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CONTINUING MEDICAL EDUCATION: SEXUALLY TRANSMITTED INFECTIONS

Cervicitis: Etiology, diagnosis and treatment☆

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ABSTRACT

Cervicitis is the inflammation of the cervix. It is usually caused by an infectious agent, usually sexually transmitted. Cervicitis is frequently asymptomatic and silent infection can cause complications of the upper genital tract. The symptoms are usually nonspecific, the most significant being an increase in vaginal discharge and/or intermenstrual bleeding. For its diagnosis, there are commercial systems based on molecular techniques that include almost all of the known pathogens associated with cervicitis, although cultures should not be abandoned due to the need to conduct studies of susceptibility to antibiotics. It is recommended to initiate an empirical antibiotic therapy that covers *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in the case of women at high risk of infection by these pathogens, especially if the follow-up is not assured or adequate diagnostic tests are not available. In women with low risk of sexually transmitted infection, antibiotic therapy should be adjusted to the results of the microbiological results.

Cervicitis: etiología, diagnóstico y tratamiento

Palabras clave:
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RESUMEN

La cervicitis es un cuadro de inflamación del cuello uterino. Suele ser causada por un agente infeccioso, generalmente de transmisión sexual. Frecuentemente es asintomática, y la infección silente puede originar complicaciones del tracto genital superior. Los síntomas suelen ser inespecíficos, y los más significativos son aumento del flujo vaginal y/o sangrado intermenstrual. Para su diagnóstico existen sistemas comerciales basados en técnicas moleculares que incluyen la casi totalidad de los patógenos conocidos asociados a cervicitis, aunque los cultivos no deben abandonarse por la necesidad de realizar estudios de sensibilidad a los antibióticos. Se recomienda iniciar un tratamiento empírico que incluya *C. trachomatis* y *N. gonorrhoeae* en el caso de mujeres con elevado riesgo de infección por dichos patógenos, sobre todo si el seguimiento no está asegurado o no se dispone de pruebas diagnósticas adecuadas. En mujeres con bajo riesgo el tratamiento deberá ajustarse a los resultados de las pruebas microbiológicas.

Introduction

Cervicitis is a process characterised by inflammation of the cervix. It was recognised for the first time as an important clinical condition in 1984, described as "the counterpart in women of urethritis in men".[1] Inflammation is localised mainly in the columnar epithelial cells of the endocervical glands, but it can also affect the squamous epithelium of the ectocervix.

It is usually caused by an infectious agent, generally transmitted sexually.

On many occasions it does not cause noticeable symptoms and the importance of its detection and correct treatment lies in the fact that silent infection can result in complications such as salpingitis, endometritis and pelvic inflammatory disease (PID) and have severe consequences in pregnant women.

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Despite the fact that there are not many studies which have evaluated the frequency of cervicitis, it is estimated that it is a common condition, with prevalences as high as 20–40% in women seen in consultations for sexually transmitted infections (STIs).[2]

Anatomy and physiology of the cervix

The cervix consists of a matrix of connective tissue covered by two different types of epithelium: columnar and squamous. The columnar epithelial cells line the endocervical canal and form the target for the pathogens most frequently associated with cervicitis, such as *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. On the other hand, the ectocervix is lined with squamous epithelium, which is adjacent to the vaginal mucosa and, consequently, susceptible to pathogens associated with vaginitis, including *Trichomonas vaginalis* and *Candida* spp. Both epithelia differ, not only in the susceptibility to certain microorganisms, but also in the endogenous defence mechanisms, their response to hormonal changes, their secretory capacity and their vulnerability to HIV.[2]

Hormones have multiple effects on the cervicovaginal mucosa. Thus, oestrogens (both endogenous and exogenous) promote cervical ectropion, i.e. the protrusion of the columnar epithelium of the endocervix towards the visible ectocervix, present in adolescents, pregnant women and women who take oestrogen-containing contraceptives. In addition, they are fundamental for the maintenance of an appropriate thickness of the cervicovaginal squamous epithelium. On the contrary, progesterone may cause this epithelium to become thinner. The quality of the endocervical mucus is also influenced by these hormones, and a direct modulator role has even been proposed for them in humoral and cell-mediated immune responses. Furthermore, endocervical mucus has considerable intrinsic antimicrobial activity provided by lactic acid, a low pH and the presence of antimicrobial peptides.[3]

Signs and symptoms

From the clinical point of view, cervicitis tends to classified as acute or chronic, with the latter being responsible for a large number of cases. Inflammation of the cervix is frequently asymptomatic, and in symptomatic women the symptoms are often nonspecific, with the most significant being the presence of increased vaginal discharge and/or intermenstrual bleeding, usually related to sexual intercourse.

In gynaecological examination, cervicitis is typically manifested by the presence of mucopurulent endocervical exudate in the endocervical canal ("mucopurulent cervicitis") and/or bleeding, which is easily induced by light rubbing with a cotton swab through the external cervical os ("friability"). Both signs can be present or there may only be one of them, and friability is as common, or even more so, than the presence of exudate. Therefore, although the oldest works refer to the term "mucopurulent cervicitis", this terminology is not precise and the clinical practice guidelines have used the term "cervicitis" since 2006 to include all cases.[4]

Chronic cervicitis, generally asymptomatic, is very common in adult women (at least that which can be seen only microscopically) and its importance lies in the fact that subclinical infection can extend to the upper genital tract, resulting in complications such as endometritis, salpingitis and PID. It can also lead to adverse effects in pregnant women and in newborns. The sequelae of PID include chronic abdominal pelvic pain, infertility and increased risk of ectopic pregnancy. In addition, chronic inflammation of the cervix could contribute to the development of cervical cancer.[5]

Aetiology

There are multiple agents, both infectious and non-infectious, potentially involved in cervicitis. Current availability of molecular techniques is increasing the number of microorganisms recognised as potential aetiological agents.

Infectious agents

Sexually transmitted pathogens

- *C. trachomatis* and *N. gonorrhoeae*. These are pathogens typically associated with cervicitis, although both microorganisms are detected in less than half of cases. The rest can be produced by other pathogens, by non-infectious agents and, occasionally, by systemic inflammatory processes. *C. trachomatis* is the most frequently identified cause in women with cervicitis, with a frequency of isolation that varies from 10 to 50% in the published studies,[1,6] depending on the population studied, the criteria used in the case definition and the methods used for diagnosis. Nevertheless, only 10–20% of cases of *C. trachomatis* infection in women are associated with clinical signs of cervicitis, which could be due to both differences in susceptibility of the host and to variability in the pathogenicity of the strains.[7] The percentage of cases of cervicitis due to *N. gonorrhoeae* is highly variable in relation to the marked differences in the prevalence of this infection in the populations studied.[8]
- *T. vaginalis*. Other pathogens which typically cause STIs may also lead to cervicitis. Among them, *T. vaginalis* has been associated with cervical inflammation[2,9] and with an increased risk of HIV transmission. *T. vaginalis* can cause erosive inflammation of the ectocervical epithelium which can result in a wide range of epithelial alteration, from small petechiae to large haemorrhages. The pathogenesis of these lesions could be due, at least partly, to cytotoxic factors produced by *T. vaginalis*, such as proteases capable of degrading some endogenous factors that protect the integrity of the cervicovaginal epithelium, mainly the so-called secretory leucocyte protease inhibitor.[10] Similar to what happens with *C. trachomatis*, the reason for which trichomoniasis only causes evident signs of inflammation of the cervix in some women is unknown. Among the possible causes could be the greater pathogenicity of some strains, the number of microorganisms present or intrinsic factors of the host that could increase its susceptibility.[11]
- *Mycoplasma genitalium*. Another possible aetiological agent involved in cervicitis is *M. genitalium*. This microorganism was identified for the first time in 1980 in the urethra of two patients with non-gonococcal urethritis. The frequency of *M. genitalium* as a pathogen causing an STI is still not well known, due in particular to the difficulty of its detection, since it is a bacterium which does not grow well in conventional culture media and it is necessary to resort to nucleic acid amplification (NAA) techniques for its diagnosis. Nevertheless, it is estimated that it is one of the microorganisms most commonly associated with genital tract infections, with a prevalence in men with urethritis of up to 30–40%.[12] Its potential as a sexually transmitted pathogen has been confirmed in studies that demonstrate the presence of the microorganism in the sexual partners of infected patients[13] and the concordance of the genotypes present in members of the couple.[14] Most prevalence studies have been carried out in risk populations, mainly in patients from STI clinics, which implies a bias and limits the conclusions with respect to the frequency of *M. genitalium* infection in the general population. Some authors have estimated its overall prevalence in women between 1 and 6.4%,[15,16] and in studies carried out in women seen in STI clinics the frequency varies from 0.1% found in asymptomatic women[17] up to 20% in the study by Gaydos et al.,[18] in

which almost 70% of patients presented signs or symptoms of cervicitis. After the discovery of *M. genitalium*, the capacity of this bacterium to infect the female genital tract was revealed, causing an inflammatory response, via its inoculation in small apes. Acute infection of the endocervical mucosa is able to destroy the microvilli and cause an increase in the formation of secretory vesicles.[19] Furthermore, infection of the endocervical cells in vitro by *M. genitalium* causes a proinflammatory response with secretion of several interleukins and other substances related to inflammation.[20] Levels of proinflammatory cytokines are elevated in women with chronic *M. genitalium* infection, which could give the idea that, similar to what occurs with *C. trachomatis*, persistent, untreated infection could lead to chronic inflammation, with harmful effects for the female reproductive system.[21] With regard to its pathogenic role in women, Manhart et al.[22] analysed by PCR a total of 719 endocervical samples from a collection from patients who had been seen in an STI clinic and found that women infected by *M. genitalium* had a three times greater likelihood of presenting with mucopurulent cervicitis. Subsequent studies have confirmed this connection.[18] Furthermore, *M. genitalium* infection in women can cause complications which affect the upper genital tract, such as endometritis and PID, infertility and adverse effects in pregnancy and birth.[12,23] Recently, Lis et al.[24] carried out a meta-analysis in which they analysed the link between *M. genitalium* infection and several female genital tract syndromes. The study concluded that *M. genitalium* infection was significantly linked to cervicitis, PID, preterm pregnancy and spontaneous abortion. The risk of infertility in infected women was also found to be high. In addition, co-infection of *M. genitalium* with *C. trachomatis* has been documented in women with cervicitis. In the study by Bjartling et al.,[25] 5% of patients infected with *C. trachomatis* were also infected with *M. genitalium*. Similar results were found by Gaydos et al.,[18] who found a high percentage of co-infections in women with cervicitis, with the most common being *M. genitalium* with *C. trachomatis* (5.3%) and *M. genitalium* with *T. vaginalis* (4.5%).

- *Herpes simplex virus*. Genital infection by the herpes simplex virus (HSV) types 1 and 2 can be the cause of cervicitis, most commonly in women with apparent clinical symptoms of primary HSV-2 infection. In these patients, cervicitis is typically characterised by the presence of erosive and diffuse haemorrhages, usually in the ectocervical epithelium, which is frequently accompanied by ulceration. It is estimated that cervicitis occurs in approximately 15–20% of women with primary HSV-2 genital infection with clinically evident symptoms.[26] In these cases, the manifestations of primary HSV-2 infection are usually visible in the vulvar epithelium and/or the introitus. Cervicitis can also occur during clinical recurrences of genital HSV-2 infection, but with less severe manifestations than those produced during the primary infection. Asymptomatic excretion of HSV-2 does not seem to be directly related to cervicitis. HSV-1 can also cause cervicitis, although the clinical manifestations are less severe and are generally produced only during the primary genital infection.[26]

Other potentially involved genital tract microorganisms

- *Mycoplasma hominis*. This microorganism is frequently found in the female genital tract of sexually active women, and some studies suggest a pathogenic role for this microorganism in some symptoms of cervicitis and PID.[27] In a study conducted in pregnant women, it was found that the detection of *M. hominis* was frequently linked to the presence of cervicitis.[28] Other authors have found a high prevalence of *M. hominis* (26%) in women with cervicitis.[29] Nevertheless, since this microorganism is frequently present in the healthy population, as well as in the symptoms of bacterial vaginosis, it is difficult to determine its pathogenic role in this context.
- *Ureaplasma* spp. Both *Ureaplasma parvum* and *Ureaplasma urealyticum* are detected frequently in the cervix of patients with cervicitis of unknown cause, but its aetiological role is controversial. It is possible that a high bacterial load may contribute to the development of cervicitis.[30] However, it seems that at least *U. urealyticum* has a limited role as a pathogen in the female genital tract.[31]
- *Bacterial vaginosis (BV)-associated bacteria*. A possible link between BV and cervicitis has been the subject of study in some works. BV is a frequent cause of vaginal infection and is characterised by an imbalance in the vaginal microbiota, with an overgrowth of the anaerobic bacteria and a reduction of the hydrogen-peroxide (H_2O_2)-producing lactobacilli, which are the predominant vaginal flora in normal conditions. There is evidence of the link between BV and *N. gonorrhoeae* and *C. trachomatis* infection, which makes the demonstration of a possible relationship between BV and cervicitis difficult, regardless of other co-pathogens. Furthermore, BV has been associated with an increase in the risk of gynaecological complications which involve the upper genital tract, including PID, and bacteria which characterise BV can cross the endocervical mucus barrier and lead to a local inflammatory response. Marrazzo et al.[32] studied 424 women with BV and found that 63 (15%) of them had cervicitis. Only in eight of the 63 (13%) was there evidence of a concomitant infection with *C. trachomatis* or gonococcus. The authors concluded that in women with BV it is common to find cervicitis, and that this is associated with different risk factors to those existing in cervical infection caused by *N. gonorrhoeae* or *C. trachomatis*. An aspect to be highlighted from this study is the conclusion that the absence of H_2O_2-producing lactobacilli can contribute to the development of cervicitis.[32] Furthermore, in another study carried out in women who presented with BV and cervicitis, the addition of metronidazole in the form a vaginal gel to the conventional treatment of cervicitis with doxycycline and ofloxacin improved the cure rates.[33] All these data suggest that some BV-associated bacteria can contribute to the development of cervical inflammation. *Mageeibacillus indolicus* is a bacterium of the Clostridiales order which has been linked to failures in the treatment of women with BV and was detected recently in men with non-gonococcal urethritis.[34] Data available to date suggest the hypothesis that this bacterium could be a sexually transmitted agent, which is able to play a pathogenic role both in the female genital and male genital tract. In a recent study, Gorgos et al.[35] analysed BV-associated bacteria as potential causes of cervicitis. By studying the samples of a cohort of women, the authors found that *M. indolicus* could be detected in a significantly higher percentage in the cervix (42.9% vs 11.9%) and in the vagina (42.9% vs 16.7%) of women with cervicitis, compared to women without cervicitis. Therefore, they conclude that the colonisation of the endocervix by *M. indolicus* may contribute to the manifestations of cervicitis.[35] In this study, an inverse relationship was also found between the detection of *Lactobacillus jensenii* and the presence of signs of cervicitis (52.4% in the cervix of women without cervicitis compared to 14.3% in women with cervicitis). This relationship had already been reported in previous studies.[36] Given that the strain *L. jensenii* TL2937 has proven to have a mitigating role in the inflammatory response in an animal model, the potential beneficial effect of *L. jensenii* in cervicitis could derive from the capacity of some strains of this species present in the vaginal microbiota to deactivate the immune response, thereby reducing cervical inflammation. Another possible explanation would be that this bacterium acts by simply promoting the resistance to vaginal colonisation by BV-producing bacteria.[35] Furthermore,

glycosidases and proteinases produced in abundance by the flora associated with BV can degrade the cervicovaginal mucus, altering its protective role, both physical and immunological, thereby contributing to the pathogenesis of cervicitis.

Other microorganisms

There are other microorganisms which have been potentially linked to cervicitis, but there is little evidence available to date of this association. *Cytomegalovirus* can be transmitted sexually and has been detected in a limited number of patients with cervicitis. The presence of human T-cell lymphotropic virus type 1 (HTLV-1) in cervical secretions of women with cervicitis has also been reported. However, it is difficult to establish the aetiological role of both viruses in this context.

Isolated cases of cervicitis attributed to species of the genus *Streptococcus* (mainly *S. agalactiae* and *S. pyogenes*) have been published, but there is no concrete data available on their frequency or if there is a clear causal relationship.

Non-infectious agents

The etiology in a high percentage of women in whom none of the known pathogens are found is still unknown. Endocervical inflammation can be measured through numerous metabolic pathways. A local inflammatory process could be induced or maintained through different paths, including the effects of a persistent infection due to an unknown pathogen, a persistently altered vaginal microbiota or an exaggerated immune response (Table 1). Such processes are probably modulated by the effect of endogenous and exogenous hormones, including the hormonal changes that occur during the menstrual cycle and with the use of contraceptives. Endogenous hormones, as has already been mentioned, have a clear role in the maintenance of the integrity of cervicovaginal mucus. Local immune response is regulated by oestrogens (they increase the response) and progesterone (it decreases it). Women with low oestrogen levels (post-menopausal, post-partum, very low body fat or on treatment with androgenic drugs) have a greater risk of atrophic vaginitis, and their incapacity to maintain a normal vaginal pH (<4.5) may cause a gradual erosion of the endocervical mucus. Progesterone has proven to increase susceptibility to simian immunodeficiency virus infection in animal models and may increase the risk of cervicitis in women, as some studies in women who used it as a contraceptive seem to conclude.[37]

Table 1
Factors potentially involved in cervicitis with negative microbiological studies and possible mechanisms.

Factor	Mechanism
Persistent alteration of the vaginal microbiota	Uncertain mechanism (glycosidases produced by bacterial vaginosis-associated bacteria)
Hypoestrogenism (post-menopausal, post-partum, very low body fat or on treatment with androgenic drugs)	Involvement of the local immune response Greater risk of atrophic vaginitis and inability to maintain a normal vaginal pH (<4.5), which can cause erosion of the endocervical mucus
Inflammatory/autoimmune diseases (Behçet's disease, sarcoidosis, ligneous conjunctivitis)	Excessive immune response
Use of potentially irritant products (vaginal soaps, spermicides, deodorants, etc.)	They alter or irritate the cervicovaginal mucus
Persistent infection with an unidentified pathogen	The use of molecular techniques is expanding the spectrum of new pathogens involved

In addition to the aetiological agents mentioned, there is a variety of systemic inflammatory processes, both infectious and non-infectious, as well as some agents or local factors that can cause endocervical inflammation, resulting in the onset of clinical signs of cervicitis. Among the inflammatory- or immune-based processes that can occur with cervicitis are Behçet's disease, sarcoidosis and ligneous conjunctivitis. The local agents that can cause irritation and/or erosion of the cervicovaginal mucosa include soaps used in vaginal washes, chemical deodorants and some spermicides (Table 2).

Complications

The main complications of cervicitis are endometritis, PID and possible adverse effects in pregnancy. The clinical signs of cervicitis and/or endometritis may be the only ones present in patients with PID. In women with lower genital tract infections the risk of developing PID is estimated to be between 20 and 80% depending on the delay in the diagnosis, the presence of co-infection and other host-dependent factors.[6]

Furthermore, it is accepted that the presence of cervical inflammation may play a role in the transmission of HIV, increasing both the susceptibility to the infection by the virus and the excretion of it. Mechanisms by which cervicitis may favour the transmissibility of HIV include an increase in viral replication in the context of infection or inflammation, particularly in the presence of elevated proinflammatory cytokines, the disruption of cervical mucus and the greater number of HIV-infected cells in cervical secretions. A correlation between the presence of the HIV genome in cervical secretions and evidence of cervicitis has been demonstrated. In addition, the expression of HIV in the genital tract could be altered in a different way depending on the etiology of the cervicitis.[38]

There is also evidence of the involvement of chronic inflammation of the cervix in the pathogenesis of cervical cancer. Some genotypes of the human papillomavirus (HPV), particularly 16 and 18, are involved in the development of most of the genital cancers. The role of these viruses in cervicitis is more uncertain. In some studies, a direct relationship has been found between the degree of cervical inflammation and the presence of squamous intraepithelial lesions.

Complications in pregnant women

The repercussions that cervicitis can have in pregnancy and the possible adverse effects in the neonate are still subject to controversy. Most of the works published which have evaluated these effects include only the cases of cervicitis produced by classic pathogens (gonococcus and *Chlamydia*). In pregnant women, *C. trachomatis* infection has been linked to an increase in the risk of ectopic pregnancy, premature birth, premature rupture of membranes, spontaneous abortion and childhood morbidity.[39,40] However, some studies do not find statistically significant differences between the risk of premature birth or premature rupture of membranes in women with cervicitis caused by *Chlamydia* and gonococcus and pregnant women without infection,[41] while in others there is a statistically significant association between *C. trachomatis* infection and the risk of spontaneous abortion in a population with a high prevalence of infection due to this bacterium (17.4%).[42]

In the case of *M. genitalium*, a significant association has been found between infection due to this bacterium and the risk of spontaneous abortion and premature birth.[24]

Table 2
Microbial and non-microbial etiology of cervicitis.

Microbial causes		Non-microbial causes	
Pathogens producing sexually transmitted infections	Other potentially involved pathogens	Inflammatory and immune processes	Chemical agents, hormones
C. trachomatis *N. gonorrhoeae* *M. genitalium* *T. vaginalis* HSV 1 and 2	Bacterial vaginosis-associated bacteria *M. hominis* *Ureaplasma* spp. CMV HTLV-1 *Streptococcus* spp.	Sarcoidosis Behçet's disease Ligneous conjunctivitis	Soaps and vaginal deodorants Spermicides Endogenous and exogenous sexual hormones

CMV: cytomegalovirus; HSV 1 and 2: herpes simplex virus types 1 and 2; HTLV-1: human T-cell lymphotropic virus type 1.

Diagnosis

Clinical diagnosis of cervicitis was traditionally made based on the presence of suggestive findings in the clinical examination with a speculum: an oedematous and friable cervix with the presence of cervical secretion of mucopurulent appearance.[8] Nevertheless, both the degree of cervical inflammation and the accompanying signs and symptoms can be highly variable, and the predictive value of the cervical signs suggestive of cervicitis can also vary depending on age and other risk factors related to STIs. A microscopic examination using Gram stain can also be performed to confirm the existence of cervical inflammation, quantifying the polymorphonuclear leukocytes (PMN) in the endocervical secretion. A count >30 PMN/field is considered significant.[22,28]

There is a need to agree on some diagnostic criteria for cervicitis that make it possible to establish a uniform case definition that can be applied in clinical practice and in epidemiological studies. The most frequently used criteria for the case definition in studies published in recent years have been the existence of mucopurulent discharge or the presence of >30 PMN/field in the endocervical secretion. In an extensive study conducted recently, three possible case definitions were evaluated: a "clinical" (presence of mucopurulent discharge), another "microscopic" (>30 leukocytes/high-power field) and a combined "microscopic and clinical" definition. The exclusively "clinical" and the "combined" definition were the most used for the prediction of infection.[43] With the combined "microscopic and clinical" case definition, the highest positive predictive value and the highest specificity was obtained, although with a lower sensitivity to predict infection caused by the most common pathogens.[43]

The aetiological diagnosis can be performed by studying a sample of endocervical exudate, carefully obtained using a speculum during the gynaecological examination. Vaginal secretions should be removed using a dry swab, which is then disposed of. Subsequently, the cervix should be gently compressed with the speculum and a thin swab should be inserted into the endocervical canal. Swabs of calcium alginate or with a wooden stick should not be used, as they can inhibit both the growth in cell culture and the NAA techniques.[44] It is advisable to soak at least two swabs to allocate one of them to the microscopic examination and the cultures and the other swab to NAA tests.

The Gram stain of the endocervical exudate can be useful in the diagnosis of gonococcal cervicitis (presence of Gram-negative diplococci), although it has a low sensitivity and specificity and its results can be influenced both by the experience of the observer and by the possible interference with the microbiota or leukocytes of the vagina itself and not of the cervical mucus.

The sample of endocervical exudate should be cultured in normal media, including a selective medium for *N. gonorrhoeae* (Thayer-Martin or Martin-Lewis) and *T. vaginalis*. General media, such as blood agar and chocolate agar should also be used, for the recovery of less common bacteria, as there are some strains of *N. gonorrhoeae* that can be inhibited in selective media.

NAA techniques should be used for the diagnosis of *C. trachomatis* since, as it is an intracellular bacterium, it requires cell cultures and antigen detection techniques lack sufficient sensitivity.[45] There are different platforms on the market for the joint detection of *C. trachomatis* and *N. gonorrhoeae* in the same sample, using NAA techniques. These systems differ in their amplification methods and in the sequences used as target, and, in general, they all offer a high sensitivity (>90%) and a very high specificity (>99%). Due to its high sensitivity, it is important to adjust the working conditions to prevent contamination.

Despite the advantages offered by the NAA techniques, it is recommended not to disregard cultures, as the detection of *N. gonorrhoeae* may have important connotations, even of a judicial nature, and because the recovery of the strains allows their antibiotic resistance profiles to be studied.

Cell cultures for *Chlamydia* should also be maintained in reference centres, both to monitor the onset and the evolution of resistances over time and to be able to study and characterise the strains with epidemiological and research purposes (e.g. strains associated with lymphogranuloma venereum and other rare infections caused by variants or mutant strains).[46]

Vaginal samples show a sensitivity and specificity comparable to endocervical samples when NAA techniques are used, and, therefore, can be a valid alternative for the diagnosis of cervicitis in women who cannot have a full gynaecological examination. In these cases, the vaginal exudate can be obtained by the patient herself (self-exam) with good results. On the contrary, fractional urethral urine is a less useful sample for the diagnosis of cervicitis due to *C. trachomatis* and *N. gonorrhoeae* as it provides a lower sensitivity.[46]

Serological tests for detecting an immune response are not useful in the diagnosis of active *C. trachomatis* infections.[46]

T. vaginalis infection can be diagnosed by means of a fresh microscopic examination of the cervical secretion, but the sensitivity of this technique is low, meaning that for its diagnosis it is necessary to perform a culture in the appropriate media or to use a NAA technique.

NAA techniques are the techniques of choice for the diagnosis of *M. genitalium* and HSV types 1 and 2. Some of the molecular techniques currently marketed allow the joint detection of *M. genitalium* and of mutations associated with macrolide resistance. Various commercial systems based on NAA techniques (generally multiplex PCR), which include almost all of the known pathogens associated with cervicitis and other STIs, are available.[47] The cervical sample collected in transport medium for liquid-based cytology

(e.g. ThinPrep® or SurePath®) can be used in some of these pieces of equipment, which is beneficial when the detection of HPV needs to be done simultaneously.

Treatment

The decision to perform empirical or targeted treatment of women with cervicitis should be taken after considering factors such as age, the epidemiological context and the availability of rapid diagnostic tests. It is advisable to start empirical treatment that includes *C. trachomatis* and *N. gonorrhoeae* in the case of women with a high risk of infection due to these pathogens (age <25 and those with a new sexual partner or with a partner diagnosed with an STI), especially if follow-up is not guaranteed or if appropriate diagnostic tests are not available (e.g. NAA tests not available). For women with a low risk of STI the treatment can be delayed, awaiting the results of the diagnostic tests.[48]

The empirical treatment regimen recommended in most guidelines is azithromycin, 1 g orally in a single dose, or doxycycline, 100 mg orally, twice daily for seven days. If the patient has a high risk of gonococcal infection, this pathogen should also be covered, preferably with ceftriaxone 500–1000 mg, intramuscularly, in a single dose.

Azithromycin is also the treatment of choice if the pathogen identified is *M. genitalium*, but resistant strains associated with clinical failure have been reported. In these cases, the recommended treatment is moxifloxacin, 400 mg/day for 7–14 days.[48] Carrying out a test of cure (repetition of the diagnostic tests one month after finishing treatment) is not necessary unless the symptoms persist or in pregnant patients.[48]

In the follow-up of patients in whom the aetiological agent is a sexually transmitted pathogen, screening for HIV and syphilis and contact tracing should be performed.

The management of patients with cervicitis in whom no pathogenic agent can be identified is controversial. For these cases, there is not sufficient scientific evidence that justifies a treatment alternative, and each case should be assessed according to the clinical context and the presence of other non-infectious factors.

Management of contacts (sexual partners)

Sexual contacts from the last 60 days of women with cervicitis must be assessed and treated with the same antibiotic regimen recommended for the identified or suspected sexually transmitted pathogen.

To minimise the risk of contagion and reinfection, patients should be advised to abstain from having sexual intercourse until the symptoms have resolved and their sexual partner(s) have also been duly treated.

Special considerations for treatment

HIV infection

Women with cervicitis and HIV infection should be treated with the same antibiotic regimen as those not infected. It has been suggested that cervical inflammation increases the elimination of HIV; consequently, appropriate treatment of cervicitis in HIV-infected patients could reduce the excretion of the virus and reduce the risk of it being transmitted to sexual partners.

Pregnancy

The diagnosis and treatment of cervicitis in pregnant women does not differ from that of non-pregnant women.[48]

Chronic cervicitis (persistent or recurrent)

Cervicitis can persist or recur after completing one or several cycles of antibiotic treatment. In these cases, it is recommended that patients be re-assessed after ruling out possible re-exposure or treatment failure.[48]

As has been mentioned in previous sections, the importance of chronic cervicitis lies in the fact that it can result in complications such as endometritis, salpingitis, PID, chorioamnionitis and other adverse effects in pregnancy. It can also play a role in the initiation or promotion of cervical cancer.[5]

In these cases, potential microorganisms involved less frequently and not covered by the treatment administered (e.g. *Trichomonas* or BV agents) should be ruled out. Most of the guidelines recommend a full gynaecological review to rule out signs of malignancy and consider non-infectious agents, such as some chemical substances that may erode the cervicovaginal mucus or cause irritative mucositis (vaginal douches, spermicides and chemical deodorants).

In cases of chronic cervicitis in which it is not possible to find an aetiological agent, ablation therapy can be considered, although studies which evaluate its effectiveness are limited. This option should be considered as a last resort, and before its application it is necessary to always rule out a possible malignancy.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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