CRYOTHERAPY FOR THE MANAGEMENT OF GENITAL WARTS IN PREGNANCY: A FIVE-YEAR OBSERVATIONAL STUDY

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ABSTRACT

Objective: This observational study aims to review our experience in using cryotherapy for the management of genital warts during pregnancy over a five-year period.

Methods: Fifty-three pregnant women with established genital warts were managed during the period from January 2000 to April 2005. There were 23 patients in the first trimester, 22 in the second, and 8 in the third trimester. Base line laboratory investigations were performed to establish any abnormalities and any other concurrent sexually transmitted diseases before starting treatment in each patient. Sexual abstinence or the use of protective barriers was advised to all patients. Cryotherapy was performed for the treatment of all genital warts. The treatment was on an out-patient basis, and the women were followed up every two weeks throughout pregnancy, and every month afterwards until nine months post delivery. Infants were also examined at birth and at nine months of age.

Results: There was dramatic response to local cryotherapy during pregnancy against genital warts, with 84.9% clearance of lesions prior to delivery. There were no cases of premature labour or premature rupture of membranes directly related to treatment, and there were no cases of neonatal genital or laryngeal involvement. Although no recurrences of lesions were observed before delivery, there was an overall recurrence rate of 45.3% at nine months post delivery.

Conclusion: Cryotherapy is an effective and safe method for the treatment of genital warts throughout pregnancy.

Key words: Condylomata acuminata, Genital Warts, Pregnancy, Cryotherapy.

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Introduction

Genital human papillomavirus (HPV) infection is one of the most common sexually transmitted diseases in the developed world.[1,2]

The infection is usually subclinical, most commonly affecting young women of childbearing age.[1,3] Incidence rates of 10-20% have been reported in young men and women aged 18-25 years of age. Clinical infection with HPV results in the development of genital warts (condylomata acuminata) in 0.5-2.0% of the sexually active population.[3]

Currently, there are over 100 different types of HPV and more than 30 of those may be spread by sexual contact.[4] Transmission in genital areas is augmented by moisture and epithelial disruption.[5] The most frequent types causing condylomata acuminata are subtypes six and 11.[3-6]

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The importance of genital HPV infection is emphasized by its link to cervical and vulvar neoplasia. More than 90% of all cervical dysplasia and cancers are HPV positive.[1,2,7] HPV Subtypes 16 and 18 have been recovered in approximately 70% of cervical cancers.[2,4,7,8]

Genital warts are highly contagious and are spread through oral, genital and anal sex with infected partners. Approximately two thirds of individuals who have sexual contact with an infected partner develop genital warts.[4] The incubation period is believed to be around three months,[4] but may range between 3 weeks and 8 months.[9] While the vulva is the most common site for genital warts, multiple sites are observed in up to 50 % of patients.[1] The diagnosis is usually made on clinical grounds, and histopathological examination is only needed in suspicious cases, where verrucous carcinoma has to be ruled out prior to treatment.[8] Small warts may be better visualised with a magnifying glass, or by colposcopic examination. Inconspicuous lesions become more apparent after the application of acetic acid. However, this is not recommended for the diagnosis of subclinical infection in patients without visible genital warts, and it is best reserved for the identification of vulvar intraepithelial neoplasia II and III.[1]

Sixty-one percent of women with genital warts may have genital co-infection, being a sexually transmitted disease in approximately 28% of the cases.[3,4] In general, untreated genital warts may resolve spontaneously, remain the same, or increase in size and/or number.[1]

During pregnancy, there is an increased prevalence of anogenital HPV infections from the first to the third trimester. Elevated steroid hormone levels during pregnancy cause condylomas to enlarge and spread rapidly.[4,6] In addition, diffuse genital warts during pregnancy, especially those affecting the cervix, may complicate vaginal deliveries; causing difficult-to-control bleeding or causing difficult labour or 'tumour previa'.[4]

Furthermore, there is widespread concern about maternal-neonatal transmission.[3,9,10] Neonates are at higher risk for HPV exposure after vaginal delivery than after caesarean delivery (51.4% vs. 27.3% respectively).[10] However, the risk of acquiring laryngeal papillomatosis is very low and estimated to be between 1 in 400 and 1 in 1000,[1,3] and caesarean section does not protect newborns from HPV infection completely. Therefore, a caesarean section is only indicated if the genital lesions are so large that they cause a physical obstruction to spontaneous vaginal delivery, or if there is a risk of severe bleeding.[1,6,11] For all the above reasons, most clinicians tend to treat pregnant women with genital warts prior to delivery. In practice, there is no universal agreement about the best therapeutic option for the management of genital warts,[8,12] and treatment is usually reserved for visible lesions. Most treatments are painful, expensive, generally not curative, and recurrences are common.[11] The choice of treatment modality for genital warts depends on size, number and distribution of lesions, and on patient preference.

Cryotherapy is considered one of the safest methods that can be used for the treatment of genital warts in pregnancy,[1,4,13] and is easily available in most clinics. Therefore, cryotherapy should be considered as first-line therapy during pregnancy, except in cases with large lesions, which may require surgical intervention.[1] In our practice, we employed cryotherapy for the treatment of all pregnant women presenting to us with genital warts over the past five years. The goal of therapy during pregnancy was to prevent the newborn from contracting the disease by infection with HPV in the birth canal,[8,10] to avoid unnecessary caesarean sections, to reduce transmission to the sexual partners, and last but not least for cosmetic as well as psychosocial reasons,[3] as they are aesthetically unacceptable for both patients and their partners.

Methods

This study was conducted at Prince Rashed Bin Al-Hassan and Prince Hashem Bin Al-Hussein Hospital during the period from January 2000 to April 2005 included 53 pregnant women with established external genital warts. Evaluation included cervical, vaginal, and vulvar areas as well as the peri-anal region. All women had gynaecological examination, cytological Papanicolaou (Pap) smear test, and colposcopic examination before starting cryotherapy. Five percent acetic acid solution was used to aid the detection of very small Human Papilloma Virus (HPV) lesions. Biopsy was only performed in atypical lesions to confirm the diagnosis histologically.

Considering the frequent coexistence of other sexually transmitted diseases, baseline laboratory investigations were performed to establish any abnormalities and any other concurrent sexually transmitted diseases before starting treatment in each patient. Treatment of other concomitant diseases (such as vaginitis or candidiasis) was initiated before starting cryotherapy. All patients were asked to abstain from sexual activities during the course of their treatment. Sexual partners were concomitantly examined, and treated if genital warts were present. Protective barrier was advised to all patients engaged in active sexual relationships.

Table I. The sites of genital warts at presentation

Site of lesion	First trimester	Second trimester	Third trimester	Total (% of all patients)
Cervix only	0	0	0	0 (0)
Cervix + vagina	0	0	0	0 (0)
Cervix + vulva	1	1	0	2 (3.8)
Cervix + vagina + vulva	2	1	0	3 (5.7)
Vagina only	0	2	1	3 (5.7)
Vulva only	9	11	1	21(39.6)
Vagina + vulva	11	7	6	24 (45.3)
Total	23	22	8	53 (100)

Table II. Pregnancy outcome in the study group

	Gestational age at initial presentation		
	First trimester	Second trimester	Third trimester
Normal vaginal delivery	21	18	6
Caesarean section	1	2	2
Premature delivery	0	2	0
Premature rupture of membranes	1	0	0
Mean gestation at delivery in weeks	38.2 (±3.6)	39.1 (±3.2)	39.2 (±3.5)
Mean interval in weeks between last treatment and delivery	20.4 (±2.1)	15.6 (±6.4)	1.3 (±0.9)

Cryotherapy was performed with a spray gun, using liquid nitrous oxide. It was performed on each wart including its base and 1-2 mm of surrounding normal tissue.[3] The duration of freezing varied between 30 seconds and 2 minutes, depending on the size of the lesion. All visible lesions were treated each session, and treatment was repeated every 2 weeks, until all visible lesions completely disappeared. All treatments were performed without anaesthesia, and on an out-patient basis. No other forms of treatments were allowed during the study period.

Patients were examined for the presence of lesions every 2 weeks during pregnancy, and every month afterwards until 9 months post delivery. All the newborns were examined for the presence of genital, peri-anal or laryngeal involvement at birth and at 9 months of age.

Results

At first presentation, there were 23 patients in the first trimester, 22 patients in the second, and 8 in the third trimester. The mean age was 32.6±8.2 (range from 19 to 43 years), and the mean parity was 3.6 (range from 0 to 7). Of the 53 patients, five had cervical involvement in addition to condylomata acuminata of the vulva and/or vagina. These patients (three in the first trimester and two in the second trimester) were referred to the Obstetrics and Gynaecology department at King Hussein Medical Centre (KHMC) for cryosurgical management by more experienced colposcopists. The remaining 48 patients were managed at the Dermatology clinic of our hospital, and all had normal colposcopic examination and negative cervical smears before cryotherapy was used. The sites of lesions in all patients at presentation are outlined in Table I.

None of the patients examined had individual lesions larger than 10 mm in diameter. In patients with vulvar involvement (50 patients in total), the lesions covered both the minor and major labia, and in four patients there was also involvement of the peri-anal area, in whom proctoscopy was performed, but there was no intra-rectal involvement. No malignancy was diagnosed in seven (five cervical and two atypical-looking lesions in the vulva) biopsied lesions.

Out of 53 patients involved in the study, 17 patients (32.1%) required only two sessions of cryotherapy before their genital warts disappeared, 31 (58.5%) patients required three sessions, and the remaining five patients (9.4%), all with cervical involvement and treated at KHMC, required six sessions before all their condylomas disappeared. Four patients delivered within two weeks of their last cryotherapy. Seven women still had genital warts at the time of delivery, and their treatment was re-started in the post partum period. The other 42 patients delivered more than two weeks after their last cryosurgical treatment sessions. The mean gestational age at delivery was within normal range for all groups. Table II summarizes the pregnancy outcomes in the study group.

Most patients had intact membranes at start of labour, including four of the five patients who had cervical cryotherapy. However, premature rupture of membranes occurred in one patient who presented in the first trimester (eight weeks of gestation) with genital warts involving the vulva, vagina, and cervix. Her condylomas had cleared 13 weeks before rupture of membranes at 33 weeks of gestation. She delivered vaginally two weeks later. Two patients (who presented in their second trimesters) had premature deliveries: one delivered at 31 weeks of gestation, 26 days after her third cryotherapy session for cervical and vulvar warts, and was clear of lesions at time of delivery. The other patient

delivered at 29 weeks of gestation, only 14 days after her initial treatment for vulvar warts. Her infant was managed in the neonatal ward for respiratory problems and was discharged two weeks later. Her genital warts were not clear at time of delivery, and she was further treated after delivery.

Caesarean section was performed on five patients: one presented in her first trimester, two in the second, and two in their third trimesters. One of the patients who presented in her third trimester (37 weeks of gestation) delivered five days after her second treatment session. The other four patients delivered at least three weeks after their last cryotherapy. The indications for caesarean sections were: foetal distress in four patients, and cephalopelvic disproportion in one patient. The remaining 45 patients had normal, full term vaginal deliveries. Of these, two patients (both in their third trimester) had deliveries three and five days after their last cryotherapy sessions.

Overall, of the 53 patients in our series, there was dramatic response to local cryotherapy during pregnancy against genital warts, with an 84.9% clearance of lesions prior to delivery. There were no neonatal cases of genital or laryngeal condylomata reported during the study period. Women patients were re-examined at nine months post delivery, and there was evidence of recurrent genital warts in 24 patients (45.3%). These were treated by cryotherapy and/or electrocautery, with eventual clearing of the lesions.

There were no cases of premature labour or premature rupture of membranes directly related to treatment with cryotherapy. There were no abortions or intrauterine deaths in the study group. During the study, only 11 patients required oral analgesia for pain relief after cryotherapy for extensive condylomas during their first sessions.

Of the sexual partners, 38 were examined and 13 were found to have clinically apparent genital lesions. These patients were also treated by cryotherapy, and were followed up every two weeks until free of disease. The remaining 15 male partners did not attend for examination.

Discussion

The treatment of condylomata acuminata is advocated usually for cosmetic or social reasons. It also reduces the risk of malignant transformation. In addition, treatment is warranted in pregnancy for both maternal and foetal reasons, as already mentioned.

Despite the wide range of therapeutic options, most available modalities cannot be used safely in pregnancy. The only treatments that are not contraindicated in pregnancy are cryotherapy, electrocautery, surgical excision, and laser therapy.[3,6,8] Rarely, caesarean section is required in cases of severe overgrowth of warts blocking the vaginal outlet.[9]

In general, cryotherapy is effective in pregnant as well as non-pregnant women.[11] In non-pregnant women, cryotherapy is usually used for treating small genital warts, and has reported clearance rates of 63-88% after three months of therapy, and a recurrence rate of 21-39%.[3,4,9] After six months, cryotherapy has efficacy rates of 38-73%, and a recurrence rate of ~ 27%.[6] In our study, the clearance rate up to delivery was 84.9%, with a recurrence rate of 45.3% over a nine months postpartum follow up period. The recurrence is attributed to persistence of subclinical infection, re-infection or due to suboptimal treatment. To be effective, cryotherapy has to be given at an appropriate depth, and should be repeated frequently. If multiple warts are to be treated by cryotherapy, it is generally useful to use local anaesthesia (e.g. lignocaine gel) prior to treatment to make the procedure more tolerable.[3] Electrocautery, surgical excision or laser treatment should be considered when patients have obstructive symptoms, extensive disease or large lesions (greater than 10 mm in diameter).[8,9,14]

Although many trials have found similar costs and response rates for cryotherapy, compared to podophyllin, trichloroacetic acid (TCA), and electrocautery; these treatments are either not recommended for use in pregnancy or they have many drawbacks for use in community hospitals.[6,8] In contrast to cryotherapy, electrocautery and laser therapy require specialised equipment and are more expensive overall.[12] Electrocautery may be associated with severe bleeding, infection, and diffuse tissue necrosis.[3] Although laser treatment is considered safe during pregnancy,[15] and has been used with relatively good results for the treatment of genital condylomas,[5,14] this technique is generally more expensive than cryotherapy, and is not as readily available in most community hospitals.[1] Furthermore, it is performed under anaesthesia and usually requires hospital admission. Laser ablative therapy is also associated with relatively high recurrence rates, ranging from 60% to 77%.[6] Side effects of laser therapy include hyper or hypo pigmentation, and possible scarring. In contrast to laser ablative therapy, cryotherapy is performed as an out-patient procedure, and usually requires no anaesthesia, and little analgesia.[9,13]

Podophyllin, podophyllotoxin and fluorouracil are contraindicated in pregnancy as systemic absorption may occur, especially when treating large lesions.[3,4,8] This may be associated with increased abortion rate, malformations, intrauterine foetal

death, and premature labour. Although trichloroacetic acid (TCA) has been used in pregnancy,[3,6] the American Food and Drug Administration (FDA) gives it category C (i.e. its safety has not been established in pregnancy),[4] and is therefore not recommended in this setting. Although imiquimod has been used rarely in pregnancy,[16] there are no human studies of its effectiveness, and it is generally not recommended for use during pregnancy.[9,11] Chemotherapy, immunotherapy and antimetabolites also have serious foetal hazards and are not used during pregnancy.

In our study, cryotherapy was not associated with increased risk of bleeding, necrosis or infection at the site of treatment. Premature delivery and premature rupture of membranes did not occur within two weeks of treatment. Most patients were delivered at term, and had normal healthy children. Similar to previous studies, cervical cryotherapy did not seem to increase the risk of premature delivery or premature rupture of membranes.[13] Labour was unaffected by cryotherapy for genital warts, even when the cervix is involved. All caesarean sections were performed for reasons unrelated to the presence or absence of genital warts. The use of cryotherapy for the treatment of genital warts in pregnancy was successful in preventing overgrowth of these lesions, and in turn preventing unnecessary caesarean sections.

The majority of our patients (90.1%) required only two to three sessions of cryotherapy before their condylomas resolved. Only eight patients were not clear of their warts at time of delivery; all of whom did not have any negative consequences on either mother or foetus. All patients were treated as outpatients, none of them requiring admission in relation to the treatment of their warts. No anaesthesia was used prior to cryotherapy in any patient. The discomfort suffered by patients due to cryotherapy was minimal, with only eleven patients requiring oral analgesia. Although no Human Papilloma Virus (HPV) disease has been found in the newborns even at nine months of age, laryngeal papillomatosis may develop later, and it is advised that these children stay under surveillance until the age of five.[4]

Recommendations

- Male partners of female patients with genital warts should be inspected for the presence of genital lesions, and treated accordingly.
- Patients with cervical warts should undergo colposcopy and cervical biopsy, with subsequent appropriate treatment if cervical neoplasia is detected.
- Females with genital warts should undergo regular Papanicolaou (PAP) smear tests as Human Papilloma Virus (HPV) infection is associated with dysplastic changes.

Conclusions

- Cryotherapy remains a trusted tool because of its reliability, ease of use, and its low cost.
- Cryotherapy has an excellent efficacy and is considered safe for both mother and fetus throughout pregnancy.
- A limitation of the study is the lack of a direct comparison with other treatments regimens such as trichloroacetic acid (TCA), electrocautery, or laser ablation. Further, a randomised control study is recommended.

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