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Diogo Gonçalo Silva Freitas

Non-invasive treatment modalities for Vaginal Intraepithelial Neoplasia (VaIN)

Modalidades terapêuticas não invasivas no tratamento da Neoplasia Intraepitelial Vaginal (NIVA)

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DESIGNAÇÃO DA ÁREA DO PROJECTO

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Non-invasive treatment modalities for Vaginal Intraepithelial Neoplasia (VAIN)

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Ao meu Avô,

NON-INVASIVE TREATMENT MODALITIES FOR VAGINAL INTRAEPITHELIAL NEOPLASIA (VAIN)

MODALIDADES TERAPÊUTICAS NÃO INVASIVAS NO TRATAMENTO DA NEOPLASIA INTRAEPITELIAL VAGINAL (NIVA)

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ABSTRACT

Laser and Vaginal Brachytherapy showed a maximum 93% and 100% Cure Rate (CR), respectively, with a significant Persistence Rate (PR) up to 100% and 0-59% Recurrence Rate (RR). Laser has few complications and is indicated for sexually active women. Brachytherapy, due to toxicity, should be reserved for high-grade and refractory lesions. Imiquimod and 5-Flouorouracil revealed a 25-82% CR, 26-75% PR, 6-94% RR and are indicated in multifocal lesions. Expectant management has 44-60% CR with PR and RR up to 50%.

In contrast to low-grade lesions, high-grade lesions require treatment which should be selected depending on its characteristics and the patient's.

Keywords: Vaginal Neoplasms; Vaginal Intraepithelial Neoplasia; VaIN; Treatment;

INTRODUCTION

Vaginal Intraepithelial Neoplasia (VaIN) accounts for 0.4% to 1% of all intraepithelial neoplasias of the lower genital tract, with an incidence of approximately 0.2-0.3 cases/100.000 women/year [1–5], affecting women from their late teens onwards, predominantly peri- or postmenopausal [1,6].

VaIN lesions are defined as squamous cell atypia without stromal invasion and graded as vaginal low grade squamous intraepithelial lesion (vaginal LSIL), which includes VaIN1, and vaginal high grade squamous intraepithelial lesion (vaginal HSIL), which includes VaIN2 and 3 [7]. VaIN1 and 2 involve the lower one-third and two-thirds of the epithelium, respectively, and VaIN3 involves more than two-thirds of the epithelium. [1,4,7].

The main potential risk factor is Human Papillomavirus (HPV) infection with a prevalence of 98.5% in VaIN1 and 92.6% in VaIN2 or VaIN3 [8]. Other risk factors are prior pelvic radiation, history of genital condylomata, prior hysterectomy for cervical dysplasia, history of genital intraepithelial neoplasia, immunosuppression, history of *in utero* exposure to diethylstilbestrol and smoking [2,9–11].

VaIN is commonly identified as a multifocal lesion, predominantly in the upper third of vagina [3,5,12,13]. The majority of the patients are asymptomatic, just few refer: abnormal vaginal discharge or bleeding and vulvar or vaginal itching [3,5,14].

Vaginal LSIL has a spontaneous regression of over 50% [1] and vaginal HSIL is a cancer precursor with risk of progression to invasive vaginal carcinoma up to 12% [3,4,15].

The main goal of this review is to identify and characterize non-invasive treatment modalities for VaIN in order to evaluate the outcome in terms of cure, persistence and recurrence rate and HPV eradication.

MATERIALS AND METHODS

We conducted a literature search in four electronic databases: *MEDLINE/PUBMED, The Cochrane Librabry, Royal College of Obstetricians and Gynaecologists (RCOG)* and *American College of Obstetricians and Gynaecologists (ACOG)* using the following query: (Vaginal neoplasms[MeSH Terms] OR VaIN[Title/Abstract] OR (Vaginal intraepithelial[Title/Abstract] AND (Neoplas*[Title/Abstract] OR Cancer[Title/Abstract]))) AND (Therapy[Title/Abstract] OR Treatment[Title/Abstract] OR Intervention[Title/Abstract] OR Therapeutics[Title/Abstract]).

We restricted our search to human studies, published in English or Portuguese, from 01/01/2014 to 18/09/2019. Exclusion criteria established were pregnant women, HIV+ individuals and level of evidence above III.

Also, in order to provide more information about topical treatment, we included two drug information leaflets from Valeant Pharmaceuticals, from North America.

RESULTS

This review is based on a total of 23 studies: three of level 1, three of level 2 and seventeen of level 3, according to the Oxford Centre for Evidence – Based Medicine Levels of Evidence. Our search strategy is illustrated in Figure 1.

ABLATIVE TREATMENT

CO_2 LASER VAPORISATION – TABLE I [1,2,10,13,16–19]

The most common contemporary treatment for VaIN is laser vaporisation [1]. This procedure can be classified as excisional or ablative.

This technique is colposcopically guided and has short mean operation time of 42 minutes with minimal low blood loss (approximately 5 ml) [2].

Overall studies suggest that laser vaporisation is a feasible and valuable modality for all VaIN patients as primary treatment (Cure Rate 0-90%, 6 studies, total sample size = 981) or as treatment for recurrent lesions (Cure Rate 54.5-93%, 2 studies, total sample size = 82) and a recurrence rate as initial treatment of 0 to 59,1% (6 studies, total sample size = 981) and as secondary treatment 0 to 6.3% (2 studies, total sample size = 82) [1,2,10,13,16–19] .

The results of the studies are heterogenous, regarding: laser characteristics, sample sizes and study methodology. Seven studies are type III level of evidence (N=971 treated with laser). The main limitations are the retrospective and observational nature. Nevertheless, a relatively large sample allow us to provide a comprehensive analysis of this modality in the treatment of VaIN. Only one study is type I with a small sample (N=10 treated with laser). Other limitations include small sample size and a short follow-up (between 16 weeks to 72.3 months).

It is a safe procedure with few complications, high precision, and a minimal impact on psychological and sexual function [2]. Therefore, in sexually active young women, minimally invasive therapies like laser would be one of the first choices [2].

Due to surgery risk, patients with comorbidities or elderly women with notable vaginal dystrophy, where topical estrogen therapy is contraindicated, can also benefit from ablative procedures [20].

Ablative therapies are suitable for multifocal lesions when compared to excisional procedures [13]. However, it is not indicated for regions with difficult access, such as vaginal vault scars or vaginal recess' or angles [20]. Also, ablation precludes definitive tissue diagnosis, meaning that, it is important to exclude invasion through biopsies before treatment [20]. When invasion is suspected or cannot be excluded, we must not use laser therapy [20].

In these studies, the ablative technique used varied in laser characteristics. Laser power oscillated between 6 to 43 watts, as a continuous beam applied to all visible lesions, with a diameter spot between 0.5 to 2 mm and a depth of 0.1 to 3 mm [1,2,13,16–19]. It was reported that epithelial destruction to a depth of 1.5 mm should be sufficient to destroy VaIN lesions with tissue and structures preservation [2].

Overall, this procedure has a mean complication rate of 8% [2]. *Bogani et al*., 2018 described two severe local complications among 169 patients under ablative treatment: vaginal vault perforation requiring laparoscopic inspection with vaginal vault suture and one postoperative bleeding requiring hemostasis [18]. Local pain, vaginitis and stricture of the upper vagina after multiple rounds was also reported [2,19]. Systemic complications are rare. There is no need for adjustment in patients with liver and renal failure.

MEDICAL TREATMENTS

HIGH-DOSE-RATE (HDR) VAGINAL BRACHYTHERAPY (VBT) - TABLE II [13,14,21,22]

HDR-VBT is a type of internal radiation therapy where radioactive material, through a predetermined type of applicator, is placed directly into the vaginal canal restricting radiation to surrounding areas. Single channel-vaginal cylinder is the most applicator used to irradiate the whole length of the vagina in patients [21,22] With the advantage of treating the entire vagina uniformly, it can be useful in multifocal lesions, minding its correlation with late toxicity, such as urethral necrosis. [22]. Thus, the length of the irradiated vagina should be minimal and include VaIN lesions only [21]. Mere cases used the vaginal cylinder with an intrauterine catheter and interstitial (needles in cervix after supravaginal hysterectomy) [21].

Few studies (RS) are described in the literature, that reports application of HDR-VBT as a VaIN therapeutic tool [13,14,21,22]. VaIN3 was the most common histological indication. They include a total of 58 patients and observed a cure rate between 50% to 100% and recurrence and persistence rate between 0% to 50%.

Although these studies have described the effectiveness of HDR-BT, the variability in the cure rate might be explained by the differences in radiation, techniques, population, or duration of follow-up.

In spite of high cure rates, and most due to its toxicity, HDR-BT should be reserved for highly selected patients: high grade and resistant VaIN to conventional medical and surgical modalities [21]. The need of sexual function preservation should be considered as a contraindication [21]. HDR-VBT limits any future brachytherapy and excisional procedures for recurrences, because of the tissue scarring, frequently due to damage of blood vessels and connective tissue.

Zolciak-Siwinska et al., 2015 found that only dose affects the toxicity (p=0.05). Irradiation of VaIN by the scheme 35-37.5 Gy in 5 fractions given in four weeks seems to be too

toxic [21]. The use of increased dose per fraction can lead to more late normal tissue toxicity than an increase in the tumor cell apoptosis [21]. *Song et al.,* 2014 described that 40 Gy in 8 fractions given during four weeks at median 0.2 cm depth from vaginal surface was also too toxic. [22].

The depth of vaginal surface penetrated with radiation remains an important issue. Although there is no statistical significance, the prescription point in failure was lower (mean: 0.11cm) when compared to non-recurrent patients (mean: 0.26cm) [22]. The depth from vaginal surface for dose prescription should be 0.2-0.3 cm, but not deeper, because of the organ toxicity [21].

The use of HDR-VBT generally has acute and late toxicity [21,22]. *Zolciak-Siwinska et al.,* 2015 and *Song et al.,* 2014 proved minimal acute toxicity in the vagina, rectum and bladder (N=54) [21,22]. Acute reactions included transient stinging of vaginal mucosa (15%), frequency/dysuria (14.7%), frequent defecation (5.9%) and vaginal discharge (2.9%) [21,22]. Late side effects included alteration of libido (75%), vaginal discharge (10%), dryness/dyspareunia (35%), mucositis (30%), vaginal stenosis (35%), vaginitis (20%), cystitis (2.9%) and rectal bleeding (5.9%) [21,22]. Although none of these studies have shown secondary cancers due to the use of intrapelvic radiation, it is important to highlight the existing risk.

Zolciak-Siwinska et al., 2015 described decreased libido in most of the patients [21]. *Song et al.,* 2014 (N=20) observed fifteen cases of late toxicity, predominantly dyspareunia/stenosis in twelve patients [22], rectal bleeding occurred in two patients and one patient had cystitis [22].

The multichannel applicator gives the chance to mould the dose, not only to prevent complications, but also to avoid overdose [21]. Therefore, it is advised 3-D planning based on CT or MRI [21]. The use of vaginal dilator, after HDR-BT sessions, could prevent stenosis, the most serious complication for vaginal function [21].

TOPICAL TREATMENTS

IMIQUIMOD – TABLE III [1,5]

Topical 5% imiquimod is a toll-like receptor 7 agonist that stimulates local immune response, promoting the release of pro-inflammatory cytokines such as interferon-α and interferon-γ, which initiate chemokines production that induce innate and T-helper cell immunity [1,5].

Two studies (one RCT, N=10 patients under Imiquimod, level I of evidence, and a SR and MA (N=94), type II level of evidence, enrolled prospective and retrospective studies and a RCT with minimal heterogeneity) showed a imiquimod cure rate of 70 to 76.5%, persistence rate around 20%, recurrence rate of 5.6% and HPV eradication between 52.5 to 63% [1,5].

Imiquimod is an effective and safe medical treatment, which can lead to less aggressive, invasive and morbid interventions, especially among young women with multifocal lesions or postmenopausal women [5].

HPV clearance is an important factor associated with treatment effectiveness, since persistent HPV infection is correlated with recurrent disease and progression to cancer [5]. Thus, imiquimod has additional value as treatment modality.

It can be self-administered by patients as vaginal suppositories or through an applicator or even can be administered under direct colposcopic guidance [1,5]. To the best of our knowledge, 5% Imiquimod is the only dosage form proved to be effective in the treatment of VaIN. Formulation may vary between 0.25 and 12.5 mg between 1 to 3 times a week over 3 to 12 weeks [5]. It should be applied before sleeping hours and left on for 6 to 10 hours, after which time the cream should be removed by washing the area with mild soap and water [23].

The frequency of side effects differs according to the degree of inflammation associated, the dose, the number of weekly applications, product formulations and individual sensitivity [23].

According to *Tainio et al., 2016,* Imiquimod 5% is likely to cause local symptoms such as irritation of vagina and vulva (60%) or even vulvar ulceration (10%) and systemic symptoms such flu-like symptoms (90%) (fever, malaise, rigor, abdominal cramps and diarrhea) and lower abdominal pain (30%) [1,5].

Valeant Pharmaceuticals, from North America, described a number of vast adverse reactions, mostly local reactions, such as erythema (65%), erosion (31%), excoriation (18%), edema (18%), ulcerations (8%), induration (5%) and vesicles (3%) [23]. Sensation of itching (32%), burning (26%), pain (8%) and soreness (3%) may also be presented [23]. It can also cause fungal infection (11%) [23]. Systemic reactions can emerge such as gastrointestinal reactions (diarrhea 1-3%, nausea 1-4%, anorexia <3%, vomiting 1%, abdominal pain and dyspepsia), musculoskeletal reactions (fatigue, arthralgia, myalgia – 1%), central and peripheral nervous reactions (Headache – 4%), respiratory symptoms (Influenza-like symptoms - 3%) and fever (<3%) [23]. There are other reported adverse reactions, although very rare, such as angioedema, cardiovascular reactions (arrhythmias, chest pain, ischemia, myocardial infarction, syncope, cardiac failure, cardiomyopathy and pulmonary edema), endocrine reactions (thyroiditis), hematological reactions (pancytopenia, idiopathic thrombocytopenic purpura, lymphoma), hepatic reactions (abnormal liver function), neuropsychiatric (agitation, convulsions, depression, insomnia, suicide, cerebrovascular accident, paresis and multiple sclerosis aggravation), respiratory symptoms (dyspnea), urinary reactions (proteinuria, dysuria, urinary retention) and vascular reactions (*Henoch-Schölein* purpura syndrome) [23].

Imiquimod may weaken condoms and vaginal diaphragms. It appears to have low risk in pregnant women; however, it should be avoided until additional data available. It is not known if imiquimod is present in breast milk [23].

There is no need for adjustment in patients with liver and renal failure. Generally, it is well-tolerated. When patients have local skin reactions, we can temporarily interrupt treatment of up to several days [23] or reduce the treatment dose to half.

5-FLOUOROURACIL (5-FU) – TABLE IV [4,10,13,16,17]

5-FU is a cytotoxic antimetabolite drug, which acts by misincorporation of fluoronucleotides into RNA and DNA, and nucleotide synthetic enzyme thymidylate synthase inhibition [4].

Studies (one SR with MA, II level of evidence, N=358, and 4 RS, N=177, type III level of evidence) demonstrate the feasibility and efficacy of 5-FU as initial or secondary treatment in VaIN with effectiveness in low or high-grade VaIN: primary treatment with a cure rate between 25% to 82.18% (5 studies, total sample size = 535), a persistence rate between 25.5% to 75% and a recurrence rate between 16.42% to 94.4% [4,10,13,16,17]. As recurrence treatment these studies observed a cure rate between 62% to 72.32% (2 studies, total sample size = 16). It was also reported a HPV eradication of 28% [4,16].

Studies limitations include heterogeneity regarding dose, follow-up and mode of application.

This topical chemotherapeutic agent is applied to the entire vagina and targets solely the abnormal epithelium with advantage of treatment uniformity and secures coverage of any subclinical disease. Therefore, 5-FU is an ideal treatment option for young women with multifocal disease or women with recurrent disease ,especially after surgical approach [4].

Intravaginal 5-FU cream can have different therapeutic regimens: dose between 0.33 and 5 g, daily or once to twice a week, during 2 weeks to 3 months. The 5% cream is the most frequent protocol used, but also 20% cream on a tampon daily for 5 days every 4 weeks is described.

Overall, 5-FU was well tolerated with low evidence of systemic toxicity (6% systemic absorption) [24]. One of the studies showed a non-anaphylactic “allergic reaction” (2%). Most of them reported local discomfort (due to inflammation or epithelial erosion) [4], vaginal discharge (2%) and irritation and dyspareunia (12%) [4,16].

Valeant Pharmaceuticals, from North America, also reported local reactions as the most common side effects, such as burning, crusting, pruritus, scarring, rash, soreness and ulceration [24]. Systemic effects was also described such as central nervous system effects (emotional upset, insomnia, irritability), gastrointestinal effects (stomatitis, medicinal taste), hematological side effects (leukocytosis was the most common, eosinophilia, thrombocytopenia, toxic granulation), skin alterations (swelling, telangiectasia, urticaria, skin rash) and infection by Herpes Simplex [24].

This drug is associated with miscarriage and birth defect (ventricular septal defect), therefore is contraindicated in pregnancy [24]. Although there is no evidence of its presence in breast milk, it should be discontinue during breastfeeding [24].

There is no need for adjustment in cases of liver and renal failure. Those who experience side effects usually stop treatment and restart after symptomatic improvement, usually a week later [4], but patients with delayed-type hypersensitivity reactions (severe pruritus or eczema) must discontinue immediately [24]. Also, the use of zinc cream to protect external genitalia or lower 5-FU dose could decrease severity and frequency of side effects, increasing better adherence and fewer discontinuation rates [4]. However, people with hypersensitivity to 5-FU and dihydropyrimidine dehydrogenase (DPD) enzyme deficiency should not use it [24].

EXPECTANT MANAGEMENT - TABLE V [1,10,13,14]

Four studies report results regarding expectant management. Although one of the studies is a type I level of evidence (N=9), the others three (N=142) are type III level of evidence. Therefore, due to the retrospective nature of those studies, small sample size and short follow-up period conclusions are limited.

According to these studies (N=151), expectant management evidenced a cure rate 44.4% to 60%, persistence rate of 12.5%-50% and recurrence rate of 16%-50% [1,10,13,14].

Most authors suggest that patients with VaIN1 should be under surveillance because most lesions regress spontaneously [2]. Treatment of VaIN1 lesions remains a controversial issue.

In opposition to high grade VaIN, mainly due to the high risk of progression and risk of invasive vaginal carcinoma, most of the authors prefer ablative or excisional therapies as a treatment modality [1,10,13,14].

DISCUSSION – TABLE VI

Treatment of low-grade VaIN lesions remains controversial and expectant management can be a valid therapeutic option, due to usual spontaneous regression rate of 50% [1]. In contrast, high-grade VaIN requires active treatment, but still with no consensus about the ideal treatment modality [18].

A number of factors, such as age and patient comorbidities, location and number of lesions, sexual function preservation and physician's experience, need to be considered when treatment is being decided [18].

Non-invasive therapies are a relevant choice in high-grade VaIN, particularly in case of young women where vaginal length and function should be preserved or when multifocal lesions and multiple recurrences are present [4]. In case of persistence or multiple recurrence associated with high-risk surgical morbidity, more aggressive techniques such HDR-BT should be considered.

In addition, the use of non-invasive modalities is associated with an increased HPV clearance. Treatment options targeting on HPV would be more effective and decrease the risk for recurrent disease.

We consider that VaIN itself is not a localized focal disease, but an inferior genital tract disease and should always be handled as such, from a medical point of view. Therefore, once VaIN is confirmed, we need to be concerned whether prophylactic treatment of the remaining vagina should be included or not and be in mind HPV persistence with its oncological potential [25,26].

We must highlight the discrepancy between studies about time interval that differentiates persistence and recurrence. Furthermore, small sample sizes and treatment and patients' characteristics heterogeneity may lead to risks of bias that might reduce the evidence credibility of the analysis.

There are no conflicts of interest.

The reading and analysis of the articles was done by the first author, and his work was reviewed and discussed with the second author whenever doubts arose.

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ATTACHMENTS

Query: “(Vaginal neoplasms[MeSH Terms] OR VaIN[Title/Abstract] OR (Vaginal intraepithelial[Title/Abstract] AND (Neoplas*[Title/Abstract] OR Cancer[Title/Abstract]))) AND (Therapy[Title/Abstract] OR Treatment[Title/Abstract] OR Intervention[Title/Abstract] OR Therapeutics[Title/Abstract])”

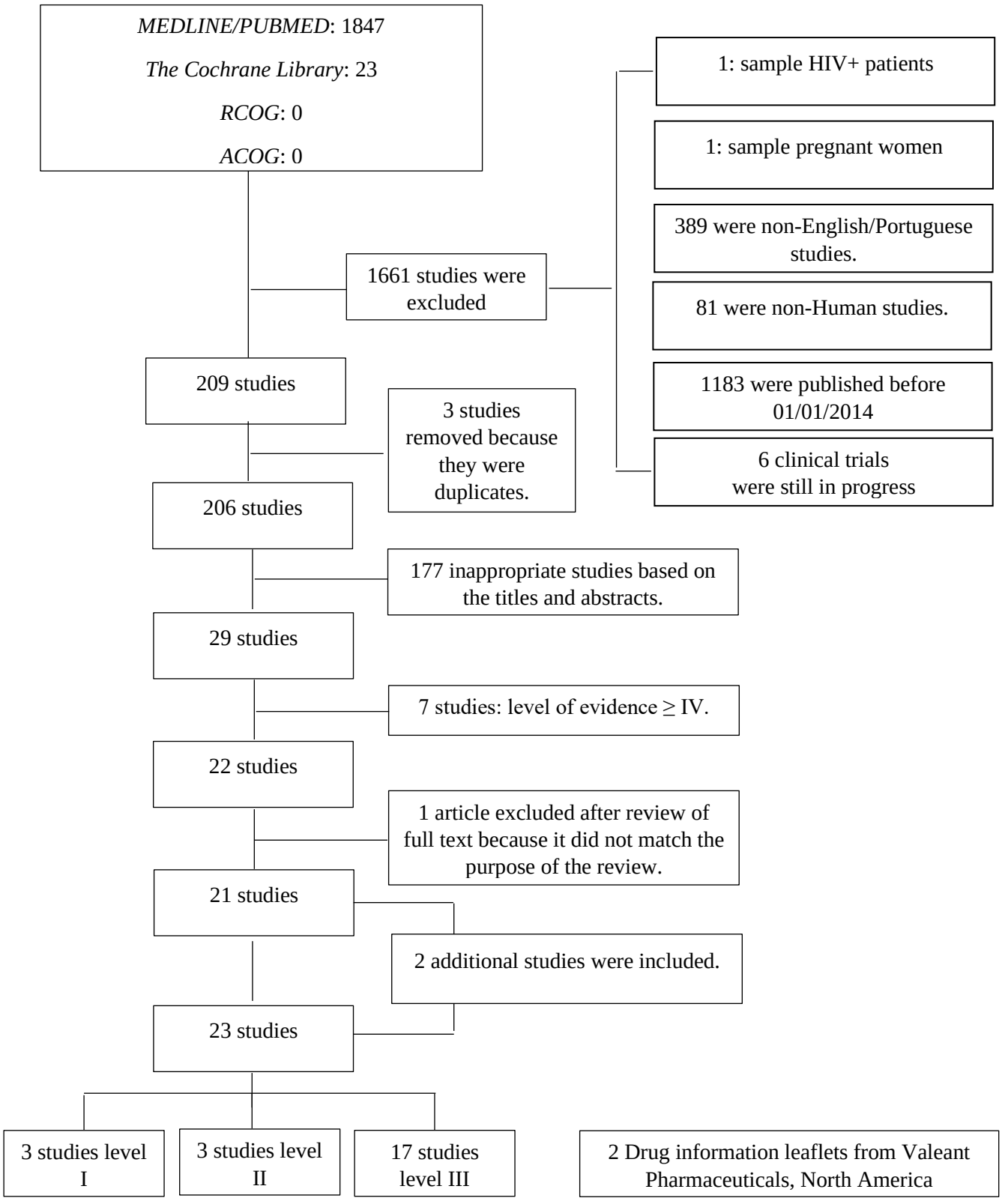

Figure 1. Flowchart of literature selection process.

TABLE I [1,2,10,13,16–19]– ABLATIVE TREATMENT - CO_2 LASER VAPORISATION

TREATMENT MODALITIES		Articles	Type of evidence	N	CR	PR	RR	HPVe	Technique	CIs	LE
ABLATIVE	CO_2 LASER VAPORISATION	*Tainio et al.*, 2016	I	10	90%	0%	NR	11%	6-12W, 2 mm margins, 2mm depth	Inability to visualize the area to be treated (ex. lesion localized on the vaginal vault scar or hidden in the recess of its angles); Preoperative histology findings indicative of malignancy;	NR
		Piovano et al., 2015	III	285	IT:75% RT:93%	NR	IT:25% RT:6.3%	NR	25-43W until 1.5-2 mm depth		NR
		Hodeib et al., 2016	III	14	57%	42.9%		NR	NR		NR
		Kim et al., 2018	III	347	74%	12.4%	11%	NR	NR		NR
		Fiascone et al., 2017	III	22	41%	59.1%		ND	NR		NR
		Bogani et al., 2019	III	95	NR	NR	53.7%	NR	20-30W, 0.5-2 mm spot diameter, 0.1-0.5mm depth		NR
		Bogani et al., 2018	III	169	NR	NR	20.7%	ND	20-30W, 0.5-2mm spot diameter, 0.1-0.5mm depth		Vaginal vault perforation (1.2%) Postoperative bleeding (1.2%)
		Wang et al., 2014	III	39	IT G1: 46.2% G2: 0% RT G1: 60% G2: 54.5%	IT G1: 28.6% G2: 100% RT G1: 0% G2:0%	IT G1:7.1% G2: 0% RT G1: 0% G2:0%	11.8%	20-35W, 1-1.5mm spot diameter, 7-10mm margins, 2-3mm depth.		Local pain (NR) Vaginitis (NR) Stricture of the upper vagina (NR)

N – number treated; CR – Cure Rate; PR – Persistence Rate; RR – Recurrence rate; HPVe – Human Papillomavirus eradication; CIs – Contraindications; LE – Lateral effects; IT – Initial Treatment; RT – Recurrence treatment; G1 – Group 1 (VaIN patients after hysterectomy due to CIN); G2 – Group 2 (VaIN patients due to cervical cancer); NR – Not Reported; ND – Not Discriminated; W – Watts;

TABLE II [13,14,21,22]– MEDICAL TREATMENT - HIGH-DOSE-RATE (HDR) VAGINAL BRACHYTHERAPY (VBT)

TREATMENT MODALITIES		Articles	Type of evidence	N	CR	PR	RR	HPVe	Technique	CIs	LE (%)
MEDICAL	HDR-VBT	*Kim et al.*, 2018	III	2	100%	0%	0%	NR	NR	prior radiation therapy to treatment area;	NR
		Zhang et al., 2017	III	2	50%	50%		NR	NR		NR
		Zolciak-Siwinska et al., 2015	III	20	90%	0%	5%	NR	7.5 Gy x 5 fractions (35%) 7.5 Gy x 4 fractions (15%) 7.5 Gy x 3 fractions (5%) 7 Gy x 5 fractions (35%) 7 Gy x 4 fractions (5%) 6 Gy x 5 fractions (5%)		Stinging of vaginal mucosa (15%) Libido effects (75%) Vaginal discharge (2.9%) Dryness/Dyspareunia (35%) Mucositis (30%) Stenosis (35%) Vaginitis (20%)
		Song et al., 2014	III	34	88.2%	5.8%	5.8%	NR	5 Gy x 6 fractions (5.9%) 5 Gy x 8 fractions (79.4%) 5 Gy x 10 fractions (5.9%) 7 Gy x 4 fractions (8.8%)		Frequency/dysuria (14.7%) Frequent defecation (5.9%) Vaginal discharge (2.9%) Cystitis (2.9%) Rectal bleeding (5.9%) Dyspareunia/Stenosis (35.2%)

N – number treated; CR – Cure Rate; PR – Persistence Rate; RR – Recurrence rate; HPVe – Human Papillomavirus eradication; CIs – Contraindications; LE – Lateral effects; NR – Not Reported;

TABLE III [1,5] - MEDICAL TREATMENT – 5% IMIQUIMOD

TREATMENT MODALITIES		Articles	Type of evidence	N	CR	PR	RR	HPVe	Technique	CIs	LE (%)
MEDICAL	IMIQUIMOD	*Tainio et al.*, 2016	I	10	70%	20%	NR	63%	12.5mg/week, 2 weeks and 12.5mg, 2x/ week, 6 weeks	Hypersensitivity to 5% Imiquimod;	Fever and flu-like symptoms (90%) Local irritation in the vagina and vulva (60%) Lower abdominal pain (30%) Vulvar ulceration (10%)
		Tranoulis et al., 2017	II	94	76.5% (95% CI= 59.4-98.5) I^2=0.0% p=0.835	NR	5.6%	52.5% (95% CI= 29.5-93.6) I^2=0.0% p=0.062	0.25-12.5mg, 1-3x/ week, 3-12 weeks		NR

N – number treated; CR – Cure Rate; PR – Persistence Rate; RR – Recurrence rate; HPVe – Human Papillomavirus eradication; CIs – Contraindications; LE – Lateral effects; NR – Not Reported; CI – Confidence Interval;

TABLE IV [4,10,13,16,17]- MEDICAL TREATMENT – 5-FLOUOROURACIL

TREATMENT MODALITIES		Articles	Type of evidence	N	CR	PR	RR	HPVe	Technique	CIs	LE (%)
MEDICAL	5-FLOUOROURACIL	*Tranoulis et al*., 2018	II	358	IT:82.18% (95% CI= 69.80%-88.82%) I^2 = 77.86%, p<0.0001 RT:72.32% (95% CI=48.12%-91.05%)	NR	16.42% (95% CI= 7.39%-28.14%)	NR	*	Women who are or may become pregnant during therapy; Hypersensitivity to 5-FU; Dihydropyrimidine dehydrogenase (DPD) enzyme deficiency;	NR
		Hodeib et al., 2016	III	8	25%	75%		NR	NR		NR
		Kim et al., 2018	III	50	42%	30%	26%	NR	NR		NR
		Fiascone et al., 2017	III	47	IT:74% RT: 62%	25.5%		28%	1g, 5% cream, 1x/week at bedtime, 8 weeks		Vaginal and vulvar irritation (12%) Vaginal discharge (2%) Non-anaphylactic "allergic reaction" (2%)
		Bogani et al., 2019	III	72	NR	NR	94.4%	NR	1x/week, 6 weeks		NR

N – number treated; CR – Cure Rate; PR – Persistence Rate; RR – Recurrence rate; HPVe – Human Papillomavirus eradication; CIs – Contraindications; LE – Lateral effects; IT – Initial Treatment; RT – Recurrence treatment; NR – Not Reported; CI – Confidence Interval;

*High heterogeneity between studies

TABLE V [1,10,13,14]– EXPECTANT MANAGEMENT

TREATMENT MODALITIES	Articles	Type of evidence	N	CR	PR	RR	HPVe	CIs
EXPECTANT MANAGEMENT	*Tainio et al*., 2016	I	10	44.4%	33.3%	NR	17%	When invasion is suspected or cannot be excluded;
	Hodeib et al., 2016	III	4	50%	50%		NR	
	Kim et al., 2018	III	56	50%	12.5%	16%	NR	
	Zhang et al., 2016	III	82	59.8%	40.2%		NR	

N – number treated; CR – Cure Rate; PR – Persistence Rate; RR – Recurrence rate; HPVe – Human Papillomavirus eradication; CIs – Contraindications; LE – Lateral effects; NR – Not Reported;

TABLE VI – SUMMARY OF THE EVIDENCE

TREATMENT MODALITIES	Type of evidence	N	CR	PR	RR	HPVe
CO_2 LASER VAPORISATION	I [1], III [2,10,13,15,18,17,19]	981 (Initial treatment)	0%-75%	0%-100%	0%-59.1%	11%-11.8%
		82 (Recurrence treatment)	54.5%-93%	0%	0%-6.3%	
HIGH-DOSE-RATE (HDR) VAGINAL BRACHYTHERAPY (VBT)	III[13,14,21,22]	58 (Initial treatment)	50%-100%	0%-50%	0%-50%	NR
5% IMIQUIMOD	I [1], II [5]	104 (Initial treatment)	70%-76%	20%	5.6%	52.5%-63%
5- FLOUOROURACIL	II [4], III [10,13,15,18]	535 (Initial treatment)	25%-82.18%	25.5%-75%	16.42%-94.4%	28%
		16 (Recurrence treatment)	62%-72.32%	NR	NR	
EXPECTANT MANAGEMENT	I [1], III [10,13,14]	152 (Initial treatment)	44.4-59.8%	12.5-50%	16-50%	17%

N – number treated; CR – Cure Rate; PR – Persistence Rate; RR – Recurrence rate; HPVe – Human Papillomavirus eradication; NR – Not Reported;

ACTA OBSTÉTRICA E GINECOLÓGICA PORTUGUESA

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2. Todos os artigos são submetidos à revista por iniciativa dos seus autores, excepto os artigos de revisão que poderão também ser elaborados a convite dos Editores.

3. Os dados constantes do artigo não podem ter sido previamente publicados, total ou parcialmente, noutras revistas. Deste âmbito, exclui-se a publicação sob forma de resumo em actas de reuniões científicas.

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- **ESTUDO ORIGINAL**
- **ARTIGO DE REVISÃO**
- **CASO CLÍNICO**
- **IMAGEM DO TRIMESTRE**
- **ARTIGO DE OPINIÃO**
- **CARTA AO EDITOR**

Uma subsecção dos artigos de opinião intitulada "**Para lá da Ciência**" permite a submissão de textos sobre a vivência pessoal na área da Obstetrícia e Ginecologia e sobre aspetos históricos da Obstetrícia/Ginecologia Portuguesa.
A revista publica também **Normas de Orientação Clínica** da responsabilidade das Sociedades pertencentes à Federação das Sociedades Portuguesas de Obstetrícia e Ginecologia (FSPOG).

3. Todos os artigos necessitam de um **título em Inglês** que não pode exceder 150 caracteres incluindo espaços.

4. A **lista de autores** deve incluir o **primeiro** e **último(s) nome(s)** de cada um, juntamente com as funções académicas e hospitalares atuais. Para os artigos de revisão, artigos de opinião e casos clínicos não se aceitam mais do que **5** autores; para os artigos Imagem do Trimestre um máximo de 3 autores. Para os estudos originais são aceites até **8** autores, podendo este número ser excedido em estudos corporativos que envolvam mais de dois centros. Um dos autores é designado "responsável pela correspondência" e os seus contactos devem ser fornecidos na página de submissões da revista. Pelo menos para o autor correspondente, deverá ser fornecido o ORCID e o research ID.

5. Os estudos originais, artigos de revisão, casos clínicos e Imagem do Trimestre necessitam de incluir um **resumo em inglês** que não pode exceder 300 palavras tratando-se de estudos originais e 100 palavras nos restantes. Este texto não pode incluir qualquer referência aos autores ou à instituição onde o estudo foi realizado. A estrutura é diferente de acordo com o tipo de artigo:

- **ESTUDO ORIGINAL** – parágrafos com os títulos **Overview and Aims**, **Study Design**, **Population**, **Methods**, **Results**, and **Conclusions**.
- **OUTROS** – estrutura livre.

6. Os estudos originais, artigos de revisão, artigos de opinião e casos clínicos necessitam de incluir 1 a 5 **palavras-chave**, segundo a terminologia MeSH (www.nlm.nih.gov/mesh/meshhome.html).

7. Todos os artigos necessitam de um **título em Português** que não pode exceder 150 caracteres incluindo espaços.

8. Os artigos submetidos como Casos Clínicos e Imagem do Trimestre deverão **ser integralmente redigidos em inglês.**

9. Os autores devem enviar uma carta de submissão na qual têm a oportunidade de apresentar o trabalho ao editor chefe, salientado os resultados mais importantes e as novidades.

INFORMATION FOR AUTHORS

GENERAL RULES FOR SUBMMITING ARTICLES

1. Manuscripts should be **submitted exclusively** to Acta Obstétrica e Ginecológica Portuguesa (AOGP) and may not be under simultaneous consideration for publication in other journals. Manuscripts that have been previously rejected by other journals will be considered for publication, and authors are free to submit those that have been rejected by this journal elsewhere.

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4. Authors may re-submit a rejected article once, within 3 months of the decision. Re-submitted articles will be considered as new submissions.

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- **REVIEW ARTICLE**
- **CASE REPORT**
- **IMAGE OF THE TRIMESTRE**
- **OPINION ARTICLE**
- **LETTER TO THE EDITOR**

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3. All articles must contain a **title in English,** which should not exceed 150 characters in length, including spaces.

4. The **list of authors** should include their first and last name(s), together with current academic and hospital positions. No more than **5** authors are accepted for review articles, opinion articles and for case reports; for "image of the trimester" a maximum of **3** authors. For original studies up to **8** authors will be accepted, and this number may be exceeded in corporate studies involving more than two centres. One of the authors will be designated as "responsible for correspondence" and his/her contact information should be made available at the journal submission site. At least for corresponding authors, ORCiD and research ID should be indicated.

5. Original studies, review articles, opinion articles, case reports and "images of the trimester" must include an **abstract in English**, which should not exceed 300 words for original studies and 100 words for all other submissions. The text must not include any reference to the authors or to the institution where research took place. The structure of the abstract varies according to the article type:

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8. All articles submitted as Case Reports and Images of the Trimester should be **entirely written in English.**

9. Authors should include a cover letter, which is an opportunity to introduce your study to the editor, highlighting the most important findings and novelty.

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1. Os ficheiros submetidos com o texto principal do artigo, tabelas e figuras não devem ter qualquer referência aos autores ou à(s) instituição(ões) onde a investigação foi realizada.

2. Todos os textos submetidos devem ter **duplo espaço entre linhas**, usando a fonte **Times New Roman** de **11 pontos**.

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- **ESTUDO ORIGINAL** – secções divididas com os títulos: **Introdução**, **Métodos**, **Resultados** e **Discussão**; dimensão máxima **3000** palavras.
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4. As investigações que envolvem seres humanos ou animais devem incluir no texto a referência de que foram seguidas as normas éticas internacionais e da existência de aprovação prévia por uma **Comissão de Ética** apropriada (idealmente incluir o número da aprovação). No caso de casos clínicos ou imagens do trimestre é necessário que haja referência à obtenção de **consentimento informado** dos participantes.

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Exemplo de **artigos publicados em revistas***:*
Grant JM. The whole duty of obstetricians. BJOG 1997;104:387-92.

Exemplo de **Capítulos de livros:***:*
Goldenberg RL, Nelson KG. Cerebral Palsy. In: Maternal-Fetal Medicine (4th Edition). Creasy RK, Resnik R (eds). WB Saunders;1999:1194-214.

13. Os **quadros** são submetidos em formato digital, separadamente do texto principal. Devem ser numerados sequencialmente em numeração romana (I, II, III, IV etc.) e não apresentar linhas verticais internas; as únicas linhas horizontais a incluir são na margem superior e inferior do quadro e após os títulos das colunas. Os dados contidos nos quadros e nas legendas devem ser concisos e não devem duplicar a informação do texto. As **legendas dos quadros** devem ser submetidas nos mesmos ficheiros dos quadros.

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- **OPINION ARTICLE** – free structure; limit of **1500** words.
- **CASE REPORT** – separate sections with headings: **Introduction**, **Case Report** and **Discussion**; limit of **1500** words.
- **IMAGE OF THE TRIMESTRE** – free structure; limit of **500** words. Maximum number of images: 2.

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8. At the end of the main text, authors may include the **aknowlegments** that they would like published in the article.

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10. At the end of the main text, should be included the individual contribution of each author to the article.

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Example of **Book chapters:** Goldenberg RL, Nelson KG. Cerebral Palsy. In: Maternal-Fetal Medicine (4th Edition). Creasy RK, Resnik R (eds). WB Saunders;1999:1194-214.

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