo a aderência das mulheres ao tratamento. A falta de critérios claros de indicação das drogas disponíveis e seu uso livre devido à automedicação pelas mulheres têm contribuído para a crescente resistência antifúngica verificada em alguns ensaios clínicos.

O esquema mais utilizado para tratamento da CVVR consiste de 10 a 14 dias de terapia de indução com um agente antifúngico tópico ou no uso de fluconazol oral 150mg, em dose única, seguido de fluconazol, 150 mg, via oral, por semana durante 6 meses (20,21). Foi visto que mulheres com CVVR com escoriação vulvar, maior tempo de doença e história familiar de doença atópica têm maior risco de não responder ao tratamento de manutenção com fluconazol (22).

O CDC recomenda duração prolongada da terapia inicial, com 7 a 14 dias de terapia tópica ou uma dose oral de 100 mg, 150 mg ou 200 mg de fluconazol a cada três dias num

total de 3 doses, nos dias 1, 4 e 7, para tentar a remissão micológica antes de iniciar um regime antifúngico de manutenção. O fluconazol oral em doses de 100 mg, 150 mg ou 200 mg semanalmente por 6 meses é o regime de manutenção de primeira linha. Tratamentos tópicos usados de forma intermitente também podem ser considerados para profilaxia de recorrências (16).

Outros esquemas de tratamento para CVVR incluem: Itraconazol via oral, 200 mg, duas vezes ao dia (1 dia) ou 200 mg ao dia (3 dias); cetoconazol via oral, 200 mg, uma vez ao dia durante 14 dias ou cetoconazol via oral, 400 mg, uma vez ao dia por 14 dias (16, 17), seguidos de tratamento supressivo: cetoconazol via oral, 400mg ao dia por 5 dias, 1 vez ao mês, no período perimenstrual por 6 meses ou 100 mg ao dia por 6 meses, itraconazol via oral, 50 - 100 mg ao dia (6 meses) ou fluconazol via oral 150 mg por semana (6 meses) (23-28).

O tratamento local engloba o uso de creme, óvulos ou comprimidos intravaginais por períodos que variam de 1 a 14 noites consecutivas e incluem: clotrimazol (29,30), terconazol (31,32), fenticonazol (33-36), miconazol (37-40), butoconazol (41,42), nistatina (43, 44), entre outros antifúngicos (45-48), seguido de tratamento supressivo via oral ou via vaginal por 6 meses. O uso de cetoconazol a longo prazo deve ser feito com cautela e acompanhamento, pelo risco de toxicidade sistêmica (17,18).

Na última década, foram relatados casos isolados de mulheres com CVVR que não responderam à terapia de indução com fluconazol. Após se excluir a falta de aderência ao tratamento, a resistência ao fluconazol deve ser considerada (13, 50-52). Estudos recentes também já relatam aumento da resistência aos demais derivados azólicos por espécies de Candida (4, 5, 10, 49-53), tornando a escolha do melhor esquema terapêutico um desafio ao ginecologista.

O tratamento deve ser associado a higiene cuidadosa da região genital, não sendo recomendado o uso de duchas vaginais. A utilização de sabonetes específicos para uso íntimo, com pH mais ácido que o habitual ajuda na manutenção da flora genital. A associação de outros tratamentos ao uso de antifúngicos pode ser realizada para recuperação da flora vaginal, normalização do pH e alívio dos sintomas (54).

São habitualmente prescritos banhos de assento com solução de bicarbonato de sódio 30 a 60 g, dissolvido em 1000 ml de água, ácido bórico cápsula vaginal, 600 mg ao dia, durante 14 dias, reposição dos lactobacilos vaginais por ingestão de substâncias probióticas ou por uso de óvulos vaginais (55).

O uso de probióticos, embora promissor, ainda não possui eficácia comprovada no tratamento e na prevenção de recidivas, pela falta de evidências demonstradas em estudos bem delineados. Efeitos no uso a longo prazo de probióticos são desconhecidos e seu uso deve ser cuidadoso e personalizado (56).

A recomendação do tratamento dos parceiros sexuais na candidíase recorrente é controversa e deve ser realizado apenas naqueles sintomáticos (55).

A eficácia dos protocolos de tratamentos antifúngicos na candidíase vulvovaginal recorrente pode ser avaliada pelas taxas de cura e de recorrência clínica e micológica, pelo tempo transcorrido até o reaparecimento dos sintomas da doença e pela proporção de pacientes que apresentam recidivas ao longo dos períodos de tratamento e profilaxia.

A taxa de cura clínica refere-se a proporção de mulheres que permaneceram livres de sintomas de candidíase, durante os períodos de tempo dos estudos pesquisados, medida em porcentagem. A taxa de cura micológica diz respeito a proporção de pacientes que permaneceram com culturas vaginais negativas para *Candida sp*, durante os mesmos períodos, medida em porcentagem.

As taxas de recorrência são calculadas a partir da proporção de novos casos de candidíase, sendo a recorrência clínica decorrente do reaparecimento de sintomas clínicos e a recorrência micológica devido ao ressurgimento de microscopia com presença do fungo (hifas e/ou esporos) ou cultura positiva para *Candida sp*. que ocorreram em mulheres já tratadas com a droga escolhida, no período mínimo de seguimento de cada estudo, após o início do tratamento, medida em porcentagem.

O tempo para a primeira recorrência é definido como o número de dias livres da doença após o tratamento com a droga escolhida até o reaparecimento dos sintomas ou do retorno das leveduras na vagina, medido em dias.

As taxas de cura e de recorrência da CVVR são avaliadas a curto e a longo prazo pelos diversos estudos que avaliam protocolos de tratamento da doença. Consideramos curto prazo as avaliações realizadas até 6 meses após o início dos tratamentos antifúngicos e longo prazo aquelas realizadas até 12 meses após a instituição da terapia.

Portanto, nota-se que existem muitas opções de tratamento da VVCR, porém, não há clareza de qual deles se apresenta como a melhor ou mais razoável orientação a ser seguida. Infelizmente, não são muitos os trabalhos científicos conduzidos com rigor metodológico. Os “Clinical Trials” com randomização e cegamento ainda não testaram todas as opções de tratamento oferecidas para as VVCR. Desta forma, ao se avaliar se

existe diferença na eficácia dos diversos protocolos de tratamentos antifúngicos habitualmente propostos para tratamento da CVVR, buscamos embasar práticas clínicas que impactem na redução da morbidade dessa patologia e na diminuição da resistência aos fármacos utilizados.

2. OBJETIVOS

2.1. OBJETIVO GERAL:

Avaliar a eficácia e a segurança dos protocolos de tratamentos com antifúngicos administrados por vias oral e/ou vaginal para a Candidíase vulvovaginal recorrente (CVVR).

2.2. OBJETIVOS ESPECÍFICOS:

- Comparar a eficácia dos diversos protocolos de tratamento utilizados para a CVVR entre si e entre placebo a curto e longo prazo no tratamento da CVVR.
- Comparar taxas de cura e recorrência clínica e micológica dos protocolos.
- Avaliar a segurança e os efeitos colaterais apresentados pelos tratamentos utilizados para a CVVR administrados por via oral e orais e vaginal.

3. METODOLOGIA

3.1. DESENHO

Revisão sistemática de ensaios clínicos randomizados com metanálise de dados.

3.2. SELEÇÃO DOS SUJEITOS

Este estudo de revisão sistemática seguiu os critérios: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. O protocolo desta revisão sistemática está disponível em publicação anterior, apresentada nos resultados.

3.3. TIPOS DE ESTUDOS SELECIONADOS

Ensaios clínicos randomizados, cegos, avaliando os tratamentos para candidíase vulvovaginal recorrente em mulheres imunocompetentes, foram considerados para inclusão.

3.4. TIPOS DE PARTICIPANTES

Foram incluídas na análise estudos que incluíram mulheres com 3 ou mais episódios de candidíase vaginal confirmados pela presença de sintomas e uma cultura ou sintomas e microscopia positiva, nos últimos 12 meses antes da inclusão.

3.5. TIPOS DE INTERVENÇÃO

Intervenções consideradas: tratamentos com antifúngicos:

- Antifúngicos administrados por via intravaginal: butoconazol, clotrimazol, econazol, fenticonazol, isoconazol, miconazol, omoconazol, oxiconazol, terconazol, tioconazol, natamicina, sertaconazol e anfotericina ou nistatina.
- Antifúngicos orais: fluconazol, cetoconazol, itraconazol, posaconazol, voriconazol e oteseconazol.

As seguintes comparações foram analisadas:

- Diferentes tratamentos entre si;
- Qualquer tratamento versus placebo;
- Curta duração do tratamento versus maior duração do tratamento;
- Tratamento sistêmico versus local;

- Comparação de diferentes doses do mesmo agente.

3.6. TIPOS DE DESFECHO

Desfechos primários

- Recorrência clínica e micológica por paciente por ano (recorrência definida como características clínicas e cultura positiva ou microscopia).

Desfechos secundários

- Tempo para a primeira recorrência.
- Proporção de participantes com pelo menos uma recorrência durante o tratamento e período de acompanhamento.
- Complicações.
- Eventos adversos.

3.7. MÉTODOS DE BUSCA PARA IDENTIFICAÇÃO DOS ESTUDOS

Identificamos tanto estudos publicados como inéditos, que avaliaram as intervenções que visam o controle da CVVR. Utilizamos tanto a busca eletrônica nas bases de dados como a busca manual. Nenhuma restrição de idioma ou data foi utilizada.

3.8. BUSCA EM BASES ELETRÔNICAS

Uma pesquisa abrangente foi realizada nas seguintes bases de dados: PubMed, Embase, Scopus, Web of Science, SciELO, Cochrane Controlled Trials Register (CENTRAL), CINAHL, BVS e bases de dados de ensaios clínicos (www.trialscentral.org; www.controlled-trials.com; www.trials.gov)

3.9. ESTRATÉGIA DE BUSCA

Foi utilizado o seguinte caminho de busca: (candida OR candidiasis OR candidosis OR yeasts OR vaginitis OR vulvovaginal) AND (antifungal OR butoconazole OR clotrimazole OR econazole OR fenticonazole OR isoconazole, miconazole OR omoconazole OR oxiconazole OR terconazole OR tioconazole, natamycin OR sertaconazole OR amphotericin OR fluconazole OR ketoconazole OR itraconazole OR posaconazole OR voriconazole OR nystatin) AND (randomized controlled trial) OR (blind method) OR (clinical trial). As estratégias de busca para cada base podem ser vista na Tabela 1.

3.10. AVALIAÇÃO DA ELEGIBILIDADE DOS ESTUDOS

Todos os artigos que foram triados na fase anterior tiveram sua elegibilidade confirmada pela leitura mais detalhada do estudo, através da leitura do texto completo do artigo.

Três autores da revisão avaliaram independentemente a elegibilidade para inclusão dos ensaios identificados pela pesquisa. A avaliação foi feita pela leitura dos textos completos dos artigos encontrados pela estratégia de busca, nas bases de dados. Desentendimentos foram resolvidos por discussão, envolvendo a contribuição de um quarto autor.

Nesta etapa, a razão primária da exclusão foi registrada para composição do fluxo de seleção dos artigos.

3.11. COLETA DE DADOS

Após a seleção dos estudos participantes desta revisão sistemática, os dados, assim como na etapa de seleção dos artigos, foram extraídos por dupla de revisores de maneira independente. Discordâncias nos dados coletados foram resolvidas ou por consenso entre a dupla ou por consulta ao terceiro revisor.

3.12. EXTRAÇÃO E GERENCIAMENTO DOS DADOS

O software Review Manager (RevMan 2010) foi utilizado para executar a análise estatística da metanálise. Para avaliar a eficácia entre os tratamentos propostos, os dados dicotômicos foram extraídos de cada estudo e inseridos em uma tabela de contingência 2 × 2. Calculamos o OR para dados dicotômicos e diferença de média de peso (MD) para dados contínuos com 95% de IC associado, para obter uma estimativa global resumida.

A heterogeneidade foi avaliada pela estatística I2: (<25%, sem heterogeneidade; 25% a 50%, heterogeneidade moderada; e >50%, forte heterogeneidade). O modelo de efeito fixo foi escolhido pela baixa heterogeneidade entre os estudos. Usamos o gráfico de funil de Egger para avaliar o possível viés de publicação nas metanálises com pelo menos 6 estudos. Uma abordagem de regressão linear foi utilizada para avaliar a assimetria do gráfico de funil.

3.13. RISCO DE BIAS

Três revisores independentes aplicaram a Ferramenta Cochrane Risk of Bias para avaliar a sequência aleatória de geração, ocultação de alocação, cegamento dos participantes e avaliação de resultados clínicos.

Também avaliamos os dados de resultados incompletos, relatórios seletivos, financiamento e potencial conflito de interesses associados aos ensaios individuais. O risco de bias foi classificado usando critérios predeterminados como segue: baixo, alto ou pouco claro, apresentados na tabela 4.

3.14. APRESENTAÇÃO DOS DADOS

A metodologia de seleção dos estudos foi resumida em um diagrama de fluxo PRISMA (Figura 1).

As características e os resultados principais dos estudos incluídos estão apresentados na forma de tabelas (Tabelas 2 e 3). Outras características e resultados foram resumidos narrativamente.

Os resultados das metanálises são apresentados na forma de tabelas com forest plots e a avaliação do viés de publicação é mostrado na forma de gráficos de funil de Egger.

3.15. CONFIANÇA NA EVIDÊNCIA CUMULATIVA

Para descrever a força da evidência para os dados incluídos, utilizamos o sistema GRADE (Grading of recommendation Assessment, Development and Evaluation), que atribui níveis de evidência e classifica a força da recomendação para questões em saúde. O sistema Grade foi avaliado através da ferramenta online grade pro, acessível gratuitamente em gradepro.org.

A avaliação da qualidade da evidência foi realizada para o desfecho principal de cada estudo incluído utilizando o conjunto disponível de evidência, por 2 pesquisadores de forma independente e um terceiro autor revisou a avaliação e resolveu divergências

O sistema grade oferece diversas vantagens em comparação a outros sistemas de graduação de evidências. Uma vantagem importante do Grade é separar a avaliação da qualidade da evidência da avaliação da força da recomendação.

A qualidade da evidência diz respeito ao grau de confiança que se pode ter em uma determinada estimativa de efeito. A força da recomendação reflete o grau de confiança no balanço entre os efeitos desejáveis e indesejáveis de um tratamento. A qualidade da evidência é um dos elementos que determina a força da recomendação. No entanto, não basta haver grande confiança na estimativa de efeito de um tratamento para definir o sentido e a força da recomendação.

Embora a qualidade da evidência inicialmente dependa do delineamento do estudo, critérios adicionais são levados em conta para rebaixá-la ou elevá-la. Esses critérios são o delineamento do estudo, limitações metodológicas (risco de viés), inconsistências, evidência indireta, imprecisão e viés de publicação.

Considerando o delineamento do estudo, os ensaios clínicos randomizados começam com nível de evidência alto e estudos observacionais começam com nível de evidência baixo. Ambos podem ter a qualidade da evidência reduzida, devido à presença de limitações metodológicas referentes ao seu delineamento ou execução.

O risco de viés pode variar de acordo com diferentes desfechos quando cada um deles é informado. As possíveis inconsistências observadas nos resultados dos estudos individuais, se não forem explicadas por análises de sensibilidade, diminuem a confiança na estimativa do efeito.

A evidência pode ser considerada indireta por quatro motivos: os participantes avaliados nos estudos não representam adequadamente a população de interesse; as intervenções avaliadas nos estudos diferem daquelas de interesse; quando há ausência de comparações diretas entre as alternativas avaliadas e quando os desfechos avaliados não são aqueles de interesse primário para a tomada de decisão.

A imprecisão das estimativas é julgada pela amplitude do intervalo de confiança de 95%; quanto maior o intervalo de confiança, maior a imprecisão das estimativas.

O viés de publicação é a tendência em publicações científicas de evidências positivas terem maior probabilidade de serem publicadas do que evidências negativas.

A qualidade da evidência foi identificada como alta (o verdadeiro efeito fica próximo ao da estimativa do efeito), moderada (o efeito verdadeiro provavelmente está próximo da estimativa do efeito, mas há uma possibilidade de que seja substancialmente diferente), baixo (o efeito verdadeiro pode ser substancialmente diferente da estimativa do efeito) ou muito baixo (o verdadeiro efeito é provavelmente substancialmente diferente da estimativa de efeito).

4. RESULTADOS

4.1. Artigo 1 (Já publicado): ANTIFUNGAL (ORAL AND VAGINAL) THERAPY FOR RECURRENT VULVOVAGINAL CANDIDIASIS: A SYSTEMATIC REVIEW PROTOCOL

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ANTIFUNGAL (ORAL AND VAGINAL) THERAPY FOR RECURRENT VULVOVAGINAL CANDIDIASIS: A SYSTEMATIC REVIEW PROTOCOL

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ABSTRACT

Introduction: Vulvovaginal candidiasis (VVC) is frequent in women worldwide and usually responds rapidly to topical or oral antifungal therapy. However, some women develop recurrent vulvovaginal candidiasis (RVVC), which is arbitrarily defined as four or more episodes every year. RVVC is a debilitating, long-term condition that can severely affect the quality of life of women. Most VVC is diagnosed and treated empirically and women frequently self-treat with over-the-counter medications that could contribute to an increase in the antifungal resistance. The effective treatment of RVVC has been a challenge in daily clinical practice. This review aims to assess the efficacy of antifungal agents administered orally or intravaginally for the treatment of RVVC, in order to define clinical practices that will affect the reduction of the morbidity and antifungal resistance.

Methods and analysis: A comprehensive search of the following databases will be carried out: PubMed, Embase, Scopus, Web of Science, SciELO, the Cochrane Central Register of Controlled Trials (CENTRAL), BVS/BIREME, CINAHL, and in the clinical trials databases (www.trialscentral.org; www.controlled-trials.com; www.clinicaltrials.gov). The risk of bias will be assessed according to the Cochrane Risk of Bias tool. We will perform data synthesis using the Review Manager (RevMan) software V.5.2.3. To assess heterogeneity, we will compute the I2 statistic.

Ethics and dissemination: This study will be a review of published data and it is not necessary to obtain ethical approval. Findings of this systematic review will be published in a peer-reviewed journal.

Trial registration number for International Prospective Register of Systematic Reviews 2018: International Prospective Register of Systematic Reviews 2014: CRD42018093817

Strengths and limitations of this study

- The results obtained in this systematic review will indicate through evidence-based medicine if there is a more effective antifungal therapeutic regimen for the treatment of recurrent vulvovaginal candidiasis.
- Two independent reviewers will select the studies included in this review, extract data without different variables and assess the risk of bias.
- There may be a limitation of outcome from treatment variation, routes of administration, different doses and quality of the randomized trials used in the systematic review.

- This review and meta-analysis aim to combine the results of different studies that have comparable sizes of effect that can be computed.
- However, it may be that we have only a small sample size and a limited number of studies, which may influence the validity and reliability of the findings

INTRODUCTION

Description of the condition:

Vulvovaginal candidiasis (VVC) is frequent in women worldwide and usually responds rapidly to topical or oral antifungal therapy. However, some women develop recurrent vulvovaginal candidiasis (RVVC), which is arbitrarily defined as at least three symptomatic episodes in the previous 12 months [1,2,3].

It is estimated that RVVC affects approximately 138 million women worldwide annually and 492 million over their lifetimes [1,2]. Women reported the period of RVVC to be 1-2 years although a substantial number had symptoms for 4 or 5 years and some very much longer, with risk and symptoms lasting decades [4,5].

Candida albicans is responsible for the majority of infections in women with RVVC; however, adequate treatment of RVVC requires species determination confirmed by laboratory findings and effective treatment [2].

Several factors have been associated to RVVC such as genetic (polymorphism, familial, ethnicity), immune mechanisms (HIV, uncontrolled diabetes, steroids, antibiotics, hormone replacement therapy), behavioral (oral sex, oral contraceptive, intercourse frequency) and idiopathic [6-10].

Fluconazole is inexpensive and well-tolerated medication that is easily administered orally and is the most used antifungal drug. However, in the last decade, fluconazole-resistance has been reported of women with RVVC. Earlier epidemiologic studies found that almost all women diagnosed with fluconazole-resistant *C albicans* had experienced previous exposure to fluconazole [11]. The rates of azole resistance are highly variable, and they may be influenced by the prescribing patterns of clinicians for both the treatment of and prophylaxis.

In Addition, is still important to recognize that the excessive use and overuse of such topical agents have had other adverse consequences such as edema, irritability of the skin and maybe even chronic vulvar pain condition (vulvodynia) [12,13].

Furthermore, it is recognized that are several factors (genetics, polymorphisms, behavioral and host factors), associated with the pathogenesis of RVVC. In this context, it is unlikely to find one regimen fit for all patients. However, no published studies are comparing different antifungal regimens; thus, this review based on evidence must be useful for practitioners and physicians.

Description of the intervention:

Current treatment options for vulvovaginal candidiasis include antifungal agents sold without a prescription for oral or intravaginal use. Fluconazole has been used extensively while having an unknown impact on fungal susceptibility [11].

The most commonly used regimen for RVVC consists of 10 to 14 days of induction therapy with a topical antifungal agent or oral fluconazole, 150mg, followed by fluconazole, 150mg per week for 6 months [14, 15]. It was seen that women with RVVC with vulvar excoriation, longer disease time and family history of atopic disease are at greater risk of not responding to maintenance treatment with fluconazole [16].

In the last decade, isolated cases of women with RVVC who have not responded to fluconazole induction therapy have been reported. After excluding lack of adherence to treatment, resistance to fluconazole should be considered [2, 17-19].

A previous Cochrane review aimed to compare the clinical cure rate of topical versus oral treatment for the treatment of vulvovaginal candidiasis [20] and found no difference in the efficacy of oral and vaginal treatment but found that women generally preferred oral treatment. The recommended treatment regimen for RVVC, as described in the clinical guidelines [21] whether oral or topical, is not effective for all women [17]. Side effects reported include headache, abdominal pain and nausea with oral treatment [22, 23, 24] and dyspareunia or irritation with vaginal treatment [24]. In addition, long-term treatments are expensive, and approximately 50% of women experience recurrence of symptoms a few months after treatment completion [25].

Effective treatment of RVVC, with adequate control of symptoms and eradication of the fungus, represents a challenge in daily clinical practice. Many antifungal regimens are available for treatment, some of them with adverse effects that end up reducing women's adherence to treatment. The lack of clear criteria for indication of available drugs and their free use due to self-medication by women has contributed to the increasing antifungal resistance found in some clinical trials.

How the intervention might work:

Antifungal agents generally act as fungistatics and most often work by just destroying the cell wall. Nowadays, despite the great diversity of antifungal agents available for vaginal or systemic use and the large number of clinical trials performed, there are actually very few that compare their efficacy along with the risk of developing resistance.

Why it is important to perform this review:

In order to find a rational use of the antifungal medications available for the treatment of RVVC, as well as the choice of the best route of administration, it is necessary to evaluate comparatively the various proposed schemes normally used. In this way, the choice of the best treatment can be made according to the proven and acceptable safety and efficacy dictates.

By avoiding drugs of doubtful or unproven efficacy, as well as high risk / benefit index, drug combinations of the same formulations or duplicity of drugs for the same clinical indication, the quality of medical care can be improved.

This study also contributes to the assessment of whether there is a more cost-effective and efficient therapeutic approach for the patient and the health system, between two or more equally effective treatments.

If there is similarity of efficacy between different antifungal drugs used in an oral treatment regimen, one can recommend the one that presents less side effects, more dosage convenience or even lower cost.

In cases of vaginal treatments with superior or similar efficacy to those used orally, they may be chosen as the first option, especially for patients with oral side effects.

Since the sale of antifungal drugs is not subject to prescription control by pharmacies, the indiscriminate use of antifungal drugs by self-medication and without medical prescription has contributed to the increase of antifungal resistance to these drugs. Knowing the efficacy profile of each drug in the treatment of recurrent vulvovaginal candidiasis will enable the creation of a treatment protocol for the pathology and also decrease the risk of increased antifungal resistance.

OBJECTIVES

To evaluate the efficacy of different antifungal protocols usually used orally and vaginally in the treatment of RVVC.

METHODS

This systematic review study with probable meta-analysis will follow the criteria: Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) guidelines. This protocol has been registered with the International Prospective Register of Systematic Reviews, registration number CRD42018093817.

Criteria for considering studies for this review

Types of studies:

Randomized, blind, clinical trials evaluating treatments for recurrent vulvovaginal candidiasis in immunocompetent women will be considered for inclusion.

Types of participants:

Women who will be included in the analysis will have had 3 or more episodes of vaginal candidiasis confirmed by the presence of symptoms and a culture or symptoms and positive microscopy. Women with diabetes mellitus and pregnant women will be included in the review but analyzed separately in subgroups. Women with immunosuppressive conditions or users of immunosuppressive drugs will be excluded.

Types of interventions:

Interventions to be considered will be antifungal protocols treatments: administered intravaginally (e.g. butoconazole, clotrimazole, econazole, fenticonazole, isoconazole, miconazole, omoconazole, oxiconazole, terconazole, tioconazole, natamycin, sertaconazole, nystatin and amphotericin) or orally (e.g. fluconazole, ketoconazole, itraconazole, posaconazole and voriconazole)

The following comparisons was be made: Any treatment versus other or placebo; Short duration of treatment versus longer duration of treatment; Systemic versus local treatment; comparison of different doses of the same agent.

Types of outcome measures:

Primary Outcome: number of clinical recurrence per patient per year (recurrence defined as clinical characteristics and positive culture or microscopy;
Proportion of participants with at least one clinical recurrence during the treatment and follow-up period.

Secondary outcomes:Time for first recurrence; Number of symptomatic days per year; Number of mycological recurrences per patient per year; Proportion of participants with at least one mycological recurrence during treatment and follow-up period; Duration of symptoms after starting treatment; Complications; Adverse events and Patient preference

Search methods for identification of studies

Electronic searches:

We try to identify as many published studies as unpublished ones, which evaluate the interventions that aim at the control of RVVC. We will use the electronic search in the databases as the manual search. No language restrictions will be used. The list of Databases is shown in box 1.

Table 1 - List of Databases

PubMed
Embase,
Scopus
Web of Science
SciELO,
The Cochrane Central Register of Controlled Trials (CENTRAL)
BVS/BIREME
CINAHL
Clinical trials databases (www.trialscentral.org;www.controlled-trials.com; www.clinicaltrials.gov)

Other sources:

The aim of the computerized bibliographic research will be extended using the reference lists of selected articles.

Search strategy:

The search strategy for Pubmed is shown in table 1.

Table 1 - Pubmed search strategy

	Search items
1	candida
2	candidiasis
3	candidosis
4	yeasts
5	vaginitis
6	vulvovaginal
7	OR /1-6
8	antifungal
9	butoconazole
10	clotrimazole
11	econazole
12	fenticonazole
13	isoconazole
14	miconazole
15	omoconazole
16	oxiconazole
17	terconazole
18	tioconazole
19	natamycin
20	sertaconazole
21	amphotericin
22	fluconazole
23	ketoconazole
24	itraconazole
25	posaconazole
26	voriconazole
27	nystatin
28	OR/8-28
27	(randomized controlled Trial)

28	(blind method)
29	(clinical Trial)
30	OR/27-30
31	7 AND 28 AND 30

Data collection and analysis

Selection of studies:

Two review authors (JFL and AKG) will independently evaluate the eligibility for inclusion of the trials identified by the survey. Disagreements will be resolved by discussion, involving the contribution of a third author (PCG). The trial authors will be contacted if more information is needed before deciding to include. The selection of the study is summarized in a PRISMA flow diagram (figure 1). Thus, papers that met the criteria will be reviewed in full. After the full review, papers not considered having adequate methodological quality according to the GRADE guidelines will be excluded. A list of excluded studies will be provided, with a brief mention of the reason for exclusion.

Data extraction and management:

We will use the Review Manager software (RevMan 2010) to perform statistical analysis. The experimental populations, methods and measurements of results are considered similar and, in the absence of statistical heterogeneity, we will group the data using a fixed model effect. If statistical heterogeneity is present, we will not group or use a random effects model.

The data will be entered into the Review Manager software (RevMan 5.3), which allows the user to enter protocols as well as complete reviews, including text, study characteristics, comparison tables and study data, as well as perform the meta-analysis of the inserted data.

To assess safety and efficacy among the proposed treatments, the dichotomous data will be extracted from each study and inserted into a contingency table, with subsequent individual determination of odds ratio (OR), to obtain a global summary estimate.

Models of fixed effects or random effects will be chosen depending on the absence or presence of heterogeneity between the studies.

Risk of bias assessment:

Two independent reviewers, JL and AKM, will apply the Cochrane Risk of Bias Tool to evaluate the random sequence of generation, allocation concealment, blinding of participants, and evaluation of clinical outcomes. We will also evaluate data from incomplete results, selective reporting, financing and potential conflicts of interest associated with individual trials. The risk of bias will be classified using predetermined criteria as follows: low, high or unclear

Measurements of treatment effect:

This will be carried out using the RevMan Analyses statistical package in Review Manager 5.3. We will calculate the OR for dichotomous data and weight mean difference (MD) for continuous data with associated 95% CI.

Unit of analysis issues:

For the cure rate of RVVC, the unit of analysis will be defined as 21 and 30 days after the initiation of therapy. For the recurrence rate of RVVC, 3 months and 6 months following the intervention will be considered as short-term and long-term follow-up, respectively.

Addressing missing data:

We will try to get any missing data by contacting the first author or co-authors of the article via phone, email or post. If we do not receive the necessary information, data will be excluded from our discussion in the Discussion section.

Assessment of heterogeneity:

Statistical heterogeneity among the studies will be assessed by the I2 statistic (<25%, without heterogeneity, 25% -50%, moderate heterogeneity, and> 50%, strong heterogeneity). When a significant heterogeneity exists between included studies (I2> 50%), a random effects model will be used for the analysis; otherwise, the fixed effects model will be used. In addition, we will use the Egger funnel chart to evaluate the possible publication bias.

Assessment of reporting biases:

We will use the Egger funnel chart to evaluate the possible publication bias. A linear regression approach will be used to assess the asymmetry of the funnel plot.

Data synthesis

This will be carried out using the RevMan Analyses statistical package in Review Manager V.5.3. For dichotomous outcomes, we will derive the OR and 95% CI for each study. Where there is heterogeneity (I^2 ≥;75%), a random-effect model will be used to combine the trials to calculate the relative risk (RR) and 95% CI, using the DerSimonian-Laird algorithm in The Meta for Package, a meta-analysis package for R.

Other study characteristics and results will be summarized narratively if the meta-analysis cannot be performed for all or some of the included studies.

Sensitivity analyses:

We will conduct sensitivity analyses to explore the robustness of the findings regarding the study quality and sample size. Sensitivity analyses will be shown in a summary table.

Subgroup analyses:

In the subgroup analysis and heterogeneity investigation, we plan to perform the following subgroup analyzes:

1. Sexually active versus non-sexually active women
2. Pregnant vs. Non-Pregnant Women
3. Women with diabetes mellitus versus non-diabetic women
4. Intervention - duration: short versus long treatment
5. Route of administration: topical versus systemic
6. Candida albicans versus non-albicans

Confidence in cumulative evidence:

To describe the strength of the evidence for the included data, we will use the GRADE (Grading of Recommendation Assessment) system, which assigns levels of evidence and classifies the strength of the recommendation for health issues. The quality of the evidence will be identified as high if the real effect is close to the estimate effect, moderate if the real impact is probably close to the expected outcome. Addicionally, the evidence can be low or very low that significantly different from effect estimate) or very low (the true effect is likely

to be substantially different from the estimated effect. Only the studies of moderate to a high level of evidence will be included in the review.

Patient and Public Involvement

The research will be performed by a wide and comprehensive search of literature from databases and the individual patient data are not included. Thus, the authors no involved patients in setting the research question, as well as, the outcome measures, the design and implementation of the study, and the dissemination of its results.

DISCUSSION

RVVC is a prevalent and relevant gynecological problem, with an impact on women's health. Considerable progress has been made in understanding the pathogenesis of RVVC. It is recognized that diversified factors (genetics, polymorphisms, behavioral, hormonal and host factor), are involved in this process. Thus, it is unlikely to find one regimen fit for all patients. However, no published studies are comparing different antifungal regimens, in theory, differently in the clinical practice, the different antifungals have similar efficacies, and both routes promote appropriate treatment. In this context, we intend to identify the most effective and safe oral and intravaginal antifungal agents for most women, so this review based on evidence must be useful for practitioners and physicians.

This analysis will provide information on the most effective therapeutic regimens for this prevalent disease, to justify the elaboration of an effective treatment protocol.

Ethics and dissemination

This study will be a review of the previously published data so it will not be necessary to obtain approval from the Ethics Committee. Findings from this systematic review will be published in a peer-reviewed journal.

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Contributors

JFL and AKG contributed to the design of this review. JFL drafted the protocol manuscript, and AKG revised it. JFL and AKG developed the search strategies and JFL and RLA will implement them. JFL and AKG will track potential studies, extract data and assess quality. In case of disagreement between the data extractors, PCG will advise on the methodology

and will work as the referee. JFL, AKG, RLA, ACAS, APFC and PCG will complete the data synthesis. All authors have approved the final version for publication.

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4.2. Artigo 2 (submetido BMJ Open): EFFICACY OF ANTIFUNGAL PROTOCOLS OF TREATMENT FOR RECURRENT VAGINAL CANDIDIASIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Juliana Lírio, Paulo Cesar Giraldo, Rose Luce Amaral, Ayane Cristine Alves Sarmento, Ana Paula Ferreira Costa, Ana Katherine Gonçalves, Ricardo N Cobucci, Humberto Saconato, Jose Eleutério Junior, Heury Sousa Ferreira.

ABSTRACT

Objective: To assess the efficacy of antifungal treatment (orally or intravaginally) for recurrent vulvovaginal candidiasis (RVVC). **Design**: A systematic review with meta-analysis looked to see if different antifungal treatment protocols are effective as a prophylactic action preventing new episodes of vulvovaginal candidiasis. Search strategy: databases from PubMed, Embase, Scopus, Web of Science, SciELO, the Cochrane Central Register of Controlled Trials (CENTRAL), BVS/BIREME, CINAHL, and clinical trials were searched until September 2020. Search terms included “candidiasis” and “antifungals”. No language or date restrictions were applied. **Eligibility criteria**: Randomized clinical trials that evaluated treatments of RVVC with any type of antifungal. **Data extraction and synthesis**: Literature search and data extraction were performed independently. Summary odds ratio (OR) and 95% confidence intervals (CIs) were estimated using a fixed-effect model. **Results**: Thirteen studies were included in the systematic review and 9 in the meta-analysis. There was a significant reduction in mycological recurrence when the treatment was performed with Fluconazole, Clotrimazole, Ketoconazole, and Oteseconazole (OR 0.36; 95% CI 0,24-0,55, p <0.001). The first three antifungals also significantly reduced clinical recurrence (OR 0.36; 95% CI 0,24-0,54; p<0.001). The recurrence time of the first symptoms was significantly longer with fluconazole and itraconazole compared with placebo (10.92 days). Two studies comparing clotrimazole with other treatments (ketoconazole and fluconazole) evaluated the clinical cure rates. There was no difference in effectiveness when comparing clotrimazole.**Limitations**: It was not possible to perform the meta-analysis for all studies and outcomes. **Conclusions**: Treatment with fluconazole, miconazole, ketoconazole, and oteseconazole reduced the micrological and clinical recurrence at 12 months, with high and

moderate evidence strength. The recurrence time was shorter in the placebo groups, and there was no difference in effectiveness between fluconazole, clotrimazole, and ketoconazole in curing rvvc. All protocols are safe. PROSPERO registration: CRD42018093817

Strengths and limitations of this study

► This systematic review with meta-analysis combined the evidence from randomized controlled trials only.

► We used a quality assessment tool (GRADE) to rate the quality of articles included in the review.

► Potential missing data and biases, heterogeneity, limited the quality of evidence.

► Lack of data has restricted our ability to explore the characteristics of the studies, the effects of treatments, and the link between dose and treatment response, as well as assessing the potential for publication bias.

INTRODUCTION

Vulvovaginal candidiasis (VVC) is a common fungal infection caused by *Candida* species, predominantly *C. albicans*. However, recurrent vulvovaginal candidiasis (RVVC) compromises women's quality of life significantly, causing severe symptoms of itching and pain, dyspareunia, dysuria, and leukorrhea, this remains a challenge for patients and experienced gynecologists.[1,2,3] RVVC is a condition arbitrarily defined as three episodes of VVC in the previous 12 months. However, some investigators demand yet another additional event, i.e., four attacks.[1,2] Worldwide, recurrent vulvovaginal candidiasis affects about 138 million women annually (range 103-172 million), with a global annual prevalence of 3871 per 100 000 women.[4]

The etiopathogenesis of RVVC is still unclear. Different elements are involved in this condition, such as immune mechanisms (HIV, uncontrolled diabetes, steroids, antibiotics, hormone replacement therapy), genetic mutations (polymorphism, familial, ethnicity), and

behavioral patterns. However, the etiological factor remains unknown, hindering the clinical management of women.[5-7]

A greatly increased number of topical and oral imidazole (azole) agents are available in various formulations with clinical and cure rates ranging from 80% to 90%.[1,2,3] Fluconazole has been the most used, and it is an inexpensive and well-tolerated antifungal drug which is easily administered orally. Meta-analyses demonstrated that fluconazole was effective in reducing 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. Earlier epidemiologic 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, cure of RVVC remains elusive especially in this era of fluconazole drug resistance.[3]

We conducted a meta-analysis based on randomized controlled trials on the efficacy of antifungal drugs in the treatment of RVVC, to evaluate the clinical effectiveness of different antifungal protocols and to provide an evidence-based reference for clinical use.

METHODS

Search strategy and selection criteria

This systematic review study with meta-analysis followed the criteria of the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) guidelines. This protocol has been registered with the International Prospective Register of Systematic Reviews, number CRD42018093817. Furthermore, the protocol of this systematic review is available in a previous publication.[11]

A bibliographic search was performed using the following databases: PubMed, Embase, Scopus, Web of Science, Scientific Electronic Library Online (SciELO), the Cochrane Central Registry of Controlled Trials (CENTRAL), Virtual Health Library (Virtual Library in Health) / Regional Library of Medicine (Regional Library of Medicine) (VHL / BIREME), Accumulated Nursing and Related Health Literature Index (CINAHL) and clinical trial databases (www.trialscentral.org; www.controlled-trials.com; www.clinicaltrials.gov;

Centre for Reviews and Dissemination (CRD); European Union clinical trials). Gray literature was searched using appropriate databases (e.g., OpenGrey). Reference lists of potentially eligible randomized controlled trials were also crossed.

The final electronic literature search was performed in October 2020. No language restrictions were applied. The search strategy for PUBMED is shown in Table 1.

Table 1 – Pubmed search strategy

Number	Search items
1	candida
2	candidiasis
3	candidosis
4	yeasts
5	vaginitis
6	vulvovaginal
7	OR /1-6
8	antifungal
9	butoconazole
10	clotrimazole
11	econazole
12	fenticonazole
13	isoconazole
14	miconazole
15	omoconazole
16	oxiconazole
17	terconazole
18	tioconazole
19	natamycin
20	sertaconazole
21	amphotericin
22	fluconazole
23	ketoconazole
24	itraconazole
25	posaconazole
26	voriconazole
27	nystatin
28	OR/8-28
27	(randomized controlled Trial)
28	(blind method)
29	(clinical Trial)
30	OR/27-30
31	7 AND 28 AND 30

Eligibility criteria

Randomized, blind, published, clinical trials evaluating treatments for recurrent vulvovaginal candidiasis in immunocompetent women were considered for inclusion. Women included in the analysis had at least 3 episodes of vaginal candidiasis confirmed by the presence of signs and symptoms plus a vaginal positive culture for fungus, or signs and symptoms plus a positive vaginal microscopy compatible with vaginal candidiasis (pseudohypha or blastospore). Women with immunosuppressive conditions or users of immunosuppressive drugs were excluded.

The interventions considered antifungal treatments where antifungal drugs were administered intravaginally (e.g., butoconazole, clotrimazole, econazole, fenticonazole, isoconazole, miconazole, omoconazole, oxiconazole, terconazole, tioconazole, natamycin, sertaconazole, nystatin, and amphotericin) or oral antifungals (e.g., fluconazole, ketoconazole, itraconazole, posaconazole, and voriconazole). The consensus of all the listed authors resolved any discrepancies during the review.

Type of outcome measures and intervention

Primary outcome: clinical and mycological recurrence rate at 12 months; time to first recurrence; cure rate at 30 days.

Secondary outcomes: the proportion of participants with at least one recurrence during treatment and follow-up period; complications /side events.

Data extraction and quality assessment

Three researchers (JFL, ACAS, and RLA) independently reviewed each article's title and abstract. Two review authors (JFL and AKG) independently evaluated the eligibility for the inclusion of the trials identified by the survey. Disagreements were resolved by discussion, involving the contribution of a third author (HS and PCG).

Relevant data were subsequently taken from the full text of the article by JFL, JEJ, and AKG according to the data extraction protocol. The selection of the study is summarized in a PRISMA flow diagram. Thus, papers that met the criteria were reviewed in full.

To assess the risk of bias, the Cochrane Collaboration bias risk tool was applied to evaluate the following criteria: proper sequence generation, allocation concealment, incomplete outcome data, selective reporting, and other bias risks.[9] Three authors (JFL, ACAS and APFC) evaluated each original study. The quality of the information assessed is shown in the result tables. Each of the previously mentioned criteria received one of the following ratings: "low risk of bias", "high risk of bias," or "Unclear risk of bias." Disagreements were resolved by consulting a fourth author (RNC).

For the primary outcome, we assessed the certainty of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool. The quality of evidence was identified as high when the actual effect is close to the estimated effect, moderate if the actual impact is likely to be close to the expected outcome, and low or very low, when the impact is significantly different from the estimated effect.

Data synthesis and analysis

The characteristics of the studies evaluated in the analysis included: authors, year of publication, country; follow-up, mean age, number of participants, interventions and main outcomes.

Two independent reviewers extracted outcome data of interest (JFL and ACAS), and a third author (AKG) reviewed these data.

Other characteristics and results of the studies were summarized narratively. The Review Manager software (RevMan 2010) was used to perform the statistical analysis of the meta-analysis. To evaluate the effectiveness between the proposed treatments, the dichotomous data were extracted from each study and inserted in a 2 × 2 contingency table. We calculated the OR for dichotomous data and mean weight difference (MD) for continuous data with 95% of Associated CI to obtain a global estimate summary.

Heterogeneity was assessed by the I2 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.

Patient and public involvement

No patient was involved in this review.

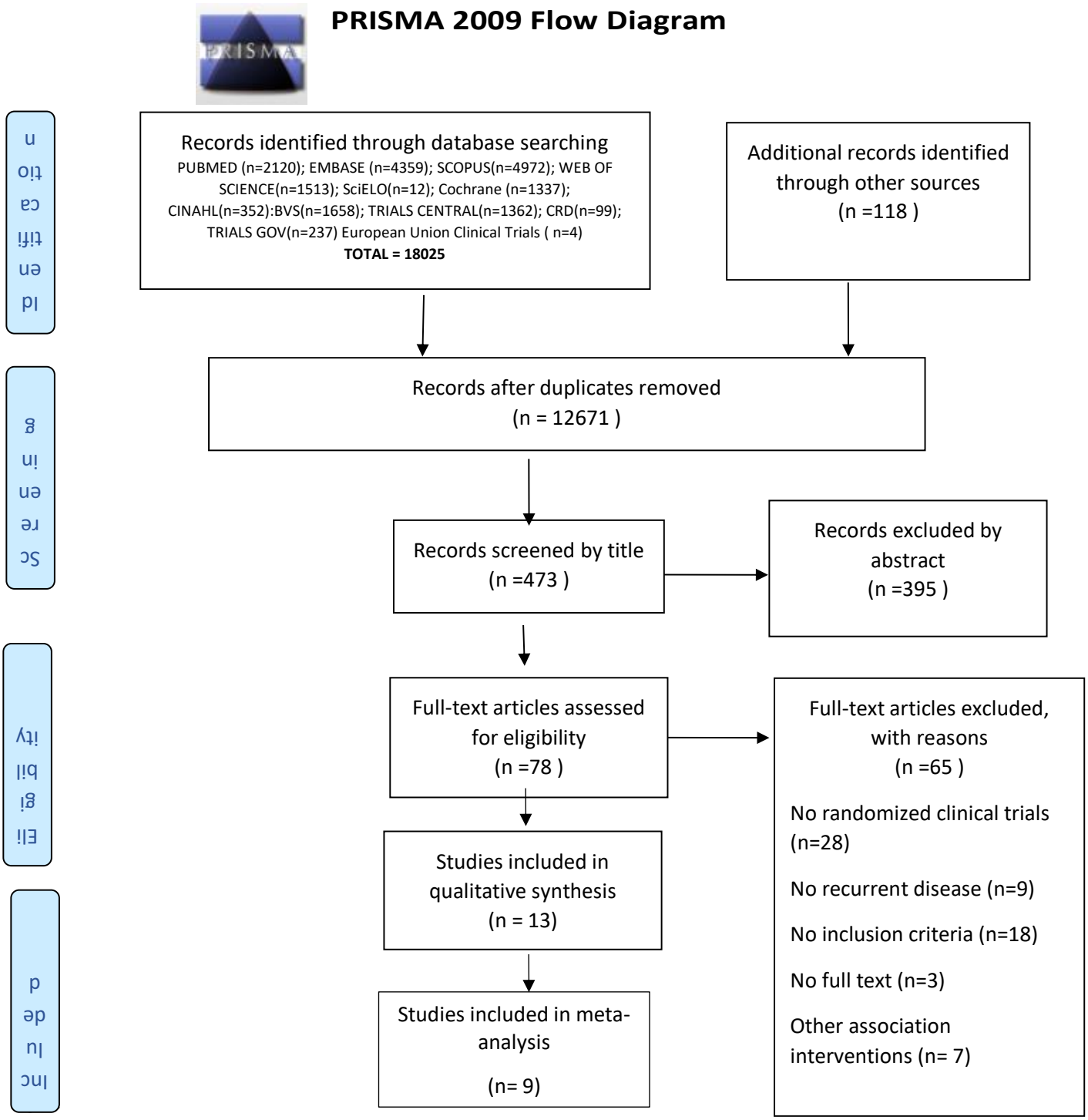
RESULTS

Data Retrieval

In summary, a total of 18,025 potential records were initially identified through the databases of PubMed (2120), Embase (4359), Scopus (4972), Web of Science (1513), SciELO (12), Cochrane (1337), CINAHL (352), BVS (1658), TRIALS CENTRAL (1362), CRD (99), TRIALS GOV (237), and European Union Clinical Trials (4). We found (118) additional records identified through other sources. Based on our review of the title and abstract, 78 full-text papers were reviewed, 13 studies (4-16) met inclusion criteria (Figure 1), and 9 studies were included in the meta-analysis

Study characteristics

This systematic review included thirteen papers, representing 1,552 women, with a mean age of 30.92 years. Most studies were from high-income countries. The study included seven studies from the USA, two from England, and one each from Sweden, Spain, Italy, and Iran. The general characteristics of all 13 included studies were summarized and are shown in Table 2 and the mean results and risk of bias are shown in Table 3.



1 - Prisma 2009 Flow Diagram. *From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Table 2 - General Characteristics of selected Studies

Author/ year	Country	Intervention	N	Mean Age	Control	N	Mean Age	Follow-up	Main Outcomes
Bolouri, F (2009)	Iran	Fluconazole 150mg Orally/week/6m	32	31.9 ± 7.5	Placebo Orally/week/6 m	32	31.8 ± 6.4	12m	Clinical recurrence; mycological recurrence
Brand, S (2018)	EUA	Oteseconazole 150mg Orally/d - 7d, +150mg/ w - 11 weeks + placebo w/12weeks. Oteseconazole 300mg Orally/d - 7d, +300mg/ w 11weeks + placebo w/ 12 weeks. Oteseconazole 150 mg Orally/d- 7d, +150 mg/ w - 23 weeks. Oteseconazole 300 mg Orally/d- 7d, +150mg/ w 23 weeks.	42 43 43 41	35.0 34.6 34.2 33.8	Placebo	46	35.4	48weeks	Proportion of individuals with 1 or more episodes of CVV (culture) at week 48.
Bushell, TEC (1988)	England	Clotrimazole 500 mg vag tablet./month - 12m. Clotrimazole 500 mg 2vag. tablet/month.	21	26.8	Clotrimazole 500 mg - vag.tablet or placebo 1 vag. tablet/ month.	21	28.9	12 months	Clinical recurrence; mycological recurrence
Davidson, F (1978)	England	Clotrimazole pessaries + vag.cream - 4 pac / 6 pessaries +1cream 1 pessarie + cream/night to 5°- 11° d - 4 menstrual cycles	20	25	Similar packages of pessaries and placebo cream	20	26	10 months	Severity of symptoms, time for symptoms to reappear; time for yeast reappearance
López-Olmos, J. (2000)	Spain	Fluconazole 150mg Orally 1 dose, in the 6° d menstruation -6m Clotrimazole 500mg 1vag.tablet in the 6°d menstruation -6 m. Itraconazol -2 caps.100mg orally in the 6°d menstruation - 6m	19 12 14	33.15 38.75 38.64	N/A	N/A	N/A	12 months	Clinical cure, mycological cure, recurrences.
Roth, A. C. (1990)	Sweden	Clotrimazole 500mg -1 dose, vag. post menstrual - 6 months	33	29 ±6.9	Placebo 500 mg 1 dose vag., post menstrual - 6m	29	27.2 ± 7.8	12 months	Clinical recurrence; mycological recurrence
Sobel, JD (1986)	EUA	Cetoconazole 400mg / 5d/m/6 m Cetoconazole 100mg/d - 6m. Cetoconazole 200mg/d /6m.	21 21 24	31.9 33.8 N/A	Placebo cp - 5d/m- 6m	21	31.9	12 months	Recurrence rate; time until clinical recurrence; adverse effects; disease-free patients
Sobel, Jd (1989)	EUA	Clotrimazole 500mg vag. sup.1x/m/6m	15	34.2	Placebo vag. 1x/m/6m	12	34.6	12 months	Rate of clinical and mycological recurrence; cure rate; average time for symptom recurrence
Sobel, JD (1994)	EUA	Cetoconazole 400mg,Orally, 14d Clotrimazole 100mg, vag. sup./7d	74 77	27.5 26.8	N/A	N/A	N/A	2 months	Clinical cure; mycological cure; clinical and mycological recurrence
Sobel, Jd (1995)	EUA	Fluconazole - 150mg, Orally, 1 dose clotrimazole 100mg vag.tablet /7d	49 44	28 29	N/A	N/A	N/A	35 days	Clinical cure, mycological cure; therapeutic response (clinical and mycological cure); recurrence rate; improvement of symptoms.
Sobel, JD (2001)	EUA	Fluconazole 150mg Orally + 2 sequential doses 72h interval	157	31	Fluconazole 150mg Orally, 1 dose+ placebo after 72h	152	31	35 days	Clinical cure; mycological cure
Sobel, Jd (2004)	EUA	Fluconazole 150mg, Orally/week/ 6 m	170	33.8	Placebo, Orally/ week/ 6m	173	33.8	12 months	Proportion of women in clinical remission at the end of the maintenance period with definitive cure.
Spinillo, A (1997)	Italy	Itraconazole 200mg, 2 doses/ 12h interval in the 4º or 5º d menstrual cycle, 1x/m/6m	55	30.2±6.6	No treatament	53	30.9 ± 6.6	12 months	Clinical and mycological recurrence; proportion of patients free of symptomatic recurrence at 6 and 12 m; mean time recurrence symptoms.

Table 3- Intervention, Outcome Results and Certainty of selected Studies

Study	Author/year	Intervention	Main Results	Risk of bias
1	Bolouri, F (2009)	Weekly oral fluconazole versus placebo	* Differences in CRR and MRR between the GF and the GP at 3 and 6 months were not significant.	?
2	Brand, S (2018)	Different doses and schedules of oteseconazole versus placebo	* Mycological recurrences in the treatment and PG groups occurred more frequently in the 1st 12 weeks. * Average time to first recurrence with positive culture: PG 28without and was not achieved in any of the treatment groups due to the low number of recurrences.	?
3	Bushell, TEC (1988)	Clotrimazole vaginal tablet versus placebo	*12-month CR: 18% regimen A and 30% regimen B. * Regimen C: 24% RR in 2m and CR: 59% in 12 months (p <0.05). There were no appreciable differences between the different regimes (p> 0.05). More than 50% of women in all groups were colonized in 3 months and in 12 months more than 85%.	?
4	Davidson, F (1978)	Monthly vaginal clotrimazole versus placebo	* CCR 10 m: (38%) patients in the PG and (30%) patients in the CG. * Most emergency packs were used in the first 2m and most of the failures in the CG occurred in the first 2m after the end of treatment, which shows that the symptoms were controlled by clotrimazole. * CRR at 4m: (52.6%) patients in the PG and (5.5%) patients in the CG required retreatment.	+
5	López-Olmos, J. (2000)	Oral fluconazole versus clotrimazole vaginal tablet versus oral itraconazole	* Among clotrimazole and fluconazole, the best was clotrimazole (p <0.05). Among itraconazole and fluconazole, itraconazole was the best (p <0.05). The general clinical efficacy was 73.33%. The best result was obtained with clotrimazole at 6m with 91.66% of CC. In 12m the best result was 64.28% of itraconazole. CCR: 57.89% fluconazole, 41.66% clotrimazole and 37.51% itraconazole. * The microbiological cure was not complete. After 6m: CCR 50% fluconazole, clotrimazole 33.3% and itraconazole 33.3%.	-
6	Roth, A. C. (1990)	Clotrimazole vaginal tablet versus placebo	* RR after 6 m: clotrimazole (30.3%) was lower (p <0.001) than placebo (79.3%). After the 6m observation period without treatment, there were no significant differences in the frequency of accumulated recurrence between the groups (clotrimazole 84-9%; placebo 86.2%).	+
7	Sobel, JD (1986)	Cetoconazole versus placebo	* CRR 6 m follow up: PG 71.4%; Group B 28.6% (p <0.01); Group C 4.8% (p <0.001) * CRR 12 m follow up: PG 23.8%; Group B: 42.9% (p> 0.05); Group C: 52.4% (p <0.05)	?
8	Sobel, Jd (1989)	Clotrimazole vaginal suppository monthly versus placebo	* 6m CRR: moderate protective effect with clotrimazole compared to placebo, CRR reduced by almost 50%. A comparison of CRR between the groups during the prophylactic phase showed significance only in the 3m period (p = 0.05). * MRR: there was no statistical difference in the 2 groups. * Average time of symptom recurrence in the prophylactic phase: PG: 1.3 months and CG: 2.5 months.	?
9	Sobel, JD (1994)	Oral Cetoconazole versus vaginal clotrimazole	* CR 7d of initial therapy - 86.4% in KG and 81.7% in CG * After 30d - 80.0% and 73.7% respectively; and after 60d - 71.2% and 64.1% respectively.	+
10	Sobel, Jd (1995)	Oral Fluconazole versus vaginal tablet clotrimazole	* CCR 14 ° d: FG 58% and CG 50% - non-significant differences (p> 0.3); CCR 35 ° d: FG 55% and CG 50% - non-significant differences (p> 0.6). MRR 14 ° d: FG 63% and CG 60% (p = 0.826); MRR 35 ° d: FG 42% and CG 37% (p> 0.05). * Therapeutic response: comparable results for the 2 groups in the 14 and 35 day evaluations.	?
11	Sobel, JD (2001)	Fluconazole single dose + placebo versus fluconazole 2 doses	There were significant differences between women with severe or recurrent vaginitis in favor of the sequential dose of fluconazole in relation to the single dose: OR for CCR or improvement of 2.4 (p = 0.049) and 1.78 (p = 0.037) in the 14th at 35 ° d, respectively. * MCR: OR 1.57 and 1.34 at 14 ° d and 35 ° d, respectively, without statistical significance. Women with RVVC, but without severe vaginitis, had no clinical benefit with the additional dose of fluconazole.	?
12	Sobel, Jd (2004)	Weekly oral fluconazole versus placebo	* Maintenance phase: CRR higher in PG than FG. * Observation period 6m after the end of therapy: CRR: significantly more episodes of clinical vulvovaginal candidiasis were observed in the FG than in thePG. * End of 12 m: CCR: 42.9% in the FG and 21.9% in the PG (p <0.001).	?
13	Spinillo, A (1997)	Itraconazole vaginal tablet versus no treatment	1st 6m: * RR: IG - 36.4%; NTG - 64.2%. OR = 0.32 95% CI: 0.14 - 0.70 (p = 0.003. After 6m of prophylaxis: * RR: GI - 38.9%; NTG - 22.2% (p = 0.36).	+

LEGEND: CRR - clinical recurrence rate; MRR - mycological recurrence rate; PG - placebo group; CR - cure rate; RR- recurrence rate; CCR - clinical cure rate; CG - clotrimazol group; CC- clinical cure; KG - ketoconazole group; FG - fluconazole group; MCR - mycological cure rate; RVVC - recurrence vulvovaginal candididasis; IG - Itraconazole group; NTG - no treatment group.

Eight studies evaluated clinical and mycological recurrence [12, 14, 17-21, 24], and five evaluated clinical and mycological solutions [17, 19-22].

Meta-analysis results:

Four meta-analysis were performed. The first meta-analysis was analyzing mycological recurrence (7 articles), the second clinical recurrence (6 articles), the third the average recurrence time (2 articles), and the fourth comparing the effectiveness of clotrimazole with other antifungals (2 articles).

The data were taken directly from the articles, for the first and second meta-analysis, we used the frequency of occurrence data for clinical recurrence in the treated and control groups, as well as the sample N of each group. Subsequently, we calculated the Odds Ratio, with a lower and upper limit for the 95% confidence interval, the value of the Z statistic and a value of P. From this information, a meta-analysis was conducted. Some articles did not have all of this information and were omitted; others did not present the information, but nonetheless it was possible to calculate it from the information provided.

The recurrence time was a crucial factor, we would only “mix” times (6 months, 12 months, 14 days, etc) if there was no other way, as this would distort the articles of greatest importance in the analysis. Time would be "pushing" the analysis for "more effect", while those with less time would be pushed for less effect, this would come under harsh criticism. We standardized the time conservatively to 12 months, and we had sufficient degrees of freedom with 7 articles to use the time thusly standardized.

It was not possible to analyze subgroups between different classes of antifungals and topical and vaginal routes due to the diversity of outcomes (recurrence rates, cure rate, means) that each analyzed, which would make comparisons with a maximum of two studies each.

Thus, the general effect was generated, presented in a table and through a Forest Plot for all analyzes,

Primary outcome:

- **Mycological recurrence at 12 months:**

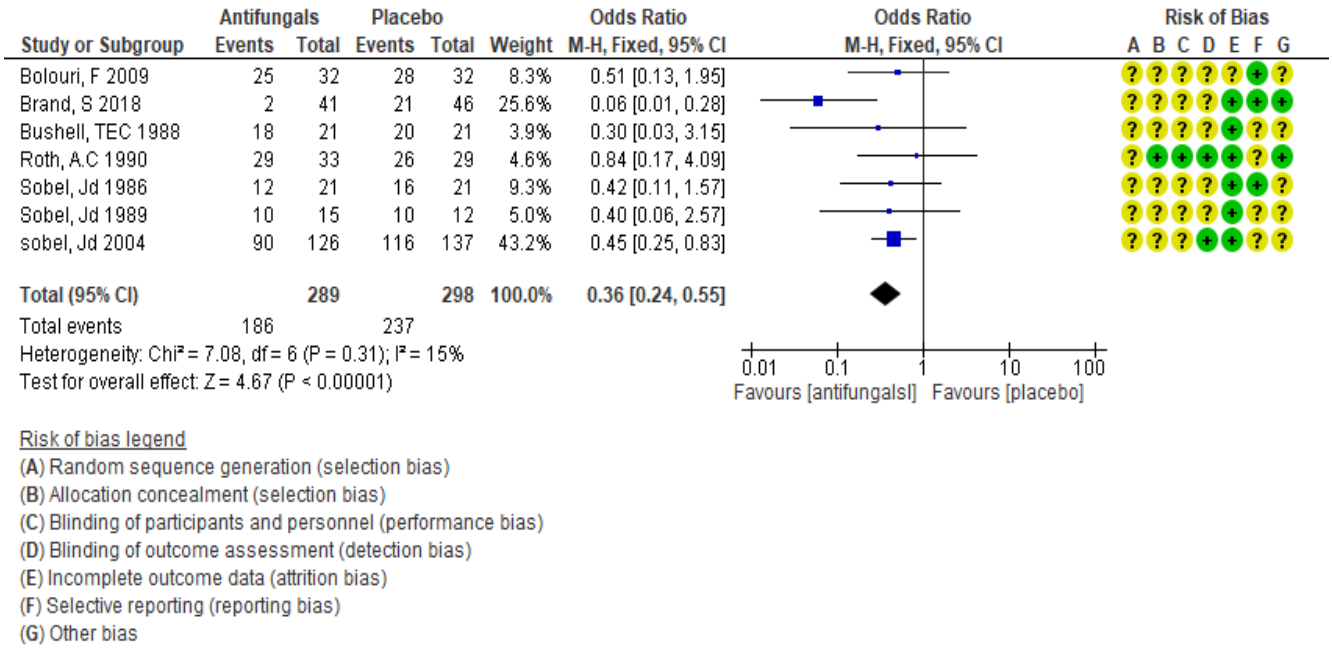


Figure 1 – Forest Plot mycological recurrence at 12 months

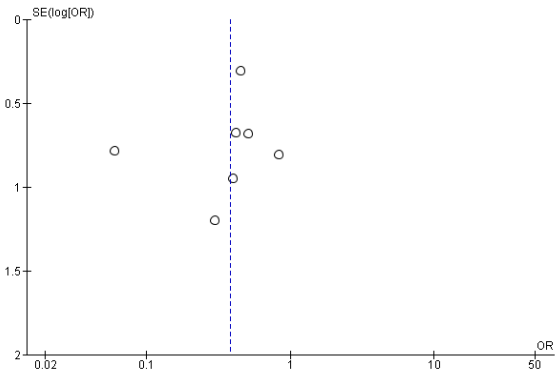


Figure 2 – Funnel Plot mycological recurrence at 12 months

The meta-analysis shows that treated people with fluconazole, ketoconazole, clotrimazole and oteseconazole have 36% of the risk of recurrence of untreated people, so the treatments are effective.

- **Clinical Recurrence at 12 months:**

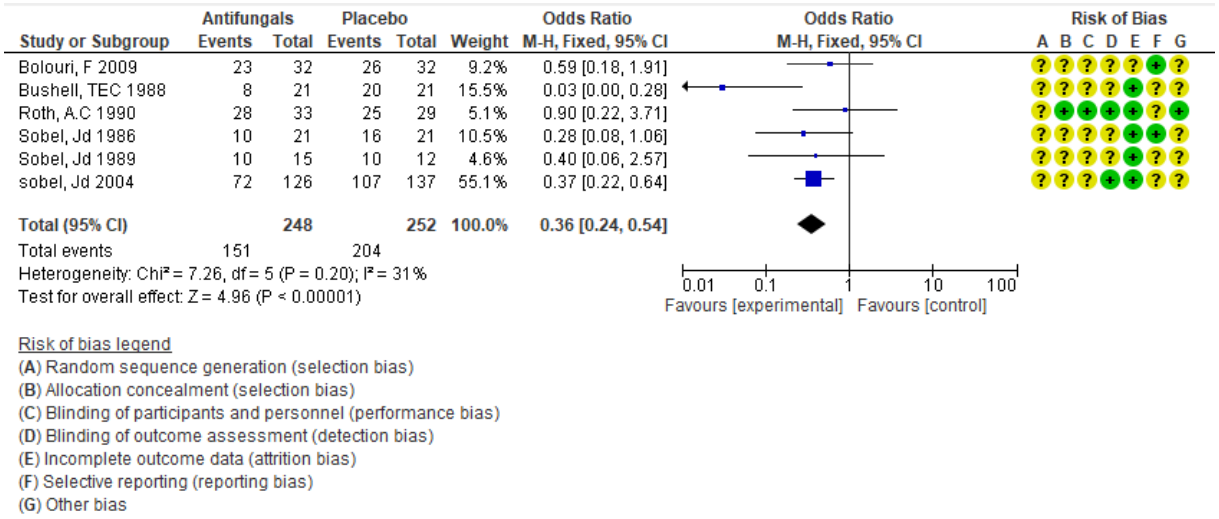


Figure 3 – Forest Plot clinical recurrence at 12 months

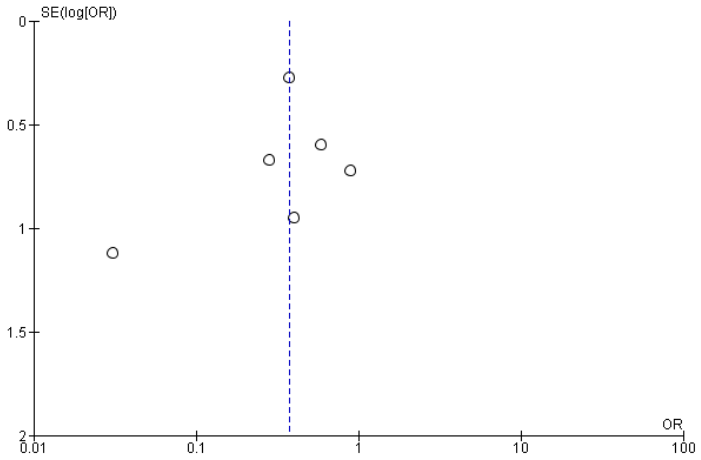


Figure 4 - Funnel Plot clinical recurrence at 12 months

Women treated with fluconazole, ketoconazole and clotrimazole have 36% of the risk of clinical recurrence in untreated women, so treatments are effective. This is a similar interpretation to the previous one and, again, the most important study was Sobel 2004.

- **Time for the first Recurrence:**

Here we have a comparison of recurrence time averages (in months). The statistics generated are standard difference between the means, standard error, variance, lower and upper limit of the confidence interval, Z statistic, and P value. To reach these results in the table above, the following information was extracted from the articles: mean, N of each group (treated and placebo) and statistical P of the test used. We also extracted the information if the test was uni or two-tailed, and what was the direction of the difference between the averages (positive, since it would be expected that the average time would be shorter in those who were not treated).

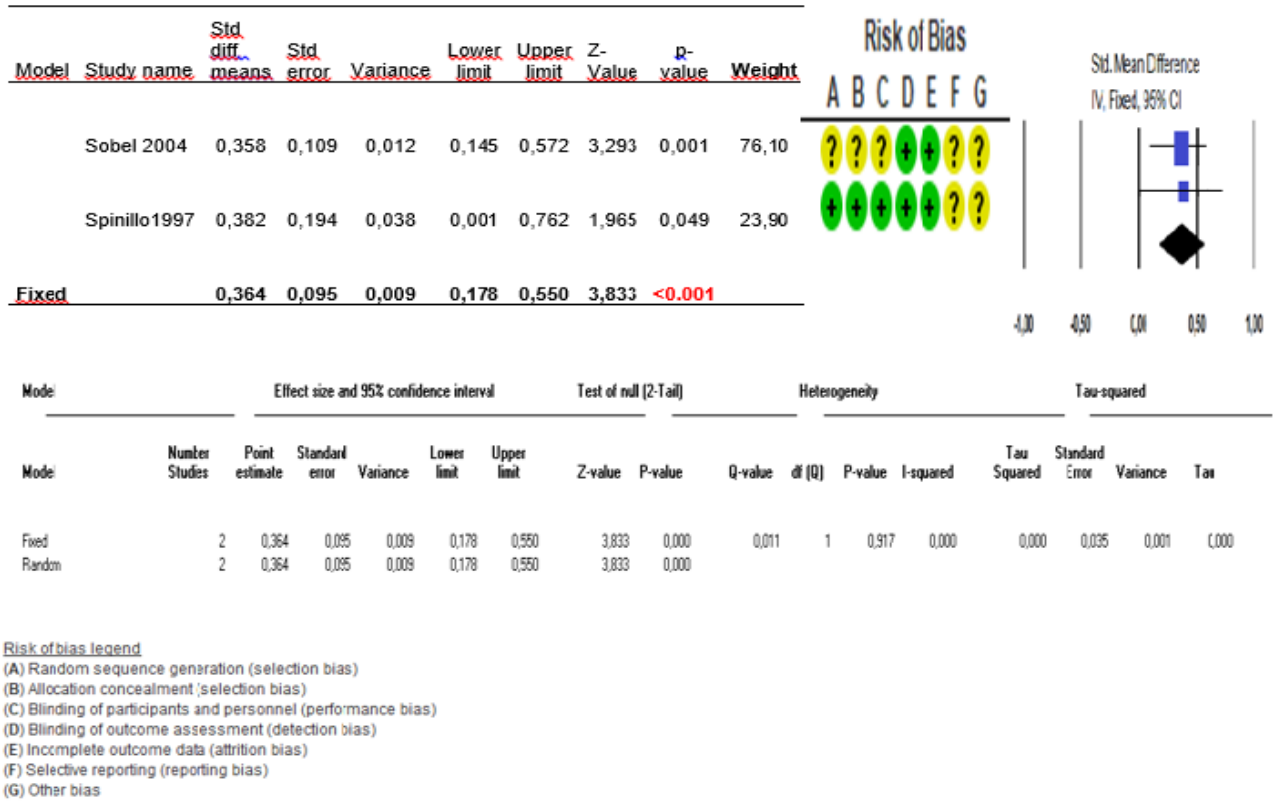


Figure 5 – Forest Plot Time for the first recurrence

The treated women with fluconazole and itraconazole have an average recurrence time of 0.364 months (10.92 days) longer than untreated people, which indicates some effectiveness. The most important study was Sobel 2004.

- **Antifungal protocol efficacy:**

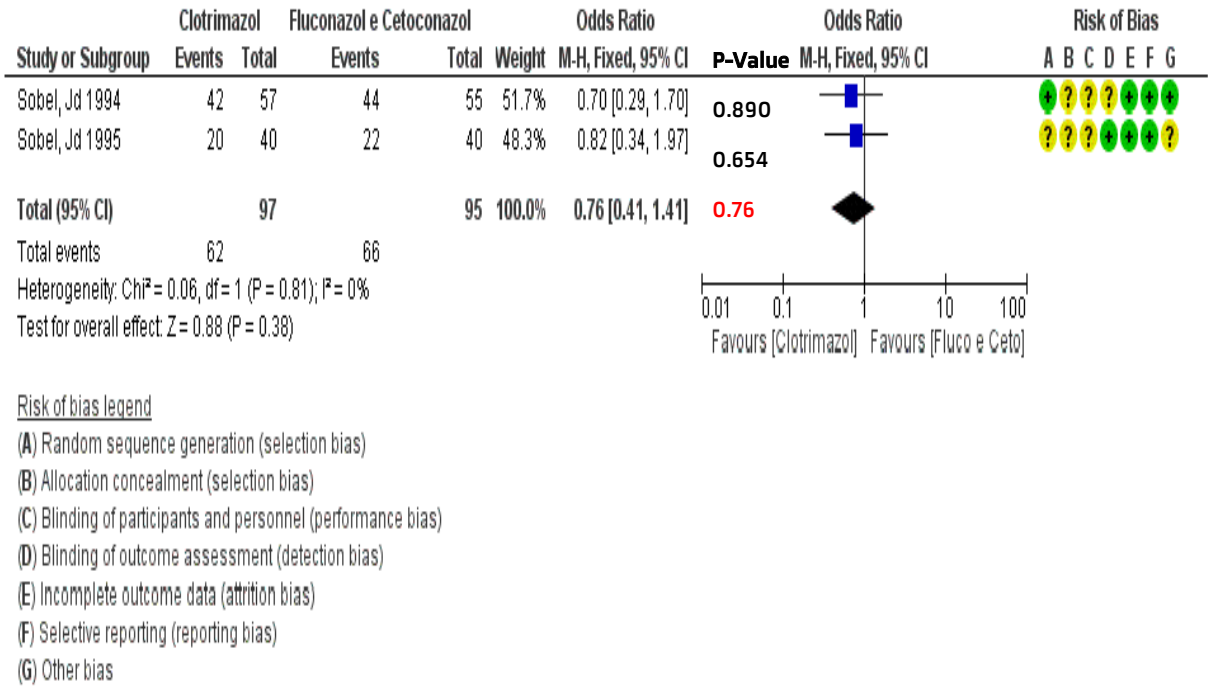


Figure 6 – Forest Plot – Antifungal Efficacy

We used data on the frequency of occurrence of cure, and we had to standardize for 30 days so that there was no bias in the conclusions.

A simple comparison was possible: Clotrimazole versus other treatments. Meta-analysis showed that there is no difference in effectiveness when comparing Clotrimazole with the other drugs (fluconazole and ketoconazole) (p=0.76).

Secondary outcomes:

- **The proportion of participants with at least one recurrence during treatment and follow-up period.**

Three studies evaluated the recurrence during treatment and follow-up period [13,23,24]. A proportion of women between 64.1% and 71.2% had at least one episode of recurrence in the control groups versus 0% to 61.1% in the intervention groups.

- **Complications /side effects.**

Seven studies evaluated complications and/or side effects [14, 18, 19, 21-23]. The most common side effects were headaches, nausea, and abdominal pain.

Risk of bias assessment

All studies were randomized; 8 were double-blind, placebo-controlled trials;[12, 13, 15, 17, 19, 22-24] only three trials described an adequate random sequence generation process and the methods used for allocation concealment.[15, 17, 24] The risk of bias assessment is shown in Table 4.

Most studies were judged to be of low or unclear risk of bias for sequence generation, allocation concealment, incomplete outcome data, and selective reporting. Because no information was provided, some studies were judged to be unclear or high risk of bias for blinding of participants and staff and for blinding of outcome assessment.

Table 4 - Quality assessment of the included studies using the Cochrane bias risk tool

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Boulori, F 2009	?	?	?	?	?	+	?
Brand, S 2018	?	?	?	?	+	+	+
Bushell, TEC 1988	?	?	?	?	+	?	?
Davidson F, 1978	+	+	+	+	+	+	+
Lopez-Olmos, J 2000	-	-	-	-	?	+	?
Roth, AC 1990	?	+	+	+	+	?	+
Sobel, JD 1986	?	?	?	?	+	+	?
Sobel, JD 1989	?	?	?	?	+	?	?
Sobel, JD 1994	+	?	?	?	+	+	+
Sobel, JD 1995	?	?	?	+	+	+	?
Sobel, JD 2001	?	?	?	?	+	+	+
Sobel, JD 2004	?	?	?	+	+	?	?
Spinillo, A 1997	+	+	+	+	+	?	?

Key: - High risk of bias; ? Unclear risk of bias; + Low risk of bias

Grade

The certainty of the evidence in accordance with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool was assessed. The results are shown in table 5.

Table 5 – Summary of Evidence from GRADE

ANTIFUNGAIS compared to PLACEBO for RVVC
Bibliography:

Certainty assessment							Summary of findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With PLACEBO	With ANTIFUNGAIS		Risk with PLACEBO	Risk difference with ANTIFUNGAIS
Antifungals versus placebo - Mycological recurrence - 12 months (follow up: mean 12 months)											
587 (7 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	237/298 (79.5%)	186/289 (64.4%)	**OR 0.38** (0.22 to 0.65)	795 per 1,000	**199 fewer per 1,000** (from 334 fewer to 79 fewer)
Antifungals versus placebo - Clinical recurrence - 12 months (follow up: mean 12 months)											
500 (6 RCTs)	not serious	not serious	not serious	serious	none	⨁⨁⨁◯ MODERATE	204/252 (81.0%)	151/248 (60.9%)	**OR 0.37** (0.20 to 0.68)	810 per 1,000	**198 fewer per 1,000** (from 350 fewer to 67 fewer)
Antifungals versus Placebo - Time for first recurrence (assessed with: Difference of means)											
451 (2 RCTs)	not serious	not serious	not serious	not serious	publication bias strongly suspected	⨁⨁⨁◯ MODERATE	226	225	-	The mean antifungals versus Placebo - Time for first recurrence was **0.364**	MD **6.2 higher** (6.12 higher to 6.28 higher)
Protocol Efficacy - Clotrimazole versus Fluconazole e Ketoconazole- (follow up: mean 30 days; assessed with: clinical cure rates)											
192 (2 RCTs)	not serious	not serious	not serious	serious	none	⨁⨁⨁◯ MODERATE	66/95 (69.5%)	62/97 (63.9%)	**OR 0.76** (0.41 to 1.41)	695 per 1,000	**61 fewer per 1,000** (from 212 fewer to 68 more)

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

DISCUSSION

Despite advances in medicine and the pharmaceutical industry, RVVC remains a challenge for experienced gynecologists. Several options of drugs and protocols have been used in the last decades; however, the poor therapeutic outcomes impact on the quality of women's health and of their partners, both physically and psychologically.

This systematic review with meta-analysis showed that clotrimazole, fluconazole, ketoconazole, fluconazole and oteseconazole at different levels, were effective in reducing the recurrence of vulvovaginal candidiasis and decreased the fungal count in culture after twelve months of treatment compared to placebo. However, in the long-term, only oteseconazole showed a difference in these results compared to the placebo.

Although the literature presents several studies evaluating the efficacy of fluconazole in the treatment of vaginal candidiasis, a minority refer to its use in the treatment of recurrent vaginal candidiasis. Some of these studies were not included in our systematic review because they did not meet the inclusion criteria. Two of the clinical trials included in this review [12, 22] did not demonstrate the efficacy of fluconazole in clinical remission and in the long-term mycological recurrence rate. Similar studies [8, 9] concluded that fluconazole appeared to be the best drug for the treatment of VVC. However, Qin et al [9] do not make it clear which outcomes were assessed in the meta-analysis and how the assessment was made. Rosa et al. [8] only highlight the effectiveness of the drug in reducing symptoms. A possible explanation for the inefficiency may be the presence of azole-resistant *Candida* species such as *C. glabrata,* and much less commonly *C. krusei*.

The individually included studies did not find effectiveness of clotrimazole, itraconazole, and ketoconazole in the clinical remission of symptoms in women with RVVC. Qin et al. [9] demonstrated greater effectiveness of these drugs but did not make it clear which outcomes were assessed. Furthermore, this study did not consider patients with RVVC. RCTs that evaluated clotrimazole and ketoconazole included few patients and may have influenced the absence of a significant difference. Since some species of *Candida* are resistant to azoles, this may have influenced the negative results of these three drugs. Nevertheless, in an RCT with high-quality evidence, Brand et al. [13] found that oteseconazole could be a promising new drug, decreasing the recurrence of symptoms and the reappearance of yeasts in the vagina. This RCT was not included in the studies by Rosa

et al. [8] and Quin et al [9]. In addition, this new antifungal is effective in vitro and may be the most effective drug in *Candida* species resistant to other azoles [25].

Fluconazole and Itraconazole increased the time of occurrence of the first episode [23, 24]. Regarding the proportion of participants with at least one recurrence during treatment and follow-up period, Sobel et al. [23] and Spinillo et al. [24] observed a higher rate of recurrences in the placebo groups.

Clotrimazole, ketoconazole, itraconazole, and oteseconazole in the studies of moderate evidence are antifungal drugs with effectiveness for RVVC treatment [13, 19, 20, 23 and 24]. Fluconazole could reduce the rate of recurrence of symptomatic vulvovaginal candidiasis. However, a long-term cure remains a challenge to achieve [23].

This review includes only randomized controlled trials involving women with RVVC and covers studies with newer antifungals that are not commonly used by professionals in the treatment. The limitations of this systematic review with meta-analysis include potential missing data and biases and heterogeneity in treatment protocols (types of drugs, dose, duration of therapy). It was not possible to perform the meta-analysis for all outcomes and include all studies. 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

- Compared to placebo, most antifungal protocols shows efficacy for rates of mycological and clinical recurrence.
- The time of recurrence was shorter in the placebo groups.
- There was no difference in effectiveness between Clotrimazole and fluconazole and ketoconazole curing RVVC.
- The protocols of fluconazole, clotrimazole, ketoconazole, itraconazole and oteseconazole were effective in the short-term treatment of RVVC. However, in the long run, oteseconazole was the only antifungal effective in the recurrence of vulvovaginal candidiasis compared to placebo.
- Adverse effects are mild and antifungal protocols are considered safe.

Patient and Public Involvement: The research was performed by an extensive and comprehensive search of literature from databases, and the individual patient data are not

included. Thus, the authors involved no patients in setting the research question, the outcome measures, the design and implementation of the study, and the dissemination of its results.

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5 - DISCUSSÃO

Embora a candidíase vulvovaginal recorrente seja uma doença prevalente na população feminina e importantes avanços na medicina e na indústria farmacêutica tenham ocorrido, o tratamento eficaz da CVVR continua sendo um desafio para ginecologistas experientes. Diversas opções de medicamentos e protocolos têm sido pesquisadas e utilizadas nas últimas décadas. Existe grande variedade de protocolos pesquisados, mas muitos dos estudos não possuem metodologias bem descritas e adequadas e a inclusão de estudos com alto risco de viés ou com resultados não descritos completamente não permite a análise estatística dos dados e pode resultar em erro de avaliação para a tomada de decisões clínicas. Resultados terapêuticos ruins impactam na qualidade da saúde das mulheres e de seus parceiros, tanto física quanto psicologicamente.

Foi possível confirmar por metanalise que fluconazol, clotrimazol, cetoconazol e oteseconazol foram eficazes, na redução da recorrência clínica e micológica da candidíase vulvovaginal. No entanto, após 12 meses, apenas o oteseconazol apresentou diferença nesses resultados em relação ao placebo.

Embora a literatura apresente diversos estudos avaliando a eficácia do fluconazol no tratamento da candidíase vaginal, uma minoria refere-se ao uso no tratamento da candidíase vaginal recorrente. Alguns desses estudos não foram incluídos em nossa revisão sistemática por não atenderem aos critérios de inclusão. A maioria dos ensaios clínicos incluídos nesta revisão sistemática (48,49) não demonstraram individualmente a eficácia do fluconazol na remissão clínica e na taxa de recorrência micológica a longo prazo, e foram considerados de baixa força de evidência e com risco de viés incerto. Estudos semelhantes (14,50) concluíram que o fluconazol parece ser a melhor droga para o tratamento da CVV. No entanto, Qin et al. (50) não deixam claro quais resultados foram avaliados na meta-análise e como a avaliação foi feita. Rosa et al (14) apenas destacam a eficácia do medicamento na redução dos sintomas. Uma possível explicação para a ineficiência do fluconazol observada nos estudos incluídos pode ser a presença de espécies de Cândida resistentes a azóis, como *C. glabrata* e muito menos comumente *C. krusei.*

Nos estudos com clotrimazol, itraconazol e cetoconazol, não houve individualmente eficácia na remissão clínica dos sintomas em mulheres com CVVR. Qin et al. (50) demonstraram maior eficácia dessas drogas, mas não deixaram claro quais desfechos foram avaliados. Além disso, este estudo não considerou pacientes com doença recorrente.

Os ensaios clínicos randomizados que avaliaram o clotrimazol e o cetoconazol incluíram poucas pacientes e podem ter influenciado na ausência de uma diferença significativa. Novamente, a resistência aos antifúngicos azólicos pode ter influenciado os resultados negativos dessas três drogas. O risco incerto de viés e a baixa qualidade das evidências impedem a avaliação da eficácia desses medicamentos.

Brand et al. (51) verificaram que o Oteseconazol pode ser uma droga nova e promissora, diminuindo a recorrência dos sintomas e o reaparecimento de leveduras na vagina. Este ECR não foi incluído nos estudos de Rosa et al. (14) e Quin et al. (50). Além disso, esse novo antifúngico é eficaz in vitro (52) e pode, com mais resultados de outros ensaios, ser a droga mais eficaz em espécies de Candida resistentes a outros azólicos.

Fluconazol, clotrimazol e oteseconazol reduziram os episódios de recorrência e aumentaram o tempo para ocorrer o primeiro episódio após o tratamento (51, 53, 54). Em relação à proporção de participantes com pelo menos uma recidiva durante o tratamento e período de seguimento, Sobel et al. (53) e Spinillo et al (54) observaram maior taxa de recorrências nos grupos placebo.

Os efeitos adversos mais comuns foram dores de cabeça, náuseas e dores abdominais, verificados com os protocolos de fluconazol e cetoconazol. Apenas cetoconazol apresentou possível complicação com elevação transitória de transaminases. Não houve eventos graves com nenhum dos protocolos utilizados. Esses achados são similares aos relatados em outros estudos (13-14, 44, 50, 56).

6. CONCLUSÃO

1. Em comparação com o placebo, a maioria dos protocolos antifúngicos mostra eficácia para as taxas de recorrência micológica e clínica.
2. O tempo de recorrência foi menor nos grupos de placebo.
3. Não houve diferença na eficácia entre o clotrimazol e o fluconazol e o cetoconazol na cura do CVVR.
4. Os protocolos de fluconazol, clotrimazol, cetoconazol, itraconazol e oteseconazol foram eficazes no tratamento de curto prazo da CVVR. No entanto, a longo prazo, o oteseconazol foi o único antifúngico eficaz na recorrência da candidíase vulvovaginal em comparação com o placebo.
5. Os efeitos adversos são leves, a cefaléia foi o efeito adverso mais prevalente e os protocolos com cetonazol e fluconazol foram os que relataram ais efeitos. Todos os protocolos antifúngicos são considerados seguros.

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8. ANEXOS

Anexo 1. Dispensa Aprovação Comissão de Pesquisa do DTG/CAISM

Gmail **Juliana Lirio <juliriomed@gmail.com>**

PROJETO 40/2018 - "TERAPIA ANTIFÚNGICA (ORAL E VAGINAL) PARA CANDIDÍASE VULVOVAGINAL RECORRENTE: REVISÃO SISTEMÁTICA E METANÁLISE"

1 mensagem

DTG Comissao de Pesquisa <dtgpesq@fcm.unicamp.br> 14 de agosto de 2018 11:45

Para: Juliana Lirio <juliriomed@gmail.com>, paulocesargiraldo@gmail.com

Prezados pesquisadores,

Por se tratar de uma revisão sistemática, o projeto "TERAPIA ANTIFÚNGICA (ORAL E VAGINAL) PARA CANDIDÍASE VULVOVAGINAL RECORRENTE: REVISÃO SISTEMÁTICA E METANÁLISE" não precisa passar pela Comissão de Pesquisa e nem pelo Comitê de Ética.

Att

Comissão de Pesquisa - DTG/CAISM

Tabela 1. Estratégia de busca nas bases

BASE	ESTRATÉGIA DE BUSCA	Nº de Artigos	ÚLTIMA DATA
PUBMED	((((((((((candidiasis) OR candidosis) OR vaginitis) OR candida) OR yeasts) OR vulvovaginal)) AND ((((((((((((((((((antifungal) OR clotrimazole) OR econazole) OR butoconazole) OR fenticonazole) OR isoconazole) OR miconazole) OR omoconazole) OR oxiconazole) OR terconazole) OR tioconazole) OR sertaconazole) OR natamycin) OR amphotericin B) OR fluconazole) OR ketoconazole) OR itraconazole) OR posaconazole) OR voriconazole) OR nystatin)) AND ((((randomized controlled trial)) OR (blind method)) OR (clinical trial))))	2120	04/10/2020
BVS / BIREME	(tw:((((((((((candidiasis) OR candidosis) OR vaginitis) OR candida) OR yeasts) OR vulvovaginal)) AND ((((((((((((((((((antifungal) OR clotrimazole) OR econazole) OR butoconazole) OR fenticonazole) OR isoconazole) OR miconazole) OR omoconazole) OR oxiconazole) OR terconazole) OR tioconazole) OR sertaconazole) OR natamycin) OR amphotericin b) OR fluconazole) OR ketoconazole) OR itraconazole) OR posaconazole) OR voriconazole) OR nystatin)) AND ((((randomized controlled trial)) OR (blind method)) OR (clinical trial)))))) AND (instance:"regional")	1658	04/10/2020
CINAHL	((((((((((candidiasis) OR candidosis) OR vaginitis) OR candida) OR yeasts) OR vulvovaginal)) AND ((((((((((((((((((antifungal) OR clotrimazole) OR econazole) OR butoconazole) OR fenticonazole) OR isoconazole) OR miconazole) OR omoconazole) OR oxiconazole) OR terconazole) OR tioconazole) OR sertaconazole) OR natamycin) OR amphotericin B) OR fluconazole) OR ketoconazole) OR itraconazole) OR posaconazole) OR voriconazole) OR nystatin)) AND ((((randomized controlled trial)) OR (blind method)) OR (clinical trial))))	352	04/10/2020
SCOPUS	(TITLE-ABS-KEY ((candidiasis OR candidosis OR vaginitis OR candida OR yeasts OR vulvovaginal))) AND ((TITLE-ABS-KEY (antifungal OR clotrimazole OR econazole OR butoconazole OR fenticonazole OR isoconazole OR miconazole OR omoconazole OR oxiconazole OR terconazole OR tioconazole) OR TITLE-ABS-KEY (sertaconazole OR natamycin OR "amphotericin b" OR fluconazole OR ketoconazole OR itraconazole OR posaconazole OR voriconazole OR nystatin))) AND (TITLE-ABS-KEY ((randomized AND controlled AND trial) OR (blind AND method) OR (clinical AND trial)))	4972	04/10/2020
WEB OF SCIENCE	TS=(candidiasis OR candidosis OR vaginitis OR candida OR yeasts OR vulvovaginal) AND TS=(antifungal OR clotrimazole OR econazole OR butoconazole OR fenticonazole OR isoconazole OR miconazole OR omoconazole OR oxiconazole OR terconazole OR tioconazole OR sertaconazole OR natamycin OR "amphotericin b" OR fluconazole OR ketoconazole OR itraconazole OR posaconazole OR voriconazole OR nystatin) AND TS=((randomized AND controlled AND trial) OR (blind AND method) OR (clinical AND trial))	1513	04/10/2020
EMBASE	((((((((((candidiasis) OR candidosis) OR vaginitis) OR candida) OR yeasts) OR vulvovaginal)) AND ((((((((((((((((((antifungal) OR clotrimazole) OR econazole) OR butoconazole) OR fenticonazole) OR isoconazole) OR miconazole) OR omoconazole) OR oxiconazole) OR terconazole) OR tioconazole) OR sertaconazole) OR natamycin) OR amphotericin B) OR fluconazole) OR ketoconazole) OR itraconazole) OR posaconazole) OR voriconazole) OR nystatin)) AND ((((randomized controlled trial)) OR (blind method)) OR (clinical trial))))	4359	04/10/2020
COCHRANE LiBRARY	((((((((((candidiasis) OR candidosis) OR vaginitis) OR candida) OR yeasts) OR vulvovaginal)) AND ((((((((((((((((((antifungal) OR clotrimazole) OR econazole) OR butoconazole) OR fenticonazole) OR isoconazole) OR miconazole) OR omoconazole) OR oxiconazole) OR terconazole) OR tioconazole) OR sertaconazole) OR natamycin) OR amphotericin B) OR fluconazole) OR ketoconazole) OR itraconazole) OR posaconazole) OR voriconazole) OR nystatin)) AND ((((randomized controlled trial)) OR (blind method)) OR (clinical trial)))) in Title, Abstract, Keywords (Word variations have been searched)	1337	04/10/2020
SCIELO.ORG	(ab:((candidiasis OR candidosis OR vaginitis OR candida OR yeasts OR vulvovaginal))) AND (ab:((antifungal OR clotrimazole OR econazole OR butoconazole OR fenticonazole OR isoconazole OR miconazole OR omoconazole OR oxiconazole OR terconazole OR tioconazole OR sertaconazole OR natamycin OR "amphotericin b" OR fluconazole OR ketoconazole OR itraconazole OR posaconazole OR voriconazole OR nystatin))) AND (ab:((randomized AND controlled AND trial) OR (blind AND method) OR (clinical AND trial)))	12	04/10/2020
WWW.TRIALS CENTRAL.ORG	**Candidiasis, vulvovaginal ; Candidiasis; Antifungal Agents**	1362	04/10/2020
WWW.CONTROLLED-TRIALS.COM	**((candidiasis OR candidosis OR vaginitis OR candida OR yeasts OR vulvovaginal) AND (antifungal OR clotrimazole OR econazole OR butoconazole OR fenticonazole OR isoconazole OR miconazole OR omoconazole OR oxiconazole OR terconazole OR tioconazole OR sertaconazole OR natamycin OR "amphotericin B" OR fluconazole OR ketoconazole OR itraconazole OR posaconazole OR voriconazole OR nystatin) AND ("randomized controlled trial" OR "blind method" OR "clinical trial"))TEXT SEARCH**	237	04/10/2020
CLINICALTRIALS.GOV / CRD	**Recurrent vulvovaginal candidiasis**	99	04/10/2020
EUROPEAN UNION CLINICAL TRIALS	**Recurrent vulvovaginal candidiasis**	4	04/10/2020

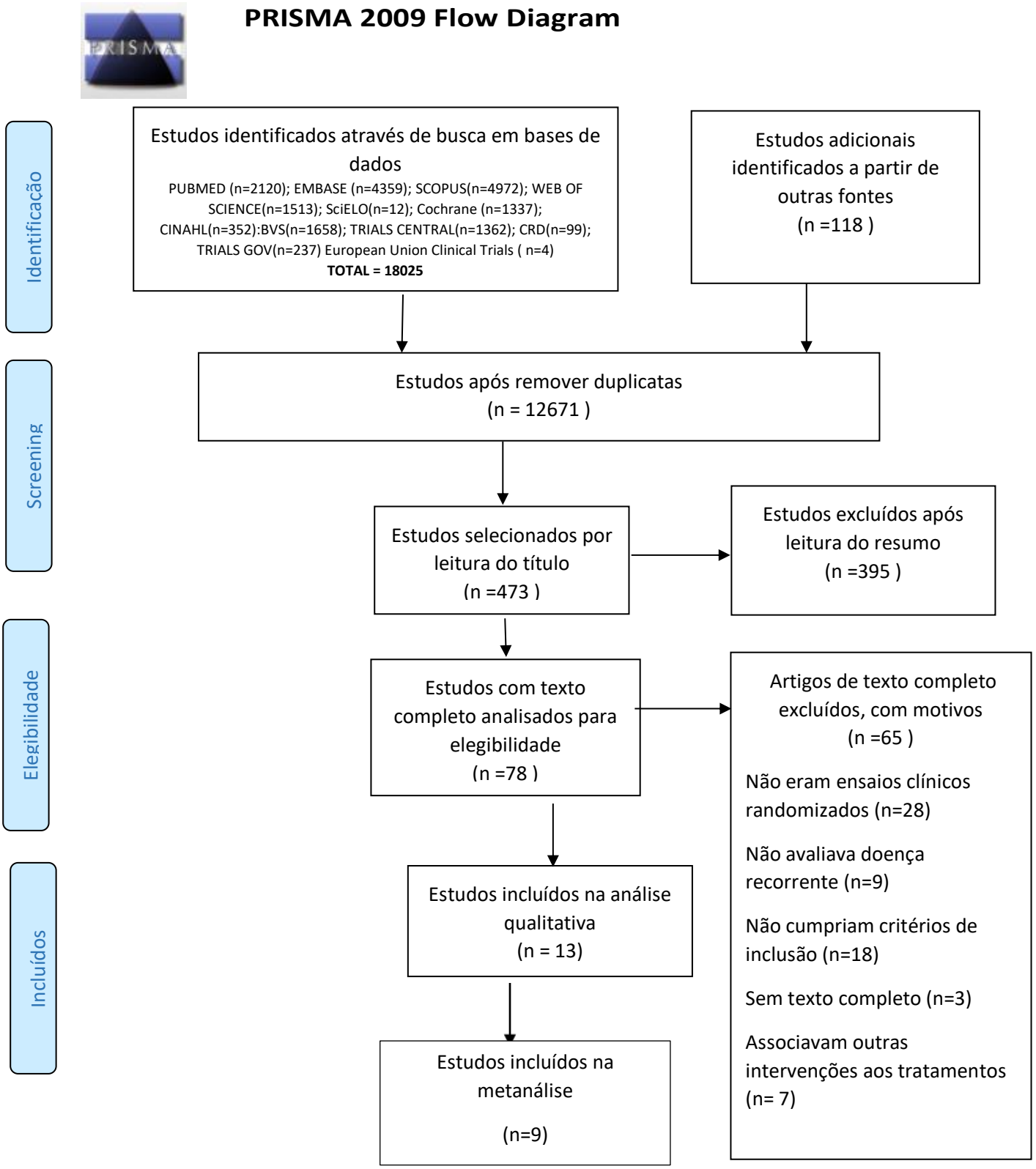

Figure 1 - Prisma 2009 Flow Diagram. *From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed100009

Tabela 2. Características dos Estudos Incluídos

Autor/ ano	Local	Intervenção	N	Idade Média	Controle	N	Idade Média	Follow-up	Desfechos principais
Bolouri, F (2009)	Iran	Fluconazol 150mg VO/ sem/6m	32	31.9 ± 7.5	Placebo VO/sem/6m	32	31.8 ± 6.4	12m	Recorrência clínica; Recorrência micológica
Brand, S (2018)	EUA	Oteseconazol 150mg VO/d - 7d, +150mg/ sem - 11 sem e placebo sem/12sem.	42	35.0	Placebo	46	35.4	48sem	Proporção de indivíduos com 1 ou mais episódios de CVV (cultura) na semana 48.
		Oteseconazol 300mg VO/d - 7d, +300mg/ sem - 11sem e placebo sem/ 12 sem.	43	34.6					
		Oteseconazol 150 mg VO/d- 7d, +150 mg/ sem - 23 sem.	43	34.2					
		Oteseconazol 300 mg VO/d- 7d, +150mg/ sem - 23sem.	41	33.8					
Bushell, TEC (1988)	Inglaterra	Clotrimazol 500 mg cp vag./mês - até 12m. Clotrimazol 500 mg 2cp. vag./mês.	21	26.8	Clotrimazol 500 mg -cp vag. ou placebo 1cp/ mês	21	28.9	12 meses	Recorrência clínica; Recorrência micológica
Davidson, F (1978)	Inglaterra	Clotrimazol pessários e creme 4 pac c/ 6 pessários e 1creme - 1 pessário e creme/noite, do 5°- 11° d- 4 ciclos menstruais	20	25	Pacotes semelhantes de pessários e creme placebo	20	26	10 meses	Gravidade dos sintomas, tempo para reaparecimento dos sintomas; tempo para reaparecimento de leveduras
López-Olmos, J. (2000)	Espanha	fluconazol 150mg VO D.U, no 6° d menstruação -6m	19	33.15	N/A	N/A	N/A	12 meses	Cura clínica, cura micológica, recidivas.
		clotrimazol 500mg 1cp.vag. no 6°d menstruação -6 m.	12	38.75					
		Itraconazol -2 caps.100mg VO no 6°d menstruação - 6m	14	38.64					
Roth, A. C. (1990)	Suécia	Clotrimazol 500mg DU vag. pós-menstrual por 6 meses	33	29 ±6.9	Placebo 500 mg D.U vag., pós-menstrual - 6m	29	27.2 ± 7.8	12 meses	Recorrência clínica; recorrência micológica
Sobel, JD (1986)	EUA	Cetoconazol 400mg / 5d/m/6 m	21	31.9	Placebo cp - 5d/m- 6m	21	31.9	12 meses	Taxa de recorrência; tempo até a recorrência clínica; efeitos adversos; pacientes livres de doença
		Cetoconazol 100mg/d - 6m.	21	33.8					
		Cetoconazol 200mg/dia /6m.	24	N/A					
Sobel, Jd (1989)	EUA	Clotrimazol 500mg sup. Vag.1x/m/6m	15	34.2	Placebo vag. 1x/m/6m	12	34.6	12 meses	Taxa de recorrência clínica e micológica; taxa de cura; tempo médio para recorrência dos sintomas
Sobel, JD (1994)	EUA	Cetoconazol 400mg,VO, 14d	74	27.5	N/A	N/A	N/A	2 meses	cura clínica; cura micológica; recorrência clínica e micológica
		Clotrimazol 100mg, sup. vag./7d	77	26.8					
Sobel, Jd (1995)	EUA	Fluconazol - 150mg, VO, D.U	49	28	N/A	N/A	N/A	35 dias	Cura clínica, cura micológica; resposta terapêutica (cura clinica e micológica); taxa de recorrência; melhora dos sintomas
		clotrimazol: 100mg cp vag./7d	44	29					
Sobel, JD (2001)	EUA	Fluconazol 150mg VO, 2 doses sequenciais 72h intervalo	157	31	Fluconazol 150mg VO, D.U - 72h depois placebo	152	31	35 dias	Cura clínica; cura micológica
Sobel, Jd (2004)	EUA	Fluconazol 150mg, VO/sem/ 6 m	170	33.8	Placebo, VO/sem/ 6m	173	33.8	12 meses	Proporção de mulheres em remissão clínica ao final do período de manutenção com cura definitiva.
Spinillo, A (1997)	Itália	Itraconazol 200mg, 2 doses/ 12h intervalo/no 4º ou 5º d ciclo menstrual, 1x/m/6m	55	30.2±6.6	Nenhum tratamento	53	30.9 ± 6.6	12 meses	Recorrência clínica e micológica; proporção de pacientes livres de recorrência sintomática aos 6 e 12 m; tempo médio recorrência sintomas

Tabela 3. Resultados dos estudos incluídos

Estudo	Autor/ano	Intervenção	Principais Resultados	Risco de vies
1	Bolouri, F (2009)	Fluconazol oral semanal versus placebo	* As diferenças na TRC e TRM entre o GF e o GP aos 3 e 6 meses não foram significativas.	?
2	Brand, S (2018)	Diferentes doses e esquemas de oteseconazol versus placebo	* As recorrências micológicas nos grupos de tratamento e PG ocorreram com mais frequência nas 1as 12 sem. *Tempo médio para a primeira recorrência com cultura positiva:PG 28sem e não foi alcançado em nenhum dos grupos de tratamento devido ao baixo número de recorrências.	?
3	Bushell, TEC (1988)	Clotrimazol comprimido vaginal versus placebo	*TC 12 meses: 18% regime A e 30% regime B. * Regime C: TR 24% em 2 m e TC: 59% em 12 meses(p <0,05). Não foram observadas diferenças apreciáveis entre os diferentes regimes (p> 0,05). Mais da 50% das mulheres em todos os grupos foram colonizadas em 3 meses e em 12 meses mais de 85%.	?
4	Davidson, F (1978)	Clotrimazol vaginal mensal versus placebo	* TCC 10 m: (38%) pacientes do GP e (30%) pacientes do GC. * A maioria dos pacotes de emergência foi usada nos 1os 2m e a maioria das falhas no GC ocorreu nos 1os 2m após final do tratamento, o que mostra que os sintomas foram controlados pelo clotrimazol. * TRC aos 4m: (52,6%)pacientes no GP e (5,5%) pacientes no GC necessitaram de retratamento.	+
5	López-Olmos, J. (2000)	Fluconazol oral versus clotrimazol comp. Vaginal versus itraconazol oral	* Entre clotrimazol e fluconazol, o melhor foi o clotrimazol (p <0,05). Entre itraconazol e fluconazol, o itraconazol foi o melhor (p <0,05). A eficácia clínica geral foi de 73,33%. O melhor resultado foi obtido com o clotrimazol aos 6 m com 91,66% de cura clínica. Em 12m o melhor resultado foi do itraconazol 64,28%. TRC: 57,89% fluconazol, 41,66% clotrimazol e 37,51% itraconazol. * A cura microbiológica não foi completa. Após 6m: TCC 50% fluconazol, clotrimazol 33,3% e itraconazol 33,3%.	-
6	Roth, A. C. (1990)	Clotrimazol comprimido vaginal versus placebo	* TR após 6 m: clotrimazol (30,3%) foi menor (p <0,001) do placebo (79,3%). Após o período de observação de 6m sem tratamento não houve diferenças significativas na freqüência de recorrência acumulada entre os grupos (clotrimazol 84-9%; placebo 86,2%).	+
7	Sobel, JD (1986)	Cetoconazol versus placebo	*TRC 6 m follow up: GP 71.4%; Grupo B 28.6% (p<0.01); Grupo C 4.8% (p<0.001) *TRC 12 m follow up: GP 23.8%; Grupo B: 42.9% (p>0.05); Grupo C: 52.4% (p<0.05)	?
8	Sobel, Jd (1989)	Clotrimazol supositório vaginal mensal versus placebo	* TRC 6m: efeito protetor moderado c/clotrimazol em comparação ao placebo, TRC reduzida em quase 50%. A comparação das TRC entre os grupos durante a fase profilática mostrou significância apenas no período de 3m (p = 0,05). * TRM: não houve diferença estatística nos 2 grupos. * Tempo médio de recorrência dos sintomas na fase profilática: GP: 1,3 meses e GC: 2,5 meses.	?
9	Sobel, JD (1994)	Cetoconazol oral versus clotrimazol vaginal	* TC 7d da terapia inicial - 86.4% no G. cetoconazol e 81.7% no G. clotrimazol. *Após 30d - 80.0% e 73.7% respectivamente; e após 60d - 71.2% e 64.1% respectivamente.	+
10	Sobel, Jd (1995)	Fluconazol oral versus clotrimazol comprimido vaginal	*TCC 14°d: GF 58% e GC 50% - diferenças não significativas (p>0.3); TCC 35°d : GF 55% e GC 50% - diferenças não significativas (p>0.6). TCM 14°d: GF 63% e GC 60% (p=0.826); TCM 35°d: GF 42% e GC 37% (p>0.05). * Resposta terapêutica: resultados comparaveis para os 2 grupos nas avaliações de 14 e 35 dias.	?
11	Sobel, JD (2001)	Fluconazol dose única + placebo versus fluconazol 2 doses	Houve diferenças significativas entre mulheres com vaginite grave ou recorrente em favor da dose sequencial de fluconazol em relação a dose única: OR para TCC ou melhora de 2,4 (p = 0,049) e 1,78 (p = 0,037) no 14°d e no 35°d, respectivamente. *TCM: OR 1,57 e 1,34 no 14°d e no 35°d, respectivamente, sem significância estatística. Mulheres com CVVR, mas sem vaginite grave, não tiveram benefício clínico com a dose adicional de fluconazol.	?
12	Sobel, Jd (2004)	Fluconazol oral semanal versus placebo	* Fase de manutenção: TRC maior no GP que GF. * Período de observação 6 m após o final da terapia: TRC: significativamente mais episódios de candidíase vulvovaginal clínica foram observados no GF do que no GP. * Final dos 12 m: TCC: 42,9% no GF e 21,9% no GP (p <0,001).	?
13	Spinillo, A (1997)	Itraconazol comprimido vaginal versus sem tratamento	1os 6m: *TRC e M: GI - 36.4%; GST - 64.2%. OR=0,32 IC95%: 0.14 - 0.70 (p=0.003. Apó 6m da profilaxia: *TRC e M: GI - 38.9%; GST - 22.2% (p=0.36).	+

Tabela 4. Risco de viés

Estudo/Ano	Geração de sequência aleatória	Ocultação de alocação	Cegamento de participantes e pessoal	Cegamento de avaliação de resultados	Dados de resultados incompletos	Relatórios seletivos	Outro viés	Final
Boulori, F 2009	?	?	?	?	?	+	?	?
Brand, S 2018	?	?	?	?	+	+	+	?
Bushell, T 1988	?	?	?	?	+	?	?	?
Davidson, F 1978	+	+	+	+	+	+	+	+
Lopez-Olmos,J 2000	-	-	-	-	?	+	?	-
Roth, A.C 1990	?	+	+	+	+	?	+	+
Sobel, JD 1986	?	?	?	?	+	+	?	?
Sobel, JD 1989	?	?	?	?	+	?	?	?
Sobel, JD 1994	+	?	?	?	+	+	+	+
Sobel, JD 1995	?	?	?	+	+	+	?	?
Sobel, JD 2001	?	?	?	?	+	+	+	?
Sobel, JD 2004	?	?	?	+	+	?	?	?
Spinillo, A 1997	+	+	+	+	+	?	?	+

Tabela 5. Grade

ANTIFUNGICOS comparado a PLACEBO para CVVR
Bibliografia:

Certainty assessment							Sumário de Resultados				
Participantes (estudos) Seguimento	Risco de viés	Inconsistência	Evidência indireta	Imprecisão	Viés de publicação	Overall certainty of evidence	Taxas de eventos do estudo (%)		Efeito relativo (95% CI)	Efeitos absolutos potenciais	
							Com PLACEBO	Com ANTIFUNGICOS		Risco com PLACEBO	Diferença de risco com ANTIFUNGICOS
Antifúngicos versus placebo - Recorrência micológica - 12 meses (seguimento: média 12 meses)											
587 (7 ECRs)	não grave	não grave	não grave	não grave	nenhum	⨁⨁⨁⨁ ALTA	237/298 (79.5%)	186/289 (64.4%)	**OR 0.38** (0.22 para 0.65)	795 por 1,000	**199 menos por 1,000** (de 334 menos para 79 menos)
Antifúngicos versus placebo - Recorrência clínica - 12 meses (seguimento: média 12 meses)											
500 (6 ECRs)	não grave	não grave	não grave	grave	nenhum	⨁⨁⨁◯ MODERADA	204/252 (81.0%)	151/248 (60.9%)	**OR 0.37** (0.20 para 0.68)	810 por 1,000	**198 menos por 1,000** (de 350 menos para 67 menos)
Antifungals versus Placebo - Tempo para a primeira recorrência (avaliado com: Diferença de médias)											
451 (2 ECRs)	não grave	não grave	não grave	não grave	viés de publicação altamente suspeito	⨁⨁⨁◯ MODERADA	226	225	-	A média antifungals versus Placebo - Tempo para a primeira recorrência foi **0.364**	MD **6.2 mais alto** (6.12 mais alto para 6.28 mais alto)
Eficácia dos protocolos - Clotrimazol versus Fluconazol e Cetoconazol - (seguimento: média 30 dias; avaliado com: taxas de cura clínica)											
192 (2 ECRs)	não grave	não grave	não grave	grave	nenhum	⨁⨁⨁◯ MODERADA	66/95 (69.5%)	62/97 (63.9%)	**OR 0.76** (0.41 para 1.41)	695 por 1,000	**61 menos por 1,000** (de 212 menos para 68 mais)

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

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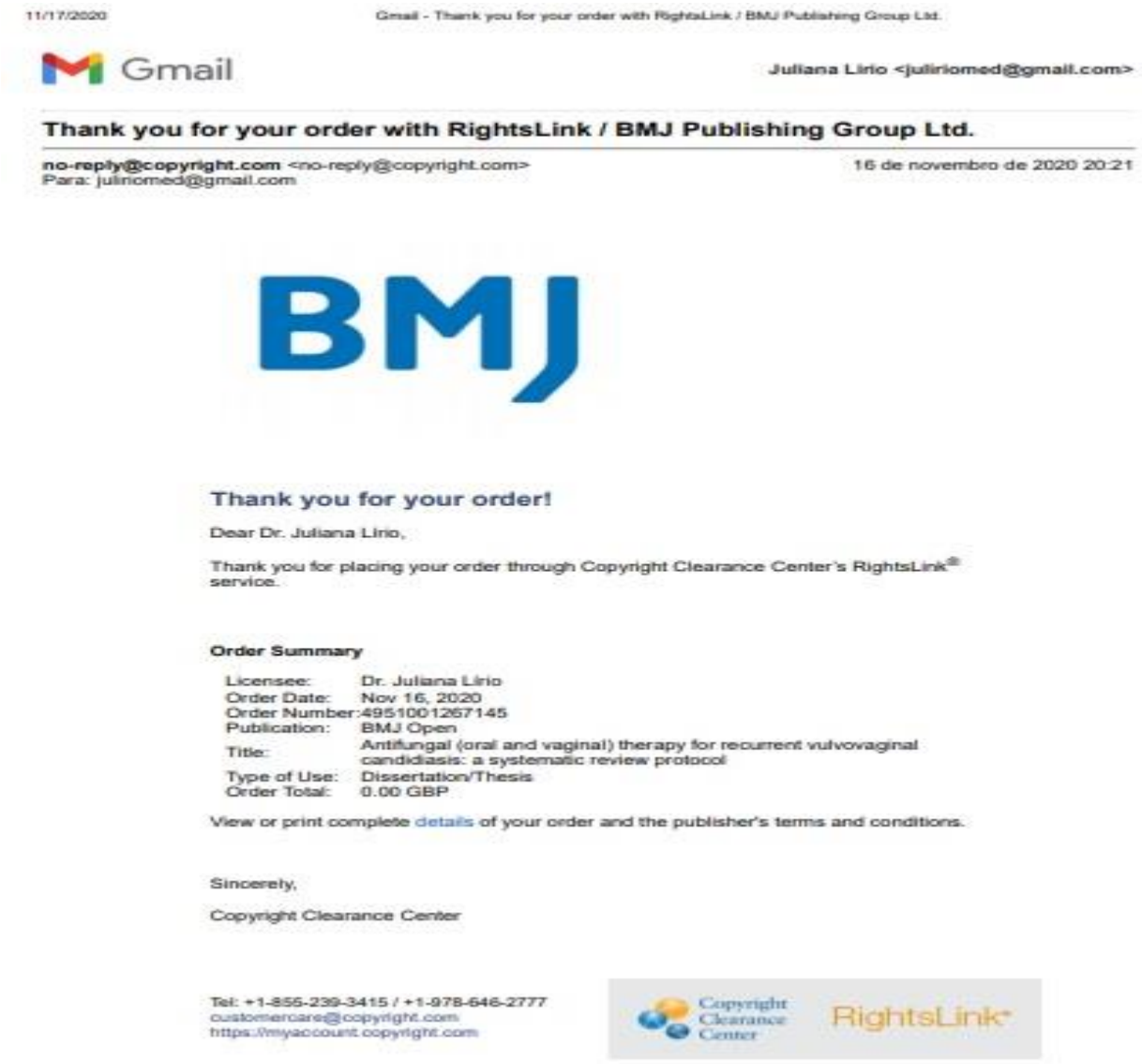

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Antifungal (oral and vaginal) therapy for recurrent vulvovaginal candidiasis: a systematic review protocol

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ABSTRACT

Introduction Vulvovaginal candidiasis (VC) is frequent in women worldwide and usually responds rapidly to topical or oral antifungal therapy. However, some women develop recurrent vulvovaginal candidiasis (RVVC), which is arbitrarily defined as four or more episodes every year. RVVC is a debilitating, long-term condition that can severely affect the quality of life of women. Most VVC is diagnosed and treated empirically and women frequently self-treat with over-the-counter medications that could contribute to an increase in the antifungal resistance. The effective treatment of RVVC has been a challenge in daily clinical practice. This review aims to assess the efficacy of antifungal agents administered orally or intravaginally for the treatment of RVVC, in order to define clinical practices that will impact on the reduction of the morbidity and antifungal resistance.

Methods and analysis A comprehensive search of the following databases will be carried out: PubMed, Embase, Scopus, Web of Science, Scientific Electronic Library Online (SciELO), the Cochrane Central Register of Controlled Trials (CENTRAL), Biblioteca Virtual em Saúde (Virtual Health Library)/Biblioteca Regional de Medicina (Regional Library of Medicine) (BVS/BIREME), Cumulative Index to Nursing and Allied Health Literature (CINAHL) and in the clinical trials databases (www.trialscentral.org; www.controlled-trials.com; www.clinicaltrials.gov). The risk of bias will be assessed according to the Cochrane Risk of Bias tool. We will perform data synthesis using the Review Manager (RevMan) software V.5.2.3. To assess heterogeneity, we will compute the I2 statistic.

Ethics and dissemination This study will be a review of published data and it is not necessary to obtain ethical approval. Findings of this systematic review will be published in a peer-reviewed journal.

Trial registration number CRD42018093817

Strengths and limitations of this study

- Two independent reviewers will select studies, extract data without different variables and assess the risk of bias, to indicate through evidence-based medicine if there is a more effective antifungal therapeutic regimen for the treatment of recurrent vulvovaginal candidiasis.
- There may be a limitation of outcome from treatment variation, routes of administration, different doses and quality of the randomised trials used in the systematic review.
- This review and meta-analysis will combine the results of various studies that have comparable sizes of an effect that can be computed.
- However, it may be that we have only a small sample size and a limited number of studies, which may influence the validity and reliability of the findings.

INTRODUCTION

Description of the condition

Vulvovaginal candidiasis (VVC) is frequent in women worldwide and usually responds rapidly to topical or oral antifungal therapy. However, some women develop recurrent vulvovaginal candidiasis (RVVC), which is arbitrarily defined as at least three symptomatic episodes in the previous 12 months.[1–3]

It is estimated that RVVC affects approximately 138 million women worldwide annually and 492 million over their lifetimes.[1 2] Women reported the period of RVVC to be 1–2 years although a substantial number had symptoms for 4 or 5 years and some very much longer, with risk and symptoms lasting decades.[4 5]

C albicans is responsible for the majority of infections in women with RVVC; however, adequate treatment of RVVC requires species determination confirmed by laboratory findings and effective treatment.[2]

Several factors have been associated to RVVC such as genetic (polymorphism, familial, ethnicity), immune mechanisms (HIV, uncontrolled diabetes, steroids, antibiotics, hormone replacement therapy), behavioural (oral sex, oral contraceptive, intercourse frequency) and idiopathic.[6–10]

Fluconazole is inexpensive and well-tolerated medication that is easily administered orally and is the most used antifungal drug.

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