IN THE NAME OF GOD

(anogenital warts): Treatment of vulvar and vaginal warts

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- **Vulvar and vaginal warts** are one of the clinical manifestations of **human papillomavirus** (HPV) infection.
- Approximately **90 percent of anogenital warts** are associated with **HPV types 6 and/or 11**, which are of low oncogenic potential.

- The presence of genital warts is concerning because of their **cosmetic appearance**, association with a **sexually transmitted disease**, **bothersome symptoms**, **absence of a cure**, and **social stigma**.

- Although treatment can eradicate the warts, **disease recurrence is common** and occurs in **20 to 30 percent** of patients overall.

Information about human papillomavirus infection

- Most patients want to know **how and when** they acquired the disease.
- Genital human papillomavirus (HPV) is spread by **direct physical contact during sex**.
- They may have acquired the infection **years prior to diagnosis since the incubation period can last for months** and their **first recognition** of a lesion may represent a **relapse** rather than a first episode.
- Therefore, **a new diagnosis of genital warts does not mean** that the **patient or her partner is having sex outside the relationship**.
- We also inform them that **condoms** provide **some protection against HPV transmission**, but contact with genital lesions not covered by the condom can result in infection.

Indications for treatment

- **Alleviation of bothersome symptoms** (pruritus, bleeding, burning, tenderness, vaginal discharge, pain, obstruction of the vagina, dyspareunia) or psychologic distress.
- Warts **do not pose serious risks to health or fertility**; therefore, **some symptomatic patients** may reasonably **choose expectant management** to see if the warts spontaneously resolve.
- There is **no medical indication for treatment of asymptomatic warts incidentally noted on physical examination**, but **patients should be made aware of the presence of these lesions**.
- There is **no reason to believe that treating vulvovaginal warts will reduce the future risk of cancer**.
- Patients **should not be treated solely for the purposed of preventing infection of sexual contacts**, as **there is no evidence that eradication of warts eliminates infectivity.**

Overview of treatment and prognosis

- They should also understand that **medical and surgical therapies** lead to **clearance of warts in 35 to 100 percent** of patients **in 3 to 16 weeks**, but **do not necessarily eradicate all HPV infected cells**.
- Because clinically and histologically **latent HPV can exist beyond the treatment area**, the possibility of **clinical recurrence or transmission of HPV to sexual partners remains**.
- The likelihood of **recurrence is variable** depending on the patient's **medical condition**, **immune status**, and the **extent of disease**, but **20 to 30 percent of patients have a recurrence within a few months**.
- Nevertheless, **most** HPV infections associated with genital warts in **immune competent** patients are **cleared within two years.**

Overview of treatment and prognosis

- Both **medical** and **surgical** options are available for treatment.

- There is **no high quality evidence** that **any treatment is significantly superior to another**; therefore, **treatment choice** is based on the **location**, **number**, and **size of the warts**; **patient characteristics** (**pregnancy**, **ability to comply with therapy**, **immunocompromise**); **availability of resources** and **clinical expertise**; and patient **preferences** after considering side effects, **cost**, and **convenience**.

Overview of treatment and prognosis

- **Medical therapies** are generally tried **first**; if the patient **has not responded** to the initial medical therapy **after 3 weeks** or **complete clearance has not occurred by 6 to 12 weeks**, a different medical therapy can be administered.

- **Surgical therapy** is typically reserved for patients with **extensive** and/or **bulky lesions** and those who have **failed to respond** adequately to medical therapy.

- Surgery results in **high initial clearance rates (90 to 100 percent)**, but **recurrence rates are similar** to those with medical therapy.

Side effects and complications of treatment

- **localized discomfort(itching, burning, erosions)**
- **hypo- or hyperpigmentation**
- **scarring**
- **chronic vulvar pain**(rarely)
- **Hypopigmentation** is most common in areas where warts were **surgically ablated** but has also been described after treatment with **imiquimod**.
- **Scarring** is most common after surgical procedures that **destroy subdermal tissue**.

PRETREATMENT EVALUATION

- Determining **the human papillomavirus type** of the warts **is unnecessary** as this information **does not affect clinical management**.

- The **presence of genital warts alone** is **not an indication for screening for additional sexually transmitted diseases**, but such screening **is indicated in high risk groups** such as individuals with **new partners or in non-monogamous relationships**, and **those ≤25 years of age**.

Indications for pretreatment biopsy

- Biopsy to rule out underlying intraepithelial neoplasia or cancer **is not mandatory** before initiating therapy, but is **recommended when**:
- The **diagnosis is uncertain**.
- The lesion has **any suspicious features**, such as fixation (infiltration of dermis), irregular and unusual pigmentation (red, blue, black, brown), induration, bleeding, ulceration, or sudden recent growth.
- The patient is **postmenopausal** or **immunocompromised**.
- The lesion is **refractory to medical therapy**.
- The biopsy should be **obtained from the most abnormal area** and **include the edge of the base of the lesion and adjacent tissue**.

TREATMENT OPTIONS

Medical therapy

- There are **two broad categories of medical therapy**:
- 1_those that **directly destroy the wart tissue** (cyto-destructive therapies)
- 2_those that **work through the patient's immune system** to clear the wart (immune-mediated therapies)
- Some of these methods can **only be applied in the clinician's office**, while others **can be self administered** by the patient at home.
- All **medical therapies are most useful for patients with limited disease (≤5 small warts)**.

Some key points regarding medical therapy:

- Podophyllotoxin(**podofilox**), **imiquimod**, **sinecatechins**, and **topical interferon** can be **self-administered**.
- **Vaginal warts** can only be treated with **trichloroacetic acid (TCA)**, **bichloracetic acid** (BCA), and **interferons**.
- **TCA** has no systemic absorption and no known fetal effects; therefore, it is the **preferred treatment for pregnant** people.

Cytodestructive therapies

- **Podophyllotoxin (podofilox)**
- **podophyllum resin (podophyllin)**

Both drugs **are avoided in pregnancy**.

Podophyllotoxin (podofilox):

- Using a cotton swab, **the patient** applies a 0.5 percent gel or solution to external genital warts **twice daily for three consecutive days**.
- No more than 0.5 mL of podofilox should be applied in one day.
- She then withholds treatment for four days, and repeats this cycle weekly **up to four times**.
- **Large areas (10 cm2 or more**) should not be treated in a single application because pain is likely when the area becomes necrotic.

Podophyllum resin:

- **The clinician** applies a 25 percent solution directly to the warts **with a cotton swab.**
- No more than 0.5 mL should be applied during each treatment session and large areas (10 cm2 or more) should not be treated in a single application because of potential pain when the area becomes necrotic.
- The area should air-dry before the patient dresses.
- In contrast to podophyllotoxin, **systemic absorption and toxicity have been documented**.
- A weaker solution (10 percent) should be used when treating large warts to minimize total systemic absorption, and application to open lesions/wounds should be avoided.

Podophyllum resin:

- Instruct the patient to **wash the area one to four hours after application of the drug**, otherwise excessive skin irritation and systemic absorption can occur.
- The treatment is **repeated weekly for four to six weeks**, or until the lesions have cleared.
- **Adverse effects** range from **mild skin irritation** to **ulceration** and **pain**, depending upon the **concentration** used and the **length of time** it is left on the skin.

Trichloroacetic acid and bichloracetic acid

- TCA is used most commonly and must be **applied by a health care provider**.
- It can be used on the **vulva** and **vagina**, and **during pregnancy**.
- An **80 to 90 percent TCA** solution is applied sparingly to the wart tissue with a cotton swab; the wart turns white as the solution dries.
- Application of an ointment or gel (such as petroleum or lidocaine jelly) to the normal tissue surrounding the wart can help prevent spreading of acid to unaffected areas.
- **The patient should not sit, stand, or dress until the treatment area has dried**.

Trichloroacetic acid and bichloracetic acid

- Excessive application of 80 to 90 percent TCA can cause extensive chemical burns of the vagina, vulva and adjacent healthy tissue.
- If excess TCA is applied, it can be neutralized by **washing with soap or sodium bicarbonate solution**.
- **Frequency of treatment:** Repeated **weekly** application is required for **four to six weeks**, or **until the lesions have cleared**.
- **Large, thick lesions** may not respond because the acid may not penetrate the entire lesion.

Fluorouracil

- In the United States, the Food and Drug Administration **(FDA) has not approved any formulation of FU for treatment of anogenital warts** and its use **is contraindicated in pregnancy**.
- A **disadvantage of topical FU** is that it is often poorly tolerated because of burning, pain, inflammation, edema, or painful ulcerations.
- Topical FU has a limited role in the primary therapy of vulvar or vaginal warts.

- **Immune-mediated therapies**
  - **imiquimod**
  - **interferon**

- Both initiate a local immune response at the site of the wart that ultimately may clear the lesions.
- Imiquimod and topical interferon may be **self-administered**
- **Injectable interferon** is given in the **office**.

Imiquimod

- Topical treatment of warts **increases local production of interferon** and **reduces human papillomavirus (HPV) virus load**.
- Two formulations are available, **Aldara (5 percent imiquimod**) and **Zyclara (3.75 percent imiquimod**), for treatment of **external genital warts**, but the manufacturers recommend against vaginal administration.
- There is insufficient information regarding the safety of imiquimod in pregnancy; animal studies suggest this therapy is low risk, but use of imiquimod in pregnancy should be avoided until more data are available.

Imiquimod

- **Hand washing before and after** cream application is recommended.
- The **patient** applies imiquimod cream directly to the clean dry warty tissue **at bedtime**, **rubbing it** in until the cream is no longer visible; this area is washed with mild soap and water **6 to 10 hours later**.
- **Sexual contact should be avoided while the cream is on the skin**.
- The **cream can weaken condoms and diaphragms**.
- **Aldara is applied three days per week (Monday-Wednesday-Friday) for up to 16 weeks**.

Imiquimod

- A **mild, local inflammatory reaction** should occur, which **is a sign the drug is working**.
- It is generally not so severe as to preclude further treatment.
- **If severe inflammation occurs, use of the drug should be stopped** until the inflammation clears and then it can be restarted at a lower frequency.
- More severe skin ulcerations and impetigo have rarely been described with imiquimod use.
- Forty to 50 percent of female patients will have complete clearance of the warts and most of the remainder will have partial clearance, but up to 30 percent will experience a recurrence within 12 weeks.

Sinecatechins

- **Sinecatechins** (Veregen) is a **self-administered** topical treatment of external anogenital warts.
- The exact mechanism of action of catechins is unknown, but they have both **antioxidant and immune enhancing activity**.
- A 0.5 cm strand of ointment is placed on each wart and a finger is used to cover the wart with a thin layer of the ointment **3 times each day for up to 16 weeks**.
- It **should not be used in the vagina or anus** and **should be washed off of the skin before sexual contact** or **before inserting a tampon into the vagina**.
- It can weaken the latex in condoms and diaphragms.

Sinecatechins

- **Sinecatechins should be avoided in immunocompromised** female patients and **those with active genital herpes lesions**.
- There is minimal information on the risk of use during pregnancy.

Interferons

- Interferons have antiviral, antiproliferative, and immune-stimulating effects, theoretically making them an ideal agent for treatment of anogenital warts.
- Interferon-alpha and -beta have been administered as a **systemic therapy** (intramuscular injection), topically, and as a subcutaneous intralesional injection.

Interferons

- The course of therapy can be **repeated 12 to 16 weeks** from the initial treatment.
- **Local anesthesia is recommended**.
- Patients receiving interferons by any route commonly experience **flu-like symptoms**, **fatigue**, **anorexia**, and **local pain**.
- Given the frequency of bothersome side effects, variable rates of effectiveness, and inconvenience of administration, we **don't use interferon for primary treatment of anogenital warts**.
- Interferons are contraindicated in pregnancy.

Surgical therapy

- Surgical management options consist of **ablative** and **excisional procedures**.
- In patients with **extensive** or **multifocal disease**, both ablative and excisional modalities are used.
- **An advantage of surgical management** is that **fewer visits for treatment** are needed.
- A disadvantage of ablative therapies: persistent hypo- or hyperpigmentation.

- A disadvantage of all surgical therapies (ablative or excisional):
- require **anesthesia**/ often need to be **performed in an operating room**/ **scarring** (especially when the subdermal layer is destroyed)
- Small lesions can be ablated or excised in the office with only sedation and local infiltration (lidocaine 1 percent with or without epinephrine) in some highly motivated patients.
- **All of the surgical options** can be used in **pregnant** persons and on both the **vulva and vagina**.

Cryoablation

- Is an **office** procedure
- **Local anesthesia**
- Liquid nitrogen is most commonly used and is applied directly to the **vulvar or vaginal lesion** with a cotton swab or a fine spray.
- The treatment is applied for **30 to 60 seconds**, until an ice ball forms and encompasses the lesion and 1 to 2 mm surrounding area.
- Repeated weekly application is required until the lesions have resolved.

Laser ablation

- Carbon dioxide laser is the most commonly utilized type of laser for treatment of vulvar warts, but requires specific training and specialized equipment.
- **Benefits:**
- Laser better maintains **normal vulvar anatomy**.
- **Preferred** therapy for **extensive** or **multifocal lesions**.
- In such cases, surgical excision is undesirable since large areas of vulvar skin would have to be removed.
- also useful for treating **vaginal warts** when surgical excision is technically challenging or not feasible.

Risks

- **Scar formation** (Up to 28 percent) ➡ occur when the laser beam penetrates too deeply
- **Pain and hypopigmentation**
- **Chronic pain and vulvodynia** (Rarely)

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- Anogenital **warts are epithelial in location**; therefore, vaporization should only be carried down to the level of the superficial (papillary) dermis and no deeper.

The surgeon and operating room personnel should wear **protective masks** when performing laser ablation since HPV DNA can be dispersed.

Health care providers who are routinely exposed to HPV are offered vaccination.

Postprocedure care

- **Pain management** and **careful attention to vulvar hygiene** are crucial.
- Take **sitz baths two to three times a day** during the initial one to two weeks following the procedure.
- **Antibacterial creams or ointments** are suggested to prevent superficial infection.

- Recurrence rate was associated with **younger age at treatment** and **multifocal** (versus unifocal) lesion treatment, while **pregnancy was not associated with recurrence**.
- For patients with multifocal or refractory disease, a combination of techniques is often effective.
- As an example, excision is used to "debulk" the warty tissue, followed by laser ablation of the base.

Electrocautery

- **Electrocautery** can also be used for **ablation of vulvar or vaginal lesions**.
- An **advantage** of this approach over cryoablation ➡ a **single treatment session is usually adequate**
- **Disadvantage** ➡ requires **administration of anesthesia and use of an operating room**.

If available, **laser ablation is generally preferable to electrocautery** because it is associated with **less bleeding and discomfort**.

Excision

- If tissue is needed for histological diagnosis, an **excisional biopsy** can be performed before an ablative procedure, or an excisional procedure can be performed.
- Typically, **exophytic lesions** are tangentially **excised or shaved** to the level of normal skin using scissors or a surgical knife, and then the **base of the lesion is cauterized**.
- For larger lesions, wide local excision is often required.

➢**Limited vaginal disease**

➢We suggest **TCA** for treatment of a **small area of vaginal warts (≤5 small warts**).

➢**TCA, bichloracetic acid (BCA), and interferons** are the **only medications** that can be used to treat **vaginal warts**, but many patients cannot tolerate intralesional interferons.

➢**Laser ablation** is our preferred surgical approach as it is possible to reach into the vagina and the depth of treatment can be controlled.

➢Extensive and/or bulky lesions

➢For patients with **extensive (>20 cm2**) and/or **bulky disease**, we suggest **surgery** as initial therapy because medical therapy alone often requires a prolonged course of treatment and is often inadequate and poorly tolerated.

➢Laser ablation is less destructive and less technically challenging than excision, and better tolerated than electrocautery.

➢**Recurrent disease**

➢The **same treatment** that resulted in **initial clearance of warts** may be used again and is likely to be successful.

➢**Refractory disease**

➢A **surgical** approach or a **combination of intralesional interferon and TCA**.

➢**An excisional procedure or biopsy <u>should</u> be performed** to exclude intraepithelial neoplasia or cancer.

Postmenopausal individuals

Postmenopausal with warty-appearing lesions **should be biopsied** before initiation of therapy, as these patients have a greater chance of having an underlying **vulvar intraepithelial neoplasia** or **vulvar cancer** than younger women.

Pregnant people

- Pregnancy is associated with a **decrease in cell mediated immunity**, which may lead to a **worsening of viral infection**.
- Few studies have evaluated human papillomavirus (HPV) in pregnancy and most showed an **increase in prevalence**.
- Indications for treatment are similar to nonpregnant patients.
- Lesions that potentially **obstruct the birth canal** (vagina and perineum) **should be treated to avoid complications during vaginal birth**.
- **Treatment may not reduce the risk of vertical transmission**.

- **Podophyllin**, **podophyllotoxin**, **interferon**, and **FU** are all **contraindicated** because of potential fetal harm.
- **Use of imiquimod or sinecatechins in pregnancy** are generally **not recommended**.
- **TCA** has no systemic absorption and no known fetal effects; therefore, it **is the preferred medical treatment for pregnant patients**.
- **Clearance rates are highest** and **recurrence rates lowest** when TCA is used in the second half of the pregnancy.

- **Cryoablation** is a **safe** and **effective treatment** for use in pregnancy.
- Use of **laser ablation** in pregnancy for bulky, potentially obstructive lesions, with success rates of 90 to 100 percent.
- The **risk of wart recurrence** appears **lowest when the treatment is delayed until the third trimester**.

Vertical transmission and mode of delivery

- Elective cesarean delivery has not been proven to prevent transmission of HPV, we suggest not performing cesarean delivery for patients with anogenital warts for the sole indication of preventing JRP or vertical transmission .

Cesarean delivery is indicated if vulvar or vaginal warts obstruct the birth canal, as the lesions may avulse and hemorrhage or cause dystocia during an attempted vaginal delivery.

Immunocompromise or HIV infection

- **The prevalence of anogenital warts is higher in HIV-positive patients.**
- **Vulvar biopsy is indicated** because **high-grade intraepithelial neoplasia is more common** in warty lesions in these patients.
- Patients with HIV who are known to carry HPV are also at increased risk of vulvar carcinoma in addition to cervical cancer, and should therefore have a thorough vulvar examination as part of routine gynecologic care.
- However, the absolute risk of invasive vulvar cancer is low.

- Following biopsy to rule-out intraepithelial neoplasia, we suggest that immunocompromised individuals **initially self-treat their warts with imiquimod**.

- Patients who cannot adhere to this outpatient therapy and those whose warts do not clear with medical treatment can be **treated surgically**.

- We prefer surgical excision to laser therapy, as the former allows pathologic analysis of removed tissue.

Involvement of the clitors

- Treat **warts on the clitoris** with the same therapies used on vulva warts.
- Surgical procedures on the clitoris should be performed by clinicians with **experience operating** in this sensitive area.

POSTTREATMENT ISSUES

- Use of **sitz baths**, mild analgesics (**acetaminophen**), and **loose clothing** can relieve discomfort and aid healing.

- Sexual activity may be resumed **when the patient feels comfortable** and after any **operative sites have healed**, but this may take several weeks.

Recommended Regimens for External Anogenital Warts (i.e., Penis, Groin, Scrotum, Vulva, Perineum, External Anus, or Perianus)*

Patient-applied: Imiquimod 3.75% or 5% cream[†]

OR

Podofilox 0.5% solution or gel

OR

Sinecatechins 15% ointment[†]

Provider-administered: Cryotherapy with liquid nitrogen or cryoprobe

OR

Surgical removal by tangential scissor excision, tangential shave excision, curettage, laser, or electrosurgery

OR

Trichloroacetic acid (TCA) or bichloroacetic acid (BCA) 80%–90% solution

* Persons with external anal or perianal warts might also have intra-anal warts. Thus, persons with external anal warts might benefit from an inspection of the anal canal by digital examination, standard anoscopy, or high-resolution anoscopy.

[†] Might weaken condoms and vaginal diaphragms.

Recommended Regimens for Vaginal Warts

Cryotherapy with liquid nitrogen. The use of a cryoprobe in the vagina is not recommended because of the risk for vaginal perforation and fistula formation.

OR

Surgical removal

OR

Trichloracetic acid (TCA) or bichloroacetic acid (BCA) 80%–90% solution

Recommended Regimens for Cervical Warts

Cryotherapy with liquid nitrogen

OR

Surgical removal

OR

Trichloracetic acid (TCA) or Bichloroacetic acid (BCA) 80%–90% solution

Management of cervical warts should include consultation with a specialist. For women who have exophytic cervical warts, a biopsy evaluation to exclude HSIL should be performed before treatment is initiated.


Thank
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