UNIVERSIDADE FEDERAL DO TRIÂNGULO MINEIRO
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ALUÍSIO GONÇALVES MEDEIROS

O IMPACTO DE DIFERENTES TERAPIAS NA ATROFIA VULVOVAGINAL E NA QUALIDADE DE VIDA EM PACIENTES COM CÂNCER GINECOLÓGICO: UMA REVISÃO SISTEMÁTICA

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O impacto de diferentes terapias na atrofia vulvovaginal e na qualidade de vida em pacientes com câncer ginecológico: uma revisão sistemática

Dissertação apresentada ao Programa de Pós-graduação em Ciências da Saúde, área de concentração Medicina Translacional, da Universidade Federal do Triângulo Mineiro, como requisito para obtenção do título de Mestre em Ciências da Saúde.
Orientadora: Profa. Dra. Juliana Reis Machado e Silva
Coorientadores: Me. José Rodrigues do Carmo Neto
Dra. Mariana Molinar Mauad Cintra

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DEDICATÓRIA

A Deus por sua imensurável luz que nos guia e ilumina no caminho da sabedoria. Á vida plena, pela oportunidade e privilégio em ser um agente modificador por meio da ciência e da prática médica. Ao meu seio familiar, amigos e colegas de pesquisa e trabalho, que se tornaram fundamentais e que sempre levarei comigo. A todos que em algum momento pude estabelecer um vínculo de confiança e bem maior. A busca constante pela evolução e desenvolvimento são eternos, mas reconhecer o valor de cada etapa é fundamental.

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À minha família e amigos, que estiveram ao meu lado e sempre incentivaram a busca pelo meu melhor potencial, oferecendo suporte emocional e compreensão, expresso minha profunda gratidão. Seu encorajamento foi essencial para superar os desafios deste caminho.

Por fim, dedico este trabalho aos pacientes e participantes da pesquisa, cuja colaboração foi indispensável para a coleta de dados. Espero que os resultados desta dissertação possam contribuir de maneira significativa para a promoção da saúde e avanço no conhecimento científico médico.

Minha sincera gratidão a todos que, de alguma forma, tornaram esta jornada acadêmica uma experiência enriquecedora e memorável.

SUMÁRIO

RESUMO

Tumores do trato genital feminino possuem incidência mundial de 17% sendo o câncer de colo do útero o mais frequente. Esses tumores são capazes de ocasionar alterações deletérias na saúde vaginal e também na vida pessoal, com impacto em relacionamento, vida sexual e identidade feminina. A atrofia vulvovaginal é uma das alterações morfologicas encontrada em pacientes com cânceres ginecológicos, tanto pelo próprio compartamento biológico dos tumores quanto pelos principais tratamentos existentes para combatê-los, seja radioterapia, quimioterapia ou exérese dos órgãos através de procedimento cirúrgico. Dessa forma, o objetivo desse trabalho foi identificar os tratamentos para atrofia vaginal, bem como o impacto na saúde emocional e sexual de mulheres com canceres ginecológicos. Para isso, a presente revisão sistemática foi conduzida de acordo com as diretrizes metodológicas propostas pelos Principais Itens para Relatar Revisões sistemáticas e Metanálises (PRISMA). As bases de dados utilizadas para realizar a pesquisa bibliográfica foram PubMed e Web of Science. Um total de 886 artigos foram obtidos na primeira busca. Após a eliminação de duplicados e triagem de artigos através dos critérios de inclusão/exclusão, 7 artigos foram obtidos e analisados de forma gráfica e descritiva. A maior quantidade de artigos publicados foi no periodo de 2017 e 2020. Sendo a maioria desses estudos desenvolvido na Itália. As intervenções foram testadas em pacientes sobreviventes dos seguintes cânceres ginecológicos: uterino, ovário, vaginal e vulvar. Além disso, cinco tipos de tratamentos foram rastreados e divididos em: supositório vaginal, medicamento oral, cirúrgico, terapia de laser de CO_2 e dilatador vaginal. Vinte e quatro desfechos (24) foram avaliados para medir a saúde vaginal e 30 para avaliar a qualidade de vida geral, sexual e emocional. De uma forma geral, todas as intervenções foram capazes de melhorar a saúde vaginal ou pelo menos a saúde sexual das pacientes. Dessa forma, todos os tratamentos apresentados no estudo representam potenciais para tratar atrofia vulvovaginal em pacientes com cânceres ginecológicos.

Palavras-chave: atrofia vaginal; câncer ginecológico; tratamentos; revisão sistemática; saude vaginal; saude sexual.

ABSTRACT

Tumors of the female genital tract have a worldwide incidence of 17%, with cervical cancer being the most common. These tumors are capable of causing deleterious changes in vaginal health and also in personal life, with an impact on relationships, sex life and female identity. Vulvovaginal atrophy is one of the morphological alterations found in patients with gynecological cancers, both because of the biological compartment of the tumors themselves and because of the main treatments available to combat them, whether it be radiotherapy, chemotherapy or surgical excision of the organs. Thus, the aim of this study was to identify the treatments for vaginal atrophy, as well as the impact on the emotional and sexual health of women with gynecological cancers. To this end, this systematic review was conducted in accordance with the methodological guidelines proposed by the Principal Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The databases used to conduct the literature search were PubMed and Web of Science. A total of 886 articles were obtained in the first search. After eliminating duplicates and screening articles using the inclusion/exclusion criteria, 7 articles were obtained and analyzed graphically and descriptively. The largest number of articles were published between 2017 and 2020. Most of these studies were conducted in Italy. The interventions were tested on patients who had survived the following gynecological cancers: uterine, ovarian, vaginal and vulvar. In addition, five types of treatments were tracked and divided into: vaginal suppository, oral medication, surgical, CO2 laser therapy and vaginal dilator. Twenty-four outcomes (24) were assessed to measure vaginal health and 30 to assess general, sexual and emotional quality of life. In general, all the interventions were able to improve the vaginal health or at least the sexual health of the patients. Thus, although with limitations, all treatments represent potential for treating vulvovaginal atrophy in patients with gynecological cancers.

Keywords: vaginal atrophy; gynecological cancer; treatments; systematic review; vaginal health; sexual health**.**

QUADROS, TABELAS, FIGURAS E ANEXOS

SÍMBOLOS, SIGLAS E ABREVIATURAS

HPV **–** vírus do papiloma humano

CC – câncer cervical

AVV – atrofia vulvovaginal

SGM – síndrome genitourinária da menopausa

VAS – Escala de avaliação vaginal

VHI – Índice de Saúde Vaginal

VuAS – Escala de avaliação vulvar

FSFI – Índice de função sexual feminina

EORTC – Organização Europeia para Pesquisa e Tratamento do Câncer

1. INTRODUÇÃO

1.1 Câncer ginecológico: conceitos e epidemiologia

O câncer ginecológico é um grupo de doenças que afetam os órgãos reprodutivos femininos, e representa uma importante questão de saúde pública em todo o mundo. A incidência e a prevalência desses cânceres podem variar de acordo com a região geográfica, fatores genéticos, ambientais e estilo de vida. De fato, de acordo com dados de 2018, a incidência de câncer está aumentando mundialmente, acredita-se que este aumento esteja relacionado com hábitos e qualidade de vida da população (Bray et al., 2018). Para a população feminina, o câncer de mama é o tipo tumoral mais prevalente, seguido de colorretal e pulmonar. No Brasil, a incidência segue um padrão parecido com a frequência mundial, sendo de 30,1% para câncer de mama, seguido de colorretal (9,7%), colo uterino (7%), pulmonar (6%) e de tireoide (5,8%) (La Rosa et al., 2020). Para casos de tumores no trato genital feminino, a incidência mundial encontrada é de 17%, sendo o câncer de útero (53%), ovário (25%) e de colo uterino (14%).

O câncer de colo do útero, também conhecido como câncer cervical, é causado principalmente pela infecção persistente pelo vírus do papiloma humano (HPV). É o terceiro tipo de câncer mais comum em mulheres, mas com a ampla disponibilidade de programas de rastreamento, como o exame de Papanicolau, a incidência e a mortalidade têm diminuído significativamente. Outro exemplo, é o câncer de endométrio, o qual se origina no revestimento interno do útero (endométrio) e é mais comum em mulheres na pós-menopausa. O uso de terapia hormonal e obesidade estão entre os principais fatores de risco. Outro caso é o câncer ovariano, conhecido como o "assassino silencioso", o qual frequentemente não apresenta sintomas óbvios em seus estágios iniciais. Isso pode dificultar o diagnóstico precoce e tornar a doença mais grave quando é descoberta. A história familiar, mutações genéticas hereditárias e a idade avançada são fatores de risco importantes. Outros exemplos são o câncer de vulva e o de vagina. O primeiro se origina nos tecidos externos da vulva, a parte externa dos órgãos genitais femininos. Pode estar associado a infecções por HPV, doenças de pele crônicas e tabagismo. O segundo, embora seja raro, pode afetar mulheres em diferentes faixas etárias. Possui como fatores de risco idade avançada, infecções por HPV e história de radioterapia pélvica.

Aproximadamente 21% das mulheres com diagnóstico de câncer ginecológico estão em idade reprodutiva, geralmente abaixo dos 40 anos (McKenzie et al., 2018). Esse fator é, de fato, preocupante, devido a maior parte dos tratamentos para esses tipos de

cânceres afetarem diretamente a função sexual e reprodutiva da mulher e aspectos psicologicos (McKenzie et al., 2018).

Em relação as neoplasias malignas que acometem o útero, podemos dividir em dois grupos principais, com características bem distintas: câncer de colo do útero e o câncer de endométrio. O primeiro, também conhecido como câncer cervical (CC), é causado principalmente pela infecção persistente pelo Papilomavírus Humano (HPV). O CC é terceiro tipo de câncer mais comum em mulheres, mas devido ao aumento na disponibilidade de programas de rastreamento, como o exame de Papanicolau, acompanhado pela implementação de campanhas de vacinação contra o HPV e educação sexual, a sua incidência e a mortalidade têm diminuído significativamente. Outro exemplo, é o câncer de endométrio, o qual se origina no revestimento interno do útero e é mais comum em mulheres na pós-menopausa. O uso de terapia hormonal e obesidade estão entre os seus principais fatores de risco para o câncer de endométrio.

Em menor incidência, porém também impactante na saúde da mulher, tem-se o câncer ovariano, conhecido como o "assassino silencioso", o qual frequentemente não apresenta sintomas óbvios em seus estágios iniciais. Isso pode dificultar o diagnóstico precoce e tornar a doença mais grave quando é descoberta. A história familiar, mutações genéticas hereditárias e a idade avançada são fatores de risco importantes.

Outros exemplos de neoplasias malignas do aparelho reprodutivo feminino são o câncer de vulva e o de vagina. O primeiro se origina nos tecidos externos da vulva, a parte externa dos órgãos genitais femininos. Pode estar associado a infecções por HPV, doenças de pele crônicas e tabagismo. O segundo, embora seja raro, pode afetar mulheres em diferentes faixas etárias. Possui como fatores de risco idade avançada, infecções por HPV e história de radioterapia pélvica.

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1.2 Tratamentos

Os tratamentos para os cânceres ginecológicos podem ser medicamentosos, cirúrgicos, quimioterápicos ou radioterápicos. Assim, as principais abordagens cirúrgicas, por exemplo, são a histerectomia, ovariectomia, vulvectomia e cirurgia pélvica.

Para o câncer de endométrio, por exemplo, tratamentos cirúrgicos podem ser a histerectomia abdominal total ou salpingooforectomia bilateral e a avaliação nodal (May et al., 2010). A radioterapia e a quimioterapia podem ser administradas de forma adjuvante com base em fatores de risco para recorrências locais e regionais (Kong et al., 2012). Essas terapias podem causar alterações significativas na estrutura vaginal normal. A radioterapia pélvica, seja ela realizada com radioterapia de feixe externo ou braquiterapia intracavitária, também apresenta o risco de desenvolver alterações na morfologia da vagina, incluindo encurtamento, estreitamento, perda de elasticidade, atrofia e ressecamento (Hofsjö et al., 2017; Jensen; Froeding, 2015). O mecanismo provável dessas alterações está relacionado ao dano direto à mucosa vaginal, aos tecidos conjuntivos e aos vasos, com desnudamento do epitélio e subsequente fibrose (Morris; Haboubi, 2015). Essas alterações, sobretudo com a formação de áreas de fibrose, podem resultar clinicamente em dispareunia, sangramento após relação sexual e até mesmo impedir exames pélvicos que são a base para a avaliação da recorrência (Denton; Maher, 2003). Além disso, em casos mais extremos, podem levar obliteração completa da vagina (Denton; Maher, 2003). Essas complicações não ameaçam a vida, mas podem afetar o funcionamento físico, sexual, psicológico e social da mulher.

No caso de câncer cervical (CC), o tratamento primário depende de uma variedade de fatores, incluindo estadiamento, características do tumor, comorbidades e características do paciente (Frumovitz et al., 2005). A terapia padrão do CC geralmente é cirúrgica. No entanto, foi demonstrado que a radioterapia é necessária em tumores em estágio avançado, tanto para o tratamento do câncer quanto para a prevenção de recorrências (Liontos et al., 2019). Além disso, a adição de quimioterapia à radioterapia pode melhorar a sobrevida global e determina uma redução significativa na recorrência local em todos os estágios da doença (Liontos et al., 2019). Embora esses tratamentos apresentem eficiência na eliminação das células tumorais, afetam diretamente na saúde sexual das pacientes. Dessa forma, esse impacto abrange mais do que a soma dos problemas de funcionamento vaginal, mas também uma complexa rede de parâmetros, que incluem alterações emocionais, de imagem corporal e de interação com o parceiro

(de Noronha et al., 2013; Hofsjö et al., 2018, 2017; Kirchheiner et al., 2022; Tramacere et al., 2022).

1.3 Impacto na qualidade de vida

Esses procedimentos podem alterar de forma definitiva diversos fatores relacionados a qualidade de vida das pacientes sobreviventes do câncer ginecológico. O principal impacto consiste na piora da qualidade de vida sexual e na saúde vaginal das mulheres (Izycki et al., 2016; Stead et al., 2007). Pode gerar a perda do prazer sexual, redução de secreção de estrógeno e consequente lubrificação vaginal, distorção da aparência vaginal e até mesmo lesões em nervos que impactam diretamente na qualidade de vida das pacientes (Izycki et al., 2016; Stead et al., 2007). Da mesma forma, o manejo a partir de quimioterapia reduz a libido, aumenta a fadiga, induz estado temporário ou permanente de menopausa e induz neuropatia no clítoris (Aerts et al., 2012; Hughes, 2008). No mesmo contexto, a radioterapia também pode causar lesão vaginal, alterando a morfologia das camadas vaginais, nervos e vasos sanguíneos, resultando em atrofia e estenose vaginal (Aerts et al., 2012; Hughes, 2008).

Além dessas alterações, uma das mais frequentes relatadas pelas pacientes é a dor durante a relação sexual (Jensen et al., 2004). Segundo alguns autores, quase 70% das pacientes ginecológicas correm risco de dispareunia associada a elasticidade vaginal prejudicada (Kollberg et al., 2015). Outros relatos incluem disfunção da lubrificação vaginal, sangramento após o intercurso sexual, diminuição da atividade sexual devido à fadiga, capacidade limitada de atingir excitação sexual e orgasmo, diminuição sensibilidade nos órgãos sexuais (Aerts et al., 2015, 2009; Wenzel et al., 2002), sensação de dormência (Andersen and Hacker, 1983), medo da atividade sexual causar danos à saúde ou que o próprio câncer possa ser transmitido sexualmente (Reis et al., 2010).

Ademais às alterações vaginais, os tratamentos para cânceres ginecológicos também possuem consequências psicológicas e sociais (de Souza et al., 2021). Nesse contexto, o impacto depende do tipo de câncer, tempo de diagnóstico e do tratamento instituído (Izycki et al., 2016). Dessa forma, disfunções sexuais decorrentes dos tratamentos influenciam de forma perturbadora suas relações pessoais ou até mesmo o senso de identidade sexual, o que afeta de forma negativa a qualidade de diferentes áreas da vida da paciente (Levin et al., 2010; Reis et al., 2010). Assim, essas pacientes são relatadas por perder interesse na vida sexual e por experienciarem uma mudança negativa na percepção da imagem corporal (Bourgeois-Law and Lotocki, 1999). Outros sintomas

relatados são ansiedade, depressão, insatisfação com relacionamento e diminuição da qualidade de vida (Aerts et al., 2012).

A falta de informação sobre o tratamento e suas consequências leva à falta de compreensão da situação e intensifica a sensação de tensão entre as pacientes (Stead et al., 2007). Dessa forma, mulheres que sentem desconforto durante a relação sexual tendem a evitar contatos sexuais. Um bom relacionamento com o parceiro constitui fator de sucesso/apoio no processo de enfrentamento desta condição (Carter et al., 2012). Além disso, a problemática também afeta mulheres no período reprodutivo e que se tornam inférteis devido ao tratamento (Reis et al., 2010). Nesse caso, as pacientes podem se sentirem sem valor, insuficientes e incompletas (Reis et al., 2010). Esses fatores podem ser favorecidos pela forte convicção de que a feminilidade corresponde à capacidade de gerar filhos (Juraskova et al., 2003).

Além do impacto psicológico, o tratamento do câncer ginecológico muitas vezes envolve mudanças na aparência do corpo. Perda de órgãos, como o útero ou os ovários, ou escarificação, para muitas mulheres tem um significado simbólico, privando-as de sua feminilidade (Cleary and Hegarty, 2011). O que, consequentemente, gera uma imagem corporal distorcida seguida por tristeza, sofrimento e insegurança sobre a sua sexualidade (Hawighorst-Knapstein et al., 2004; Reis et al., 2010). Green et al. demonstraram que pacientes que foram submetidas a vulvectomia, ou seja, a retirada total da vulva, relataram mudanças na imagem do corpo e se perceberam como inadequadas, não atendendo aos padrões comuns de beleza (Green et al., 2000). Além disso, descrições como assimétrico, incompleto e destruído são comuns para caracterizar o corpo feminino após esse procedimento, o que divide o impacto do tratamento em momento antes e após a intervenção (Green et al., 2000; Sacerdoti et al., 2010).

Visto que cânceres ginecológicos e seus diferentes tratamentos influenciam drasticamente na qualidade de vida das pacientes, é importante estabelecer intervenções que reduzam os efeitos negativos relatados. Dessa forma, o manejo e tratamento da atrofia vulvovaginal (AVV) ou síndrome genitourinária da menopausa (SGM), é uma das medidas para tentar reduzir o impacto do tratamento tumoral em pacientes com câncer ginecológico, seja durante o tratamento ou após a finalização do esquema terapêutico.

A AVV (também conhecida como atrofia vulvovaginal, atrofia geniturinária ou vaginite atrófica) é causada pela diminuição do estrogênio e está frequentemente

associada a desconforto vulvovaginal (por exemplo, secura vaginal, queimação e irritação vulvar e vaginal, falta de lubrificação, dispareunia) e menos comumente, urgência, frequência, disúria e infecções recorrentes do trato urinário (Gandhi et al., 2016). Além disso, afeta mais de 50% das mulheres na pós-menopausa e é mais prevalente em mulheres com câncer (Carter et al., 2017; Cook et al., 2017; Desimone et al., 2014). Em 2014, a International Society for the Study of Women's Sexual Health e a North American Menopause Society introduziram o novo termo síndrome geniturinária da menopausa (Burich and Degregorio, 2014). O termo inclui todos os sintomas de atrofia que um paciente pode apresentar nas regiões vulvovaginal e vesicouretral devido à perda de estrogênio que ocorre durante a menopausa (Erekson et al., 2016).

Nesse contexto, a SGM impacta negativamente o processo de excitação e orgasmo, levando à disfunção sexual (Burich and Degregorio, 2014). A prevalência de SGM confirmada por exame físico ou medição de pH foi descrita como variando de 69% a 98% em mulheres pós-menopáusicas (Nappi and Palacios, 2014; Rahn et al., 2014), mas é ainda mais frequente em pacientes jovens recebendo drogas antiestrogênicas ou antineoplásicas para câncer de mama (Knobf, 2006) e cânceres ginecológicos (Knobf, 2006). Esses sintomas associados a SGM são muitas vezes subdiagnosticados e subtratados devido à subnotificação pelas pacientes e conscientização limitada entre os profissionais de saúde (Moral et al., 2018).

Na literatura, observa-se que a maioria dos estudos se concentrou na descrição de casos de SGM relacionados a pacientes com câncer de mama, enquanto poucos se concentraram em casos de cânceres ginecológicos, sobretudo, para aquelas pacientes que foram submetidas a radioterapia pélvica. Dessa forma, o objetivo desse trabalho é executar uma revisão sistemática que contemple todos os aspectos, desde características do tumor, tipo de tratamento submetido e aspectos de qualidade de vida das pacientes com canceres ginecológicos e SGM.

2. JUSTIFICATIVA

A SGM é de extrema relevância por diversas razões fundamentais que envolvem a saúde e a qualidade de vida das mulheres. Essa síndrome se refere a um conjunto de sintomas e alterações que afetam o trato genitourinário durante o período da menopausa e pós-menopausa, sobretudo nas pacientes que são submetidas a tratamento contra o canceres ginecológicos. Pacientes que enfrentam o diagnóstico e tratamento de câncer ginecológico já enfrentam desafios significativos em relação à sua saúde física e emocional. A menopausa induzida pelo tratamento ou pelo próprio envelhecimento pode agravar os sintomas genitourinários, resultando em desconfortos adicionais. O estudo dessa síndrome em pacientes com câncer ginecológico é crucial para identificar e compreender como esses sintomas podem interagir e afetar a saúde geral dessas pacientes.

A qualidade de vida de pacientes com câncer ginecológico já é afetada pelo diagnóstico e tratamento, que podem ser invasivos e emocionalmente desafiadores. A síndrome genitourinária da menopausa pode agravar ainda mais os efeitos colaterais, como ressecamento vaginal, dor durante o sexo e infecções recorrentes, resultando em uma deterioração adicional na qualidade de vida. Compreender como esses sintomas afetam a vida das pacientes pode levar a abordagens de tratamentos específicos e direcionados.

3. OBJETIVOS

3.1 Objetivo geral

Rastrear a diversidade de tratamentos para atrofia vulvovaginal com impacto na saúde emocional e sexual disponíveis na literatura para mulheres sobreviventes do câncere ginecológico.

3.2 Objetivos específicos

- Estabelecer a pergunta norteadora para construção da revisão sistemática;

- Construir ferramenta de busca que contemple diferentes tratamentos para atrofia vulvovaginal em pacientes com câncer ginecológico;

- Traçar as características dos estudos de forma gráfica e resumir em forma de tabela;

- Elucidar a diversidade dos tratamentos e se o efeito é benéfico ou não para atrofia vulvovaginal nesse grupo de pacientes.

4. RESULTADOS

4.1 Manuscrito 1

THE EFFECTS OF VARIOUS THERAPIES ON VULVOVAGINAL ATROPHY AND QUALITY OF LIFE IN GYNECOLOGICAL CANCER PATIENTS: A SYSTEMATIC REVIEW

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ABSTRACT

Tumors affecting the female genital tract have a global incidence of 17%, with cervical cancer being the most common type. These neoplasms and their treatments have the potential to induce adverse modifications in vaginal health and impact personal aspects of patients' lives, including relationships, sexual life, and feminine identity. Vulvovaginal atrophy is one of the morphological changes observed in individuals with a history of gynecological cancer, influenced both by the biological environment of tumors and the main therapeutic modalities employed, such as radiotherapy, chemotherapy, and surgical resection of affected organs. Therefore, the purpose of this study was to identify approaches to treat vulvovaginal atrophy while assessing the impact on the emotional and sexual health of women diagnosed with gynecological cancers. To achieve this goal, a systematic review was conducted following the methodological guidelines outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The databases used for literature research were PubMed and Web of Science. Initially, 886 articles were obtained. After eliminating duplicates and applying inclusion/exclusion criteria, seven articles were selected for analysis, which was conducted graphically and descriptively. The period of highest publication activity spanned from 2017 to 2020, with the majority of these studies conducted in Italy. The evaluated interventions were applied to patients who had survived gynecological cancers such as uterus, ovary, vagina, and vulva. Five treatment modalities were identified and categorized as vaginal suppository, oral medication, surgical procedure, CO2 laser therapy, and vaginal dilator. Twenty-four outcomes related to vaginal health and 30 outcomes related to overall, sexual, and emotional quality of life were analyzed. In general, all interventions demonstrated the ability to improve vaginal health or, at the very least, the sexual health of patients. Thus, despite limitations, all treatments have the potential to address vulvovaginal atrophy in patients with a history of gynecological cancer.

Key-words: vaginal atrophy; gynecological cancer; treatments; systematic review; vaginal health; sexual health.

1. INTRODUCTION

Vulvovaginal Atrophy (VVA), also known as vulvovaginal atrophy, genitourinary atrophy, or atrophic vaginitis, is caused by decreased estrogen and is often associated with vulvovaginal discomfort (e.g., vaginal dryness, burning, vulvar and vaginal irritation, lack of lubrication, dyspareunia), and less commonly, urgency and increased urinary frequency, dysuria, and recurrent urinary tract infections (Gandhi et al., 2016). Moreover, it affects over 50% of postmenopausal women and is more prevalent in women with cancer (Carter et al., 2017; Cook et al., 2017; Desimone et al., 2014). In 2014, the International Society for the Study of Women's Sexual Health and the North American Menopause Society introduced the new term Genitourinary Syndrome of Menopause (GSM) (Burich; Degregorio, 2014). The term encompasses all atrophy symptoms a patient may experience in the vulvovaginal and vesicourethral regions due to estrogen loss during menopause (Erekson et al., 2016).

The prevalence of GSM confirmed by physical examination or pH measurement has been described as ranging from 69% to 98% in postmenopausal women (Nappi and Palacios, 2014; Rahn et al., 2014), but it is even more frequent in young patients who have received antiestrogenic or antineoplastic drugs for breast and gynecological cancers (Knobf, 2006). Symptoms associated with GSM are often underdiagnosed and undertreated due to underreporting by patients and limited awareness among healthcare professionals (Moral et al., 2018). In the literature, most studies focus on describing GSM cases related to breast cancer patients, while few have focused on cases of gynecological cancers, especially those who have undergone pelvic radiotherapy.

In this context, women with gynecological cancers, particularly those treated with radiation, have a high incidence of dyspareunia, vaginal dryness, and sexual dysfunction (Amsterdam et al., 2006; Jensen et al., 2015). Vaginal moisturizers and lubricants are typically recommended for symptom control, but unfortunately, these topical agents do not treat the underlying problem of GSM (Amsterdam et al., 2006; Del Carmen et al., 2017; Kapoor et al., 2018). Although a low dose of vaginal estrogen can help alleviate signs and symptoms, adherence to treatment is low, symptoms may return after discontinuation, and insufficient improvement has been reported with systemic and vaginal estrogen therapy (Friedman et al., 2011; Portman et al., 2014; Stefano et al., 2015; De Rosa et al., 2017). Additionally, the use of vaginal estrogens is controversial for some women with gynecological cancer (Sinno et al., 2020), and doctors often hesitate to prescribe vaginal estrogens to this population (Biglia et al., 2017). Thus, there is a need

for alternatives for GSM treatment to increase efficiency in impacting overall and sexual quality of life. Therefore, the aim of this review is to explore existing treatments in the literature for GSM and evaluate the impact of each on the overall and sexual quality of life of gynecological cancer patients who have undergone oncological treatment.

2. METHODOLOGY

2.1 Protocol and Registration

This systematic review was conducted following the methodological guidelines proposed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Galvão; Pansani; Harrad, 2015). The protocol for this review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number: CRD42023412409.

2.2 Eligibility Criteria

The guiding question for the selection of articles for analysis was: which therapies improve vaginal atrophy and quality of life in survivors of gynecological cancer? The question was divided according to the PICO model (Population, Intervention, Comparator, and Outcome). Therefore, studies were included that involved the population (P) of women with a previous diagnosis of gynecological cancer who developed vulvovaginal atrophy, underwent some form of intervention (I), compared to a group without treatment or other treatments (C), and that may or may not have a positive effect on vaginal atrophy (O).

On the other hand, reasons for excluding articles were: studies that included women without gynecological cancer with vaginal atrophy; studies that included only women with breast cancer with vaginal atrophy; studies without any form of treatment for vaginal atrophy in women with gynecological cancer; studies that lacked a control group without intervention or with another type of intervention for comparison; works that were not original articles, such as editorials, conference documents, comments, expert opinions, systematic reviews, or any other type of review, and book chapters; articles not in Spanish, Portuguese, or English.

2.3 Information Sources and Search

The databases used for literature research were PubMed and Web of Science (Supplementary Material 1 – S1). Additionally, other investigations were conducted, such

as manual searches in the reference lists of included studies. After the official search in the mentioned databases, the articles were transferred to the RAYYAN application. Subsequently, duplicate articles were removed using the tools provided by the application, followed by confirmation by the evaluators. The search strategy was developed according to the Peer Review of Electronic Search Strategies (PRESS) (MCGOWAN et al., 2016). The strategy developed for the PubMed database was considered the standard, with no restriction on the search by year of publication and language. This was slightly modified according to the criteria of each database. Below is the standard search tool used:

Search: ((Vaginal Atrophy) AND (cancer)) AND (treatment):

("vagina"[MeSH Terms] OR "vagina"[All Fields] OR "vaginal"[All Fields] OR "vaginally"[All Fields] OR "vaginals"[All Fields] OR "vaginitis"[MeSH Terms] OR "vaginitis"[All Fields] OR "vaginitides"[All Fields]) AND ("atrophie"[All Fields] OR "atrophy"[MeSH Terms] OR "atrophy"[All Fields] OR "atrophied"[All Fields] OR "atrophies"[All Fields] OR "atrophying"[All Fields]) AND ("cancer s"[All Fields] OR "cancerated"[All Fields] OR "canceration"[All Fields] OR "cancerization"[All Fields] OR "cancerized"[All Fields] OR "cancerous"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "cancers"[All Fields]) AND ("therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "treatments"[All Fields] OR "therapy"[MeSH Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "treatment s"[All Fields]).

2.4 Study Selection and Data Extraction

The selection was performed in two stages, blindly and separately by two evaluators, one of them being the main author of the manuscript, Aluísio Gonçalves Medeiros, and the other Me. José Rodrigues do Carmo Neto. Initially, the reviewers examined the titles and abstracts of all references identified in the data searches to assess their relevance within the RAYYAN application, starting the inclusion or exclusion stage by title and abstract. Subsequently, the reviewers' analyses were compared, and in cases of disagreement, these were reconciled through a discussion between them and a third reviewer, Dr. Mariana Molinar Mauad Cintra. In the second stage, all potentially eligible studies were read in full independently (Supplementary Material 2 – S2). Articles that met the inclusion criteria were selected to be part of the review. Relevant data were extracted from all included studies by two evaluators independently. In addition to data

extraction tables, the primary results of the included articles were presented graphically and descriptively throughout the "Results" section.

3. RESULTS

3.1 Flowchart and General Characteristics of Included Studies

The database search for studies addressing the use of treatments for vulvovaginal atrophy resulted in 886 articles. After excluding duplicated articles (217), a total of 669 works remained. Following the evaluation of the title and abstract of each study, 21 potential works were included and read in full. Of these 21, 14 were excluded for the following reasons: not assessing parameters related to vulvovaginal atrophy (7); not distinguishing the gynecological cancer group from the breast cancer group (4); not focusing on gynecological cancer (1); abstract only (1); unavailability (1). Finally, 7 studies were included in the systematic review and underwent qualitative and descriptive evaluation (Figure 1).

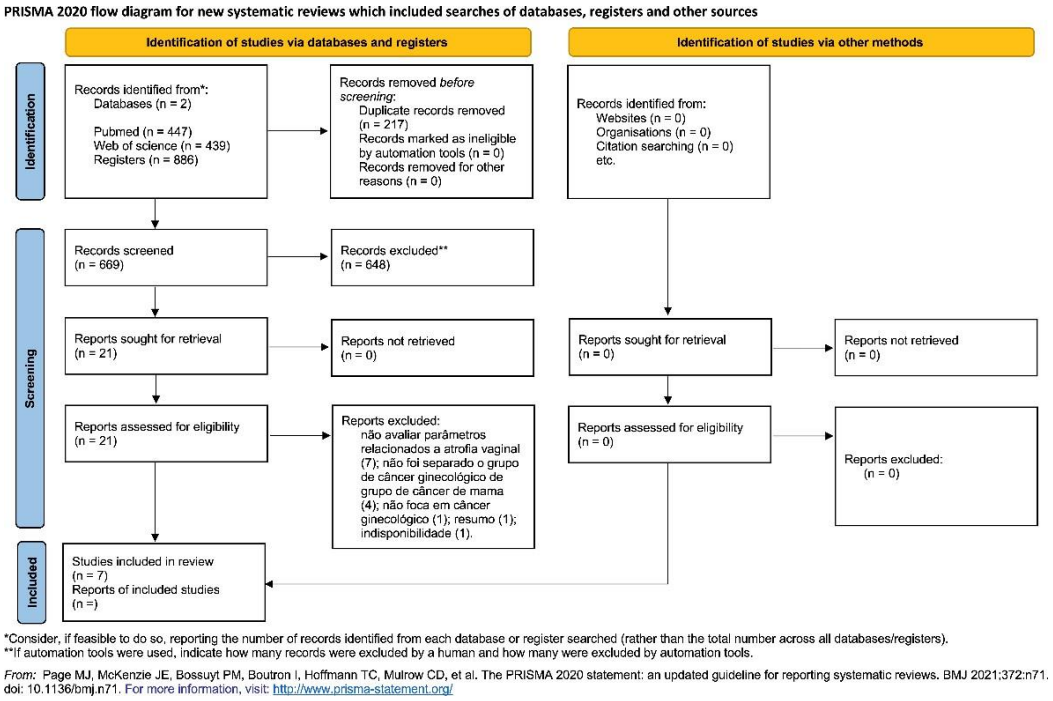

Figure 1. Official PRISMA Flowchart. List of included and excluded articles.

Regarding the general characteristics of the included studies, the analysis covered the publication year (Figure 2A), the location where the study was conducted (Figure 2B), and the study type (Figure 2C). The first article on the topic was published in 2004 (1), with a 13-year gap to the next publication year, 2017, where two articles were published.

Subsequently, publications in 2020 (2), 2021 (1), and 2023 (1) followed. Additionally, Italy had the highest number of publications (50%), followed by the United States (25%), San Marino, and France, each with the same number of studies (12.5%). Prospective studies represented most published works, accounting for 28.6% of the total included studies. The remaining studies corresponded to the same percentage, with 14.28% for pilot investigation studies, case reports, retrospective studies, prospective phase I-II clinical studies, multicenter randomized pilot-controlled studies, and single-blind studies.

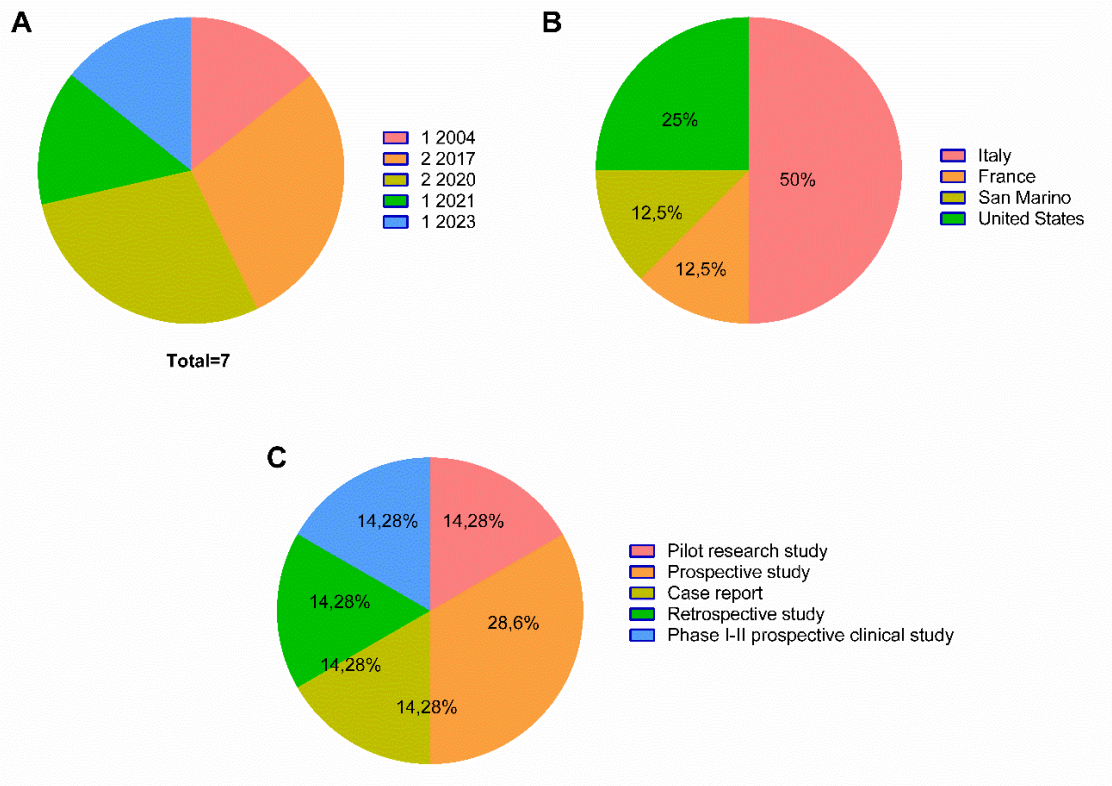

Figure 2. General characteristics of the included studies. (A) Number of articles published per year. (B) Location where the studies were conducted. (C) Type of study conducted (data extracted from the methodology of each included article).

3.2 Tumor Types and Included Treatments

Regarding the general characteristics of tumors and treatments in which vulvovaginal atrophy was evaluated, the focus was on the relationship between tumor type/location (Figure 3A) and the chosen treatment type (Figure 3B). Most studies focused on patients with uterine cancer (66.66%), followed by vaginal and ovarian cancer (13.33%), and vulvar cancer (6.68%). For treatments, radiotherapy and chemotherapy were the most reported in the included studies, accounting for 80%. Next, surgical procedures accounted for 13.4% of reports. Nevertheless, 6.6% did not report the types

of treatments the patients underwent. The complete description of treatment types is presented in Table 1.

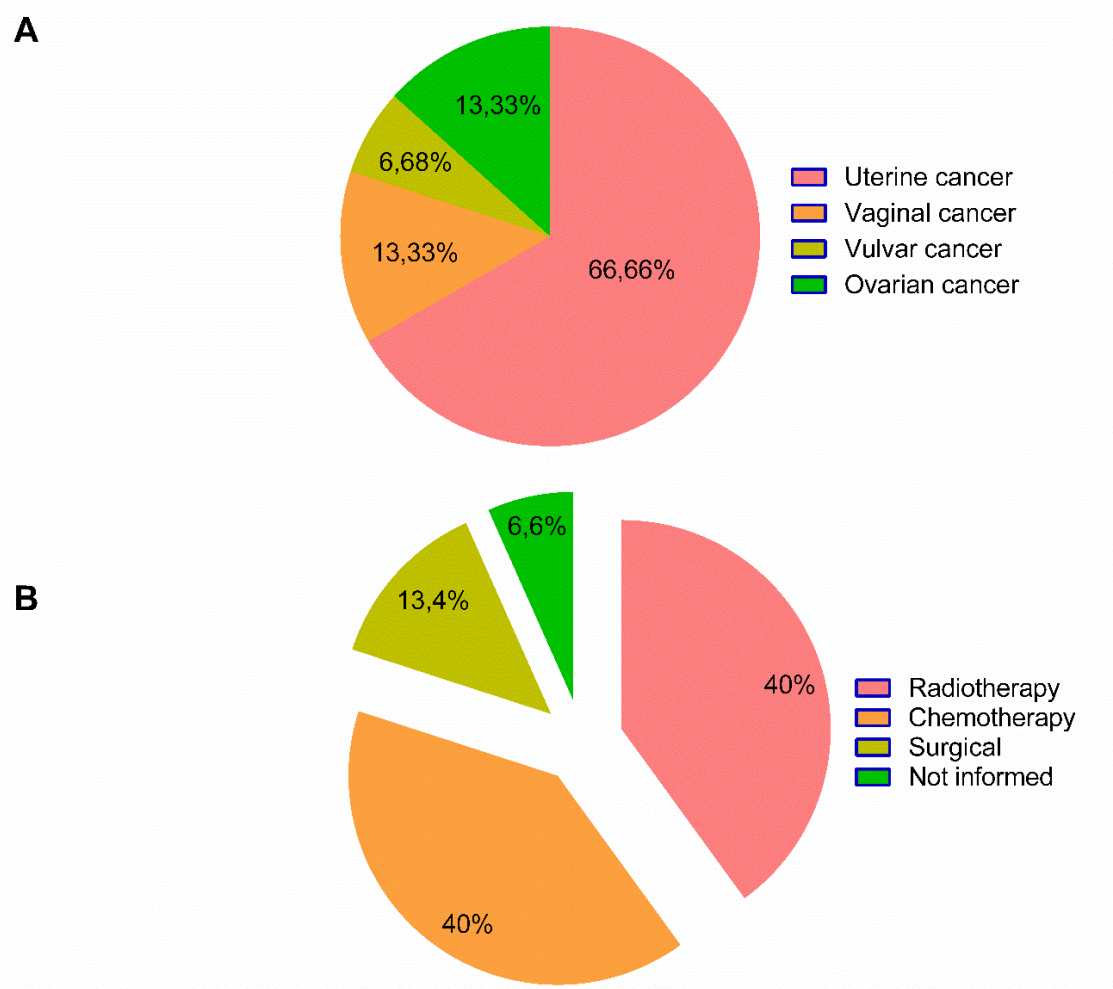

Figure 3. General characteristics related to (A) tumor type and (B) the treatment of choice highlighted by the included articles.

3.3 Interventions for Vaginal Atrophy and Evaluated Outcomes

Regarding interventions used to reduce vulvovaginal atrophy (Figure 4A), CO2 laser was the most frequent, accounting for 42.88% of reports. Subsequently, all other treatments represented the same frequency in the included studies, with 14.28% for the use of vaginal suppository, oral medication, surgical procedure, and the use of vaginal dilator. For the evaluated outcomes, i.e., assessing the impact of treatments on parameters that may be altered in cases of atrophy, various phenomena were analyzed (Figure 4B). To check if the interventions induced positive impacts, the parameter hydration and the presence of vaginal fluids were the most frequent, at 18.42%. Following this, dyspareunia

and burning were also evaluated, representing 15.79%. Subsequently, elasticity (10.53%), pH (10.53%), epithelial integrity (7.89%), and parameters related to vaginal size (7.89%) also showed higher frequencies in the included studies. Finally, the remaining parameters were analyzed less frequently in the works (fibrosis, inflammation, cellular atypia, mucosal edema, mucositis, irritation, roughness, vascularization, epithelial acanthosis, and bleeding). The complete description of the type of treatment and the methodology for evaluating outcomes is presented in Table 2.

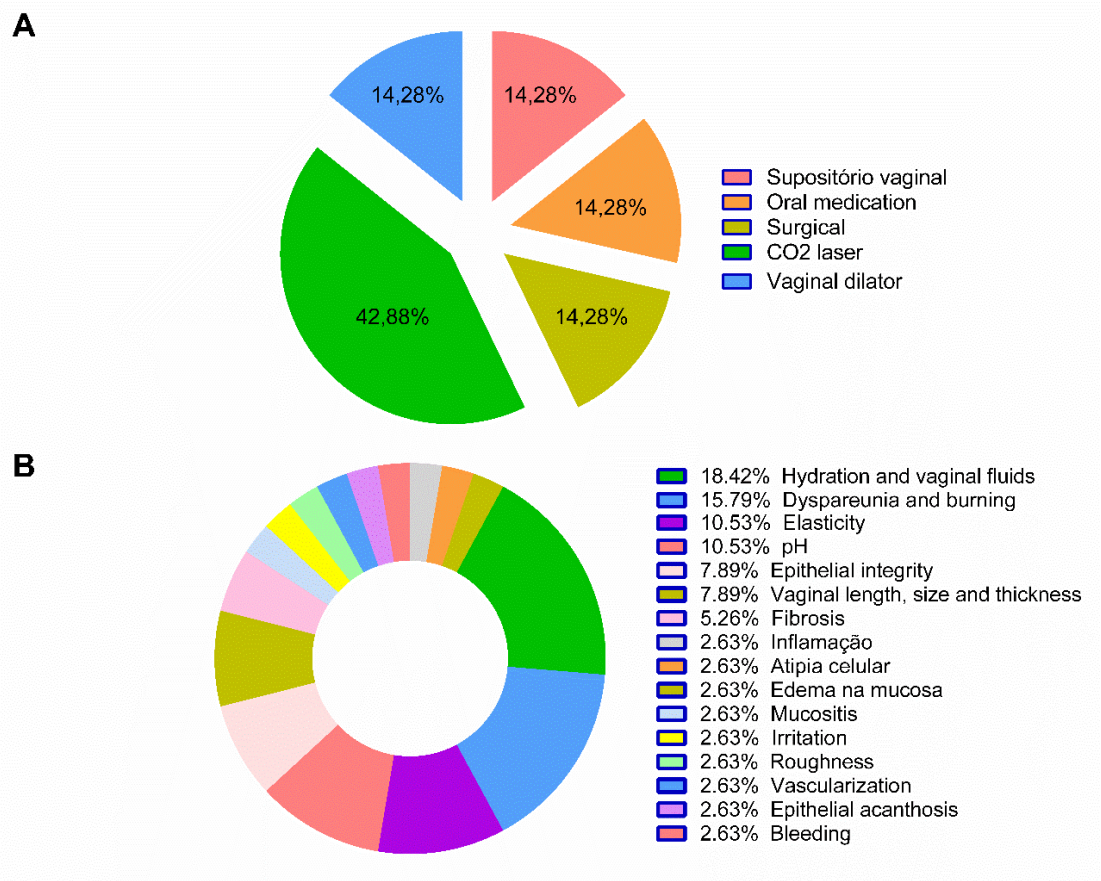

Figure 4. General characteristics related to (A) the type of treatment chosen for vaginal atrophy by the included articles and (B) outcomes.

Table 1. Specific characteristics regarding cancer treatment and the study-focused groups.

Reference	Cancer Treatment
Angioli et al. 2020	Not specified
Dinicola et al. 2015	External beam radiotherapy + Cisplatin + 5-fluorouracil

Perrone et al. 2020	External beam radiotherapy + Brachytherapy + Chemotherapy External beam radiotherapy + Brachytherapy + Chemotherapy + Surgery External beam radiotherapy + Brachytherapy + Surgery External beam radiotherapy + Chemotherapy + Surgery External beam radiotherapy + Chemotherapy External beam radiotherapy + Surgery Brachytherapy + Surgery
Quick et al. 2021	Radiotherapy Chemotherapy Surgery
Rosa et al. 2017	Radical hysterectomy + Bilateral salpingo-oophorectomy + Pelvic lymph node dissection Radical hysterectomy + Bilateral salpingo-oophorectomy + Pelvic lymph node dissection + Aortic lymph node sampling
Seror et al. 2017	Brachytherapy Chemotherapy
Quinn et al. 2023	External beam radiotherapy Brachytherapy Surgery

Table 2. Specific characteristics regarding the treatment for vaginal atrophy and the methodologies used for the evaluation of vaginal parameters, overall quality of life, sexual, emotional, and adverse effects.

Reference	**Vaginal Atrophy Treatment**	**Vaginal Parameter Assessment Methodology**	**Overall, Sexual, Emotional Quality of Life Assessment Methodology**	**Adverse Effects Assessment Methodology**
Angioli et al. 2020	Fractionated CO2 Laser	Gynecological examination + VAS	Not evaluated	Not evaluated
Dinicola et al. 2015	LMW-HA + Vitamin E + Vitamin A	Biopsy + VAS	Not evaluated	Not evaluated
Perrone et al. 2020	Non-ablative CO2 Laser	Gynecological examination + VHI	FSFI	Patient reports
Quick et al. 2021	Microfractionated CO2 Laser	Gynecological examination + VAS + VuAS	FSFI	Adverse events v4.0 (CTCAE)
Rosa et al. 2017	Ospemifene	Gynecological examination + VHI	EORTC Quality of Life Questionnaire (EORTC QLQ-CX24)	Patient reports
Seror et al. 2017	Modified Laparoscopic Davydov Colpoplasty	Gynecological examination	Not evaluated	Not evaluated

Quinn et al. 2023	Vaginal Dilator	Vaginal probe (FSFI)	(FSFI)	Not evaluated

Legend:
VAS: Vaginal Assessment Scale; VHI: Vaginal Health Index; VuAS: Vulvar Assessment Scale; FSFI: Female Sexual Function Index; EORTC: European Organisation for Research and Treatment of Cancer

Figure 5. Outcomes assessed regarding overall (A) and sexual (B) quality of life.

3.4 Parameters with Improvement after Treatment Completion and Side Effects

Regarding the impact of treatments on vulvovaginal atrophy in patients with gynecological cancer, the outcomes varied depending on the type of treatment and the

parameters analyzed in the studies (Table 3). In general, all treatments resulted in improvement in at least one parameter, whether in the analysis of vaginal changes or in parameters related to overall, sexual, or emotional quality of life, as outlined in Table 3. Concerning side effects, only one study reported adverse effects after CO2 laser treatment, while in other works, either this parameter was not assessed, or patients did not report any side effects.

Table 3. General characteristics regarding the effects of different treatments for vaginal atrophy in patients with gynecological cancer.

Reference	Intervention	Parameters with Improvement	Reported Adverse Effects
Dinicola et al. 2015	LMW-HA + Vitamin E + Vitamin A	Treatment reduced inflammation, cellular atypia, fibrosis, bleeding, pain, and mucositis	Not reported
Rosa et al. 2017	Ospemifene	Treatment increased elasticity, fluid volume, epithelial integrity, moisture, and vaginal pH; Improvement in overall health, emotional and social functioning, body image, and sexual pleasure; Reduction in scores of sexual symptom experience and concern.	No side effects reported
Seror et al. 2017	Modified laparoscopic Davydov colpoplasty	Clinical examination after four months of surgery demonstrates gratifying size and elasticity of the new vaginal cavity	No side effects reported
Angioli et al. 2020	Fractionated CO2 laser	Treatment improved dryness, dyspareunia, burning, introitus pain, and pH	No side effects reported
Perrone et al. 2020	Non-ablative CO2 laser	Treatment induced improvement in vaginal length, vaginal health index, and female sexual function index	Cystitis (1 patient) and spots (1 patient)
Quick et al. 2021	Fractionated CO2 laser	Although some patients showed improvement in some vaginal parameters, no improvement was considered statistically significant; Treatment induced improvement; Improvement in female sexual function index (orgasm and desire);	No side effects reported
Quinn et al. 2023	Vaginal dilator	Increase in vaginal length;	Vaginal discharge; Vaginal dryness; Vaginal pain; Vaginal inflammation

4. DISCUSSION

The present study summarizes and systematically characterizes the state of the art of therapeutic possibilities tested for vaginal atrophy in survivors of gynecological cancer. In general, the literature reveals five types of interventions: CO2 laser, hyaluronic acid, colpoplasty by modified Davydov laparoscopic procedure, ospemifene, and vaginal dilator. Regardless of the therapeutic approach used, all demonstrated potential application and safety for survivors of different types of gynecological cancers. Above

all, due to their use, they showed improvement in parameters related to vaginal health and the patient herself, leading to an overall improvement in general, emotional, and sexual quality of life.

The use of CO2 laser, the most frequently mentioned treatment in the included studies (42.88%), is an alternative non-hormonal approach with potential for the treatment of vulvovaginal atrophy in oncology patients, both for breast and gynecological cancers. This study demonstrated that the three included studies using this approach reported improvement in the vaginal health index (in symptoms such as dryness, dyspareunia, burning, introitus pain, pH, vaginal length, etc.). However, they did not show any significant improvement in the sexual health of the patients after the end of the analyzed period in each study (Angioli et al., 2020; Perrone et al., 2020; Quick et al., 2021).

Currently, treatments such as creams, gels, moisturizers with or without hormones, and vaginal dilators are available to combat vaginal atrophy (Alvisi et al., 2019; Miles; Johnson, 2014). However, these interventions may have some disadvantages compared to the use of CO2 laser. Topical treatments are reported to be uncomfortable and difficult to adhere to due to the method of application (Minkin et al., 2013). In another scenario, estrogen-based treatments may not be very responsive for patients who have undergone radiation therapy, as this procedure reduces receptors for this hormone (Miles; Johnson, 2014; Perrone et al., 2020).

No articles were found comparing CO2 laser and other treatments in patients with gynecological cancer and vulvovaginal atrophy. In this regard, in postmenopausal women with GSM (genitourinary syndrome of menopause), topical estrogen therapy or CO2 laser treatment were considered equivalent in improving GSM symptoms (Paraiso et al., 2020). In another study, still in postmenopausal patients, it was demonstrated that CO2 laser therapy associated with topical estriol resulted in improvement in vaginal dryness and dyspareunia, while estriol monotherapy resulted in worse outcomes (Cruz et al., 2018). Additionally, the use of CO2 laser was shown to be more effective than some topical treatments such as promestriene cream or lubricants in postmenopausal women (Gaspar et al., 2017; Politano et al., 2019).

In fact, the use of CO2 laser induces the restoration of the vaginal epithelium, with ultrastructural changes such as thickening of the stratified squamous epithelium, increased collagen and mucopolysaccharides support, increased glycogen supply in epithelial cells, increased fibroblasts, increased local vascularization, and the presence of

subepithelial papillae (Benini et al., 2022; Gambacciani; Palacios, 2017). Moreover, no treatment induced serious adverse effects for the patients, suggesting a safe therapeutic scheme and impact. However, further studies focused on morphological and molecular aspects are needed for a better understanding of the biological mechanisms.

Another form of non-hormonal intervention is based on the vaginal administration of hyaluronic acid and vitamins A and E. An included article focused on the use of this type of treatment for patients with cervical cancer. In this study, the treatment was able to reduce inflammation, cellular atypia, fibrosis, bleeding, pain, and mucositis, demonstrating that this type of intervention can be used in the context of vaginal atrophy in patients with cervical cancer (Dinicola et al., 2015).

Clinical studies demonstrate that formulations of hyaluronic acid such as liquids, gels, or suppositories can be used to reduce vaginal pain, dyspareunia, vaginal pH, vaginal dryness, vaginal itching, and burning sensation, consequently improving the vaginal health index and reducing vaginal atrophy (De Seta et al., 2021; Nappi et al., 2020). Gold et al. (2013) demonstrated that this intervention had an impact similar to CO2 laser treatment in the same group (Gold et al., 2023). Another example reported in the literature (postmenopausal breast cancer survivors) is the combination of hyaluronic acid with platelet concentrate for intramucosal administration (vaginal or vulvar). In this case, the treatment improved vaginal dryness, dyspareunia, and enhanced hydration and integrity of the vaginal epithelium, consequently improving the vaginal health index (Hersant et al., 2018). Hyaluronic acid is a glycosaminoglycan present and essential in the extracellular matrix, with a crucial lubricating and hydrating function. Widely known for its water-binding capacity, which is associated with its hydrating ability in the body (Buzzaccarini et al., 2021). By associating with water in the tissue, this phenomenon can improve vaginal dryness in oncological patients.

Ospemifene was also used with the aim of improving vaginal atrophy. Unlike the treatments mentioned earlier, ospemifene is an agonist/antagonist of the estrogen receptor, also known as a selective estrogen receptor modulator (SERM) (De Rosa et al., 2017). It is indicated for the treatment of moderate to severe vaginal atrophy in postmenopausal women, especially for those who have contraindications or are not candidates for local estrogen therapy (Palacios, 2020). The included study demonstrated that this intervention, increased elasticity, fluid volume, epithelial integrity, moisture, and vaginal pH. Moreover, it was also able to improve overall health, emotional and social functioning, body image, and sexual pleasure (De Rosa et al., 2017).

Indeed, ospemifene promotes improvement in vaginal pH, vaginal dryness, petechiae, paleness, friability, and redness of the vaginal mucosa are also parameters for which the treatment has been reported to be effective (Goldstein et al., 2014; Portman et al., 2014). Additionally, this intervention is capable of inducing collagen production (preferably type 1) in both the vaginal mucosa and vestibule, which has been associated with increased resistance and strength of the vaginal tissue (Alvisi et al., 2018). Ospemifene treatment reduce pain during sexual intercourse and increasing desire and arousal (Constantine et al., 2015; Schiavi et al., 2018). Therefore, ospemifene can be considered as a treatment for survivors of gynecological cancers with vulvovaginal atrophy.

Only one surgical procedure was used in the studies included in this work: modified laparoscopic Davydov colpoplasty. In this case report, a 36-year-old survivor of vaginal cancer, who underwent chemotherapy and radiotherapy, reported significant vaginal atrophy with vaginal shortening (Seror et al., 2017). The Davydov procedure involves creating a neovagina using a part of the pelvic peritoneum (Davydov; Zhvitiashvili, 1974), followed by bilateral nymphoplasty of the small lips to create the lower cutaneous part of the neovagina. In this study, sexual function was not assessed because the patient had not resumed sexual activity at the first post-procedure consultation (4 months) (Seror et al., 2017).

Therapy based on vaginal dilators has also been used in patients with endometrial cancer during the process of radiotherapy or surgery. The study included in this work demonstrated that the use of vaginal dilators induces the maintenance of vaginal length and an increase in sexual satisfaction, both in women who underwent surgery alone and in women who received adjuvant radiotherapy (Quinn et al., 2023). However, there is still much discussion about how this type of intervention should be used. Miles and Johnson (2014) concluded that there is data suggesting that dilation may be harmful, with a rare possibility of vaginal rupture. (Miles; Johnson, 2014). Conversely, other studies show that the use of dilators, even minimally, reduces vaginal stenosis after radiotherapy (Bahng et al., 2012; Gondi et al., 2012; Law et al., 2015) and improves sexual quality of life (Quinn et al., 2023).

Although the articles represent potential treatments for GSM, they have limitations: (1) a small number of included patients, (2) analysis of long-term side effects, (3) short intervention time, (4) lack of emotional, sexual, and social analysis, (5) methodologies consisting only of a clinical perspective and a lack of histological and

molecular analyses, and (6) analysis of short-term outcomes. In addition, the extraction and interpretation of the evaluated outcomes are complex due to the lack of standardization of terms found in the included studies.

5. CONCLUSION

All the treatments mentioned here (CO2 laser, hyaluronic acid, modified laparoscopic Davydov colpoplasty, ospemifene, and vaginal dilator) hold potential in the context of the study, whether by improving parameters of vaginal health or sexual and emotional well-being. However, further studies are needed for the development of treatments for vaginal atrophy in gynecologic oncology patients.

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5. CONCLUSÕES

A partir dos resultados dos presentes estudos incluídos nesse trabalho, é possível visualizar que mais estudos são necessários para o desenvolvimento de tratamentos para atrofia vaginal em pacientes oncológicas ginecológicas. Positivamente, todos os tratamentos citados, aqui (laser de CO2, ácido hialurônico, colpoplastia por procedimento laparoscópico de Davydov modificado, ospemifeno e dilatador vaginal) representam potencial no contexto do trabalho, seja melhorando nos parâmetros da saúde vaginal, ou e/ou da saúde sexual e/ou emocional. Entretanto, alguns dos estudos possuem limitações: (1) pequeno número de pacientes incluídas, (2) análise de efeitos colaterais a longo prazo, (3) curto tempo de intervenção, (4) falta de análise emocional, sexual e social, (5) metodologias que consistem apenas em um olhar clínico e falta de análises histológicas e moleculares e (6) análise de desfechos em curto prazo. Além disso, a extração e interpretação dos desfechos avaliados se faz complexa, devido a falta de padronização dos termos encontrados nos estudos incluídos.

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ANEXOS – MATERIAL SUPLEMENTAR

S1. Database list, search strategy and number of articles found.

Database	Search strategy	Number of articles
PubMed	#1 Search: Vaginal Atrophy (“vagina”[MeSH Terms] OR “vagina”[All Fields] OR “vaginal”[All Fields] OR “vaginally”[All Fields] OR “vaginals”[All Fields] OR “vaginitis”[MeSH Terms] OR “vaginitis”[All Fields] OR “vaginitides”[All Fields]) AND (“atrophie”[All Fields] OR “atrophy”[MeSH Terms] OR “atrophy”[All Fields] OR “atrophied”[All Fields] OR “atrophies”[All Fields] OR “atrophying”[All Fields])	2011
	#2 Search: cancer “cancer s”[All Fields] OR “cancerated”[All Fields] OR “canceration”[All Fields] OR “cancerization”[All Fields] OR “cancerized”[All Fields] OR “cancerous”[All Fields] OR “neoplasms”[MeSH Terms] OR “neoplasms”[All Fields] OR “cancer”[All Fields] OR “cancers”[All Fields]	4832335
	#3 Search: treatment “therapeutics”[MeSH Terms] OR “therapeutics”[All Fields] OR “treatments”[All Fields] OR “therapy”[MeSH Subheading] OR “therapy”[All Fields] OR “treatment”[All Fields] OR “treatment s"[All F”elds])	13007109
	#1 AND #2 AND #3 Search: ((Vaginal Atrophy) AND (cancer)) AND (treatment) (“vagina”[MeSH Terms] OR “vagina”[All Fields] OR “vaginal”[All Fields] OR “vaginally”[All Fields] OR “vaginals”[All Fields] OR “vaginitis”[MeSH Terms] OR “vaginitis”[All Fields] OR “vaginitides”[All Fields]) AND (“atrophie”[All Fields] OR “atrophy”[MeSH Terms] OR “atrophy”[All Fields] OR “atrophied”[All Fields] OR “atrophies”[All Fields] OR “atrophying”[All Fields]) AND (“cancer s”[All Fields] OR “cancerated”[All Fields] OR “canceration”[All Fields] OR “cancerization”[All Fields] OR “cancerized”[All Fields] OR	447

	"cancerous"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "cancers"[All Fields]) AND ("therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "treatments"[All Fields] OR "therapy"[MeSH Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "treatment s"["ll Fields]"	
Web of Science	#1 ALL=(Vaginal Atrophy)	1866
	#2 ALL=(cancer)	4426499
	#3 ALL=(treatment)	6135692
	Combination: #1 AND #2 AND #3	439

S2. Tracking of articles read in full and final status with justification, if excluded.

Article title	**Final situation**	**Reference**
Chemotherapy-induced dyspareunia: a case study of vaginal mucositis and pegylated liposomal doxorubicin injection in advanced stage ovarian carcinoma	Excluded (Does not evaluate parameters related to vaginal atrophy)	Krychman et al 2004
Prospective multi-center trial utilizing electronic brachytherapy for the treatment of endometrial cancer	Excluded (Does not evaluate parameters related to vaginal atrophy)	Dickler et al et al 2010
Effect of one-month treatment with vaginal promestriene on serum estrone sulfate levels in cancer patients: a pilot study	Excluded (Does not evaluate parameters related to vaginal atrophy)	Pup et al 2012
Hyaluronic acid and vitamins are effective in reducing vaginal atrophy in women receiving radiotherapy	Included	Dinicola et al 2015
Baseline characteristics and concerns of female cancer patients/survivors seeking treatment at a Female Sexual Medicine Program	Excluded (Does not evaluate parameters related to vaginal atrophy)	Carter et al 2015
Impact of Ospemifene on Quality of Life and Sexual Function in Young Survivors of Cervical Cancer: A Prospective Study.	Included	De Rosa et al 2017
Colpoplasty by laparoscopic modified Davydov's procedure.	Included	Seror et al 2017
Vaginal and sexual health treatment strategies within a female sexual medicine program for cancer patients and survivors	Excluded (Did not separate gynecological cancer group from	Carter et al 2017

	breast cancer group)	
Intravaginal Testosterone Improves Sexual Satisfaction and Vaginal Symptoms Associated With Aromatase Inhibitors.	Excluded (Does not focus on gynecological cancer)	Davis et al 2018
Effects of Vulvovaginal Laser Therapy on Postmenopausal Vaginal Atrophy: A Prospective Study	Excluded (Did not separate gynecological cancer group from breast cancer group)	Singh et al 2019
A study protocol of vaginal laser therapy in gynecological cancer survivors.	Excluded (Does not evaluate parameters related to vaginal atrophy)	Athanasiou et al 2020
Effectiveness of CO(2) laser on urogenital syndrome in women with a previous gynecological neoplasia: a multicentric study.	Included	Angioli et al 2020
Results of a Phase I-II Study on Laser Therapy for Vaginal Side Effects after Radiotherapy for Cancer of Uterine Cervix or Endometrium.	Included	Perrone et al 2020
Efficacy of fractional CO2 laser treatment in postmenopausal women with genitourinary syndrome: a multicenter study	Excluded (Did not separate gynecological cancer group from breast cancer group)	Filippini et al 2020
Vaginal estrogen use for genitourinary symptoms in women with a history of uterine, cervical, or ovarian carcinoma	Excluded (Does not evaluate parameters related to vaginal atrophy)	Chambers et al 2020
Vaginal radiofrecuency for the treatment of genital atrophy in patients with oncological history in a public hospital. Life after cancer	Excluded (Summary)	Berrio et al 2020
Pilot study of fractional CO(2) laser therapy for genitourinary syndrome of menopause in gynecologic cancer survivors.	Included	Quick et al 2021
A single-arm, prospective trial investigating the effectiveness of a non-hormonal vaginal moisturizer containing hyaluronic acid in postmenopausal cancer survivors.	Excluded (Did not separate gynecological cancer group from breast cancer group)	Carter et al 2021
Topical estrogen, testosterone, and vaginal dilator in the prevention of vaginal stenosis after radiotherapy in women with cervical cancer: a randomized clinical trial	Excluded (Does not evaluate parameters related to vaginal atrophy)	Martins et al 2021
Intravaginal dehydroepiandrosterone for genitourinary symptoms of the menopause: Is the evidence sufficient?	Excluded (Article not available)	Kearley-Shiers et al 2022
Change in vaginal length and sexual function in women who undergo surgery Â± radiation therapy for endometrial cancer.	Included	Quinn et al 2023