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Short Article

Treatment of Genital Warts in Pregnant Women

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Abstract

There are various treatments available for managing genital warts in pregnant women, but this does not mean that there is a definitive treatment protocol. We conducted a review to gain a better understanding of the available treatments for genital warts during pregnancy. We used Google Scholar, PubMed, and Web of Science databases to search for articles on this topic. To date, the most effective treatment is still unknown. Many indicators, including patient satisfaction and physiological conditions, are effective in determining treatment. Cryotherapy, laser therapy, and Trichloracetic acid 80–90% solution are among the safe treatments with the least side effects. Given that the likelihood of genital warts recurring increases due to changes in the body's immune system during pregnancy especially in younger pregnant women, more research is needed on this subject. We used the keywords pregnancy, genital warts, HPV, cryotherapy, laser therapy, electrocautery, surgery, topical treatments, and safe treatments in pregnancy in the article search process.

Keywords: *Pregnancy, genital warts, HPV, Cryotherapy, Laser therapy, Topical treatments, Common and safe treatments*

Introduction

Human papillomavirus (HPV) poses a significant public health challenge, particularly due to its role in various anogenital conditions, including condyloma acuminata. This virus consists of over 100 different types, which are categorized into low-risk and high-risk groups based on their potential to cause cancer. Low-risk types, especially HPV 6 and 11, are primarily responsible for benign lesions such as genital warts, while high-risk types, including HPV 16 and 18, are associated with cervical cancer and other anogenital malignancie.

The global prevalence of HPV infection is estimated to be between 9% and 13%, with a notably higher incidence observed among sexually active individuals aged 20 to 39 years. Genital warts, largely caused by HPV, are a considerable public health issue due to their widespread occurrence and related complications. The often asymptomatic nature of HPV infections can lead to underdiagnosis, particularly among partners of infected individuals. Research assessing the prevalence of HPV in spouses of men with genital warts revealed that many of these women were infected despite appearing healthy during clinical evaluations, highlighting the inadequacies of conventional diagnostic techniques [1-3].

Pregnancy creates a distinct environment for HPV infections, as physiological changes and a mildly immunocompromised state can affect the virus's behaviour. Evidence suggests that the rate of HPV infections increases during pregnancy, particularly in the third trimester [2,4]. Effective treatment options for genital warts are crucial, especially for vulnerable populations such as pregnant women. Among the most commonly employed treatments are cryotherapy and trichloroacetic acid (TCA), each having distinct efficacy and safety profiles. A randomized controlled trial comparing these two treatment modalities indicated that while TCA had a higher cure rate, both treatments were effective and well-tolerated by patients. This emphasizes the necessity for tailored treatment strategies that take into account patient preferences and the specific clinical situation, especially when managing genital warts related to HPV infection [5].

Managing genital warts in pregnant women presents several challenges due to the potential risks associated with various treatment options. Traditional approaches, such as surgical excision, may pose risks to both the mother and the fetus. As a result, less invasive alternatives like cryotherapy have become preferred first-line treatments because of their safety and effectiveness [2,6]. Additionally, the possibility of vertical transmission of HPV during childbirth raises concerns about neonatal health outcomes, including the risk of juvenile laryngeal papillomatosis [2]. Given the complexities involved in treating HPV-related genital warts during pregnancy, it is essential to investigate optimal management strategies for this demographic. This study aims to assess the efficacy and safety of various treatment modalities for genital warts associated with HPV in pregnant women, with a focus on minimizing risks to both maternal and neonatal health. Through this research, we aspire to improve clinical practices and contribute to the broader understanding of managing HPV-related conditions in pregnant patients.

Methods

A review of the keywords of scientific journal articles on the management of genital warts in pregnant women showed that the important issue in the management of this disease in pregnancy is the presence of the least side effects of the selected treatment on the mother and fetus, and common but teratogenic treatments are completely excluded from the treatment strategies. We tried to extracted and summarize the studies related to the title in order to provide useful information to the readers. In writing this review, the scientific databases PubMed, Scopus, Google Scholar and Web of Science were used.

HPV in Pregnancy

Human papillomavirus (HPV) infection is among the most prevalent sexually transmitted infections in both young individuals and adults. It often presents without symptoms, can remain dormant for months, and may not be detectable through routine clinical examinations. Despite its asymptomatic nature, HPV infection can progress to cancer, contributing significantly to morbidity and mortality worldwide [3]. Although HPV infections are generally transient and self-limiting, they can persist in immunocompromised individuals, and pregnancy is considered a state of immunosuppression Pregnant women are at a higher risk of HPV infection due to their altered immunological and endocrinological status [7]. In a review study with 13,640 pregnant women, the rate of HPV infection was higher than that of age-matched non-pregnant women, especially in those under 25 years of age. HPV-16 was the most common observed type [2]. This prevalence is two times higher in pregnant women compared to non-pregnant women. Furthermore, there is a potential risk of vertical transmission of HPV from the mother to the fetus during pregnancy or delivery. HPV cervical infections are also detected more frequently during pregnancy (15.53%) than in the non-pregnant population (12.6%). A systematics review that analyzed 14 articles involving a total of 7008 women demonstrated the significant association was identified between HPV infection and preterm delivery A comparative study showed a higher rate of HPV infection in women with abnormal course of the first trimester of pregnancy Compared to women with a normal pregnancy period. Intrauterine HPV infections are also possible, as HPV DNA has been detected in the placenta, amniotic fluid, and fetal membranes. Transmission to the fetus can occur through ascending infection from the vagina and cervix or via hematogenous spread. Studies further indicate that HPV can infect trophoblastic cells, potentially impacting the intrauterine environment and influencing pregnancy outcomes [7-9].

The Prevalence of HPV Infection in Pregnant Women

Pregnancy-related hormonal changes, including mild immunosuppression and elevated steroid levels, may further promote HPV replication. These physiological changes often lead to the proliferation of condyloma acuminata, resulting in larger lesions [10-12]. While some studies suggest pregnancy as a risk factor for HPV infection, findings remain inconsistent [2,13-15].

A meta-analysis by Liu et al reported a higher prevalence of HPV in pregnant women (16.82%) compared to non-pregnant women (12.2%) [2]. More recently, Ardekani and collogues, found that nearly one-third of pregnant women globally test positive for HPV based on cervico-vaginal samples. HPV infection during pregnancy has been associated with significant maternal and fetal morbidity and mortality [16,17]. Studies link HPV to placental abnormalities and adverse outcomes, including spontaneous abortion, preterm birth, premature rupture of membranes, intrauterine growth restriction, fetal death, and low birth weight [11,18]. Regarding HPV prevalence across pregnancy trimesters, results have varied. While Ardekani et al, reported the highest prevalence in the second trimester [16]. Liu et al, found the lowest prevalence during this period [2]. Ambühl et al, observed a declining trend from the first to the third trimester [14]. Globally, HPV types 16 and 18 are the most prevalent across all sampling sites [16]. Due to their oncogenic potential, these types are linked to pregnancy complications and future cancer risks, emphasizing the need for further research and preventive measures [19,20].

Treatment Strategy in Pregnant Women

Pregnancy creates a situation in which genital warts may recur and grow more rapidly in pregnant women than in non-pregnant women. Growth is most rapid between weeks 12 and 14 of pregnancy, and the lesions are larger in size. The severity of these processes is greater in new warts that develop during pregnancy. Changes such as decreased cellular immunity and increased blood vessel number, which consequently leads to increased blood flow in the genital area, increase human papillomavirus activity. Among the features of warts that develop during pregnancy, could mention their fragility of their structure, which leads to itching and bleeding [21,22]. Warts that become exceptionally large can cause labor dystonia or heavy bleeding by blocking the birth canal, and in such cases, a cesarean section is recommended for patients. There is a risk of human papillomavirus transmission from mother to fetus during childbirth. Infants infected with the virus may develop lesions on the conjunctiva, mouth, and/or genitals. [22-24]. Prenatal transmission of HPV types 6 and 11 from mother to fetus can rarely cause juvenile laryngeal papillomatosis (JLP). These clinical observations make effective management of genital warts during pregnancy essential. Our goal in this review is to provide a summary of approved and unapproved treatments for genital warts during pregnancy.

Cryotherapy

Cryotherapy is a therapeutic process in which liquid nitrogen causes tissue freezing and ultimately necrosis. Cryotherapy is one of the main treatments for genital warts, which, in addition to causing tissue necrosis, can stimulate specific immune responses against the remaining lesion tissue, resulting in the immunomodulatory function of T lymphocytes [25,26]. One of the unique features of cryotherapy is that it is safe during pregnancy. In addition, it is a simple and inexpensive treatment that rarely causes scarring or pigmentation in patients' skin [6]. The liquid nitrogen used in cryotherapy causes inflammation as it destroys the wart tissue, which subsides after a short period of time [27]. In cryotherapy, the base of the lesions and 1 to 2 millimeters of surrounding normal tissue are frozen. This treatment is continued every 2 weeks until the lesions are completely gone [27-29]. Although there have been reports of swelling, discharge, erythema, and pain in patients, all patients were able to complete the treatment. In the study by Bergman et al., cryotherapy resulted in two preterm

deliveries in 28 pregnant women (7.1%) [30,31] and in the study by Matsunaga et al., in 51 pregnant women, it resulted in five preterm deliveries (9.8%). Cryotherapy is a suitable treatment modality in non-pregnant patients, and results in satisfactory results, but it should be used with caution in pregnant women. Despite the weak evidence of the side effects mentioned, cryotherapy is considered a safe treatment for genital warts during pregnancy [28,32].

Laser Therapy

The advantages of using laser therapy include high precision of operation, reduced bleeding through vessel sealing and reduced scar surface. In addition, this treatment method has the ability to cause necrosis in a specific area. This ability leads to reduced inflammation, edema and infection . In a study conducted by Kryger and Baggesen, 15 pregnant women underwent laser therapy for genital warts. Except for one pregnant woman who experienced "symptoms of preterm labor for a few days," the rest responded to the treatment without any side effects [33,34]. The use of CO2 lasers and Nd-YAG lasers is known as effective treatment methods for removing genital warts. This treatment method reduces the risk of recurrence and complications during childbirth and prevents infection of the fetus [30,35,36]. Overall, various studies showed that the use of lasers for the removal of vascular lesions of the skin, pigmented lesions and treatment of genital warts is a safe and effective method [37].

Electrocautery and Surgery

Surgery is a mechanical procedure using a scalpel or scissors that allows for direct removal of the genital wart. The use of electrical energy during surgery is called electrosurgery, which is a more advanced method of lesion removal [28]. In a study conducted by Duus et al., it was shown that the clearance, recurrence, and postoperative side effects including pain, healing time, and scar formation of surgical treatments were similar to laser therapy [38]. One advantage of these methods is the possibility of removing all lesions in one session and creating the opportunity for pathological evaluation [30]. In addition, they are considered a suitable treatment option during pregnancy [39].

Photodynamic Therapy

Photodynamic therapy (PDT) with 5-aminolevulinic acid (ALA) method clears a very large volume of lesions and is well tolerated by the patient. This method is a unique treatment in pregnant women with genital warts with minimal adverse effects on the mother and fetus [40]. Other studies have shown that photodynamic therapy, in addition to helping to better clear the lesion, reduces the recurrence rate more than other treatment methods. However, further studies are recommended to ensure fewer side effects and the safety of this treatment in pregnant women [30].

5-Fluorouracil

In addition to inhibiting DNA synthesis, 5-fluorouracil can block thymidylate synthase, thereby inducing apoptosis [41]. It is available commercially as a 5% cream. Pain, burning, inflammation, and ulceration are known side effects of 5-fluorouracil therapy [42]. Studies have shown that 5-fluorouracil therapy should not be used during pregnancy [30,41].

Interferon

Interferon heals virus-infected cells by strengthening the immune system. Interferon can reduce the risk of relapse by treating virus-infected cells. In addition, it is also used to treat lesions that are visible to the naked eye [43,44]. Interferon is contraindicated during pregnancy [30]. Because interferon therapy is expensive, and because it is controversial in the treatment of genital warts, it is preferred for treatment-resistant cases [45]. In refractory non-pregnant patients, interferon may be used as an adjunct to other treatment strategies, such as surgical and ablative therapies. Overall, the evaluations suggest that interferon is contraindicated in pregnancy [41].

Podophyllotoxin

Topical podophyllotoxin, which is prescribed as one of the first-line medications for the treatment of genital warts, is contraindicated during pregnancy, All medications that use this compound in their structure are contraindicated during pregnancy due to its antimitotic properties, which are considered a toxic compound for the fetus [46-48]. No teratogenic effects have been observed following topical administration in animal studies, but the use of this drug during pregnancy is limited due to the limitations in extrapolating animal data to humans. The lack of teratogenic effects has also been demonstrated at doses up to 5 times the maximum recommended human dose [49-51]. Studies have shown that doses much higher than the maximum recommended human dose, approximately 19 times, administered intraperitoneally to pregnant rats resulted in fetal toxicity. However, topical application of podophyllotoxin has shown negligible systemic absorption. Avoiding topical treatments for genital warts with Topical podophyllotoxin is recommended during pregnancy [52-54].

Sinecathecins

Treatment of genital warts with syncatechin resulted in the occurrence of the side effects of urethral stricture, urinary tract irritation, genital herpes simplex, vulvitis, hypersensitivity, skin pruritus, pyelonephritis, application site reactions, phimosis, and inguinal lymphadenitis in 5% of patients, which led to discontinuation of further treatment. Sinecatechins is FDA Pregnancy Category C According to the FDA, Sinecatechins is a Category C drug and is contraindicated during pregnancy [55].

Retinoids

Retinoids are contraindicated in pregnant women and women attempting to conceive because of their teratogenic effects. Retinoid therapy during pregnancy has been associated with skeletal abnormalities that result from long-term chronic toxicity. In most cases, these symptoms correspond to the symptoms of diffuse idiopathic hyperostosis syndrome [56].

Imiquimod 5% Cream

Imiquimod was first approved by the U.S. Food and Drug Administration (FDA) in 1997 as a treatment option for genital warts. Randomized, double-blind, placebo-controlled trials have confirmed the effectiveness of imiquimod. It is a member of a class of immune response modifiers that is well tolerated. The U.S. Food and Drug

Administration does not recommend the use of imiquimod during pregnancy and has classified it as a category B drug. It should only be used as a last resort when the benefits outweigh the risks [57-59].

Trichloracetic acid 80–90% Solution

The therapeutic effect of trichloroacetic acid on genital warts is by chemical coagulation of the proteins of the wart cells, which leads to corrosion of the skin and mucous membranes. These processes ultimately lead to tissue necrosis. Because trichloroacetic acid is not absorbed through the skin and mucous membranes, it is considered a safe treatment for pregnant women. However, the effectiveness of this compound in different populations requires further study [27,30]. Studies have shown the positive effect of administering trichloroacetic acid in combination with laser therapy in pregnant women. In another study, treatment with trichloroacetic acid resulted in complete clearance of the wart lesions in 97% of women, but premature rupture of membranes in one patient at 35 weeks of gestation and acute pyelonephritis in another pregnant patient were side effects of this type of treatment. However, it is not definitively determined whether these adverse effects were side effects of the drug [60]. Despite the widespread use of trichloroacetic acid in clinical practice, this drug should be prescribed with caution [47].

Topical and Intralesional Immunotherapy

The use of immunotherapy in the treatment of genital warts has been associated with good efficacy. The advantages of this method include high safety, low recurrence rate, and clearance of untreated long-term warts. Bayoumy et al., showed showed that the use of immunotherapy in 40 pregnant women resulted in improvement in 85% of patients. Among them, 47.5% showed complete clearance with minimal side effects. This treatment leads to increased serum interleukin-12 (IL-12) and the production of Th1 cytokines such as interleukin-4 (IL-4), interleukin-5 (IL-5), IL-8 through recruitment of antigen-presenting cells. It also helps to clear warts through a general response that includes the secretion of interferon (IFN)-gamma and TNF-alpha. This treatment method is considered safe for use in children and pregnant women [61-63].

Conclusion

Given that genital warts are among one of the common sexually transmitted diseases, and that pregnant mothers are at risk of contracting this disease, it seems appropriate to pay attention to these patients and choose the appropriate treatment for them. During pregnancy, the exacerbation of genital warts and the risk of transmitting the disease to the fetus must be considered. Another important point to keep in mind is the limitations of available treatments that can be chosen for mothers during pregnancy. Cryotherapy, TCA application, Topical and intralesional immunotherapy, as well as laser and surgical treatments, are among the treatments that can be usable and safe in during pregnancy.

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