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Perspective clinical study on effect of 5-aminolevulinic acid photodynamic therapy (ALA-PDT) in treating condylomata acuminata in pregnancy☆

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ABSTRACT

Objective: To observe the clinical efficacy of 5-aminolevulinic acid photodynamic therapy (ALA-PDT) in treating vulval condylomata acuminata (CA) in pregnancy.
Methods: The clinical efficacies of ALA-PDT on 16 cases of CA in pregnancy as well as cryotherapy on 22 cases of CA in pregnancy were analyzed in this prospective study.
Results: The treatment group showed a wart clearance rate of 93.8% after 3 PDT treatments, while the control group showed a wart clearance rate of 72.7% after 3 cryotherapy treatments. After the 3-month follow-up period, the treatment group registered a recurrence rate of 6.3%, whereas the control group recorded a recurrence rate of 36.4%, indicating a statistically significant difference ($\chi^2 = 4.674$, $p = 0.031 < 0.05$). After the 1-month postpartum follow-up period, the newborns grew and developed well, without any abnormality in physical examinations.
Conclusion: ALA-PDT is safe and effective in treating CA in pregnancy.

1. Introduction

Condyloma acuminate (CA) in pregnancy refers to genital, perineal and perianal papillomavirus-like hyperplasia caused by infection with human papillomavirus (HPV) during pregnancy [1,2]. Affected by the change in estrogen and a local moist environment at the vagina, HPV is actively replicated, and CA grows rapidly during pregnancy [3,4]. During pregnancy, warts mostly occur at the vaginal orifice, cervix and vaginal wall. At these specific anatomical sites, traditional therapies, such as carbon dioxide laser, microwave and surgery, are easy to cause ulcer or local infection [5,6]; besides, some drugs for external use are not available to pregnant women. Therefore, treatment for CA in pregnancy has always been one of concern. In recent years, PDT has achieved a good therapeutic effect in treating CA, but there have still been few reports for the application of PDT in treating CA in pregnancy [7–9]. We made a clinical analysis on 38 cases of vulval CA in pregnancy in this prospective study, and achieved a good efficacy. The report is as follows:

2. Materials and methods

2.1. General information

The 38 cases were diagnosed as CA in pregnancy at our department between September 2009 and December 2013. They were aged between 19 and 32 years old, with the pregnancy period between 4 and 34 weeks. The course of the disease ranged between 4 and 6 weeks. The warts were found at the vaginal orifice, and the number ranged between 2 and 11, mean was 5.5 and 5.6 respectively in PDT group and cryo group. The mean gestational age was 15.9 and 17 weeks respectively. The inclusion criteria were cases in pregnancy, conformity with clinical diagnostic criteria of CA; occurrence of warts at the vaginal orifice; wart diameter < 0.5 cm; exclusion of HIV infection; voluntariness of receiving PDT or cryotherapy.

2.2. Materials

5-aminolevulinic acid dispersant (produced by Shanghai FudanZhangjiang Company, specification: 118 mg) was stored in dark place. LED-IB photodynamic laser therapeutic instrument (produced by Wuhan Yage Optic and Electronic Technique Co., Ltd.) can produce

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semiconductor laser, with the wavelength 633 ± 10 nm, and is equipped with a special laser probe whose light spot size can be adjusted according to the lesion area, cylindrical fiber and disposable plastic casing.

2.3. Therapeutic method

The therapies for CA in pregnancy were clinically analyzed in this prospective study. The therapies were reviewed by the ethics committee of our hospital, and the therapeutic regimens conformed to the requirements for medical ethics. Before treatment, we communicated with the patients and their husband for many times, in order to inform them of the treatment process and post-treatment cautions in details. After they accepted the above mentioned content, they signed the informed consent. PDT: ALA dispersant was prepared into 20% solution with water for injection. Sterile degreasing cotton with the solution was placed on the warts and wrapped with plastic film. Four hours later, the warts were exposed and irradiated under 633 ± 10 nm semiconductor laser, with the energy density between 90 and 100 J/cm^2, the irradiation time of 20 min/spot and the distance of 20 cm. The cases were treated once every 2 weeks. The regression of skin lesions and the changes in warts were observed after 3 treatments. Cryotherapy: The warts were frozen with liquid nitrogen one by one for 2 freezing and thawing cycles. The cases were treated once every 2 weeks. The regression of the skin lesions and the changes in warts were observed after 3 treatments.

2.4. Efficacy judgment criteria

Complete clearance: all of the warts disappeared; efficient: over 70% of the warts disappeared; inefficient: a small number of the warts (< 30%) disappeared, or no reduction or even increase in the number of warts. Clearance rate = the number of completely removed warts / the total number of warts ×100%, recurrence rate = the number of recurrent warts / the total number of warts ×100%.

2.5. Statistical processing

Data statistics was processed with SPSS19.0 software. χ^2 test showed $p < 0.05$ as statistical significance.

3. Results

3.1. Clinical efficacy

Among the cases, 16 cases in the PDT treatment group showed a wart clearance rate of 93.75% (15/16) after 3 treatments; 22 cases in the cryotherapy treatment group showed a wart clearance rate of 72.7% (16/22) after 3 treatments. After the 3-month follow-up period, the PDT treatment group showed a recurrence rate of 6.3%(1/16), and the cryotherapy treatment group showed a recurrence rate of 36.4% (8/22), indicating a statistically significant difference ($\chi^2 = 4.674$, $p = 0.031 < 0.05$).

3.2. Adverse effect

After treatment, the PDT group suffered from mild burning(15/16), pain(10/16), edema(10/16) and exudation(5/16), with no cicatrization or other adverse reactions. In the cryotherapy group, 14 cases showed edema and pain around warts after cryotherapy, while 6 cases had bleeding from the warts during cryotherapy, with no infection or cicatrization.

3.3. Birth outcome

All pregnancies resulted in healthy live births without delivery complications or low birthweight. The mean birthweight of PDT and cryotherapy groups was 3073 g and 3105 g respectively. We failed to get the Apgar scores of all the neonates. Every of the neonates whose Apgar score was obtained scored 10, three in PDT group and five in cryotherapy group.

4. Discussion

CA is a sexually transmitted disease caused by HPV, with a high recurrence rate. In addition to visible warts, latent HPV infection and subclinical infection are also important reasons for recurrent attacks of CA [10–12]. CA in pregnancy usually features a large number of fast-growing warts, which may be caused by active HPV replication due to high hormone during pregnancy [4]. HPV-DNA was detected in warts of all of 38 cases of CA in pregnancy, which were mainly type 6 and type 11. Among our patients, we found a possibility of infecting CA at any stage of pregnancy. Due to immunosuppression, change in hormone, increase in vaginal secretion, congestion and edema at the genital tract, and loosening of tissues during pregnancy, the incidence rate of CA is higher in pregnancy than non-pregnancy [3]. So far, no definite data proves that a pregnant woman infected with CA can transmit HPV to the fetus through blood; however, the fact is that most of affected fetuses are directly infected with HPV at the birth canal, and these infants are likely to suffer from laryngeal papilloma [4]. CA in pregnancy is hard to be treated due to the warts' soft tissues and easy bleeding and the possibility of affecting the fetus. Currently, the treatment of CA in pregnancy mainly aims to remove visible warts, and minimize the number of warts at childbirth, so as to reduce the opportunity for exposing the newborn to HPV [13]. In clinic, Podophyllum Resin/Podophyllotoxin and 5-FU have teratogenetic effects and thus are prohibited from pregnancy [13,14]. During pregnancy, any blind drug use may cause severe teratogenesis or even stillbirth, while non-treatment for fear of drug risk may also damage the health of the pregnant woman and the fetus. Because few pregnant women have been involved in clinical trials, there is little information available for the evaluation of correct drug use during pregnancy. Therefore, the drug use for pregnant women has always been a headache for clinicians.

The principle of PDT is that photosensitizer can be selectively enriched in abnormally proliferative lesions infected with viruses after being locally applied in warts. Under 635 nm light irradiation, photosensitizer can produce singlet oxygen, which has a killing effect on proliferative cells, and can selectively remove warts, with a slight damage to normal mucosa tissues and no severe local adverse reaction. Besides, photosensitizer ALA for external use will be retained in treated tissues for 24–48 h. After intravenous injection or oral administration, ALA is mainly discharged from the urine in its original form, and mostly excreted from the body within 6 h. Protoporphyrin IX can be cleared from the body within 24 h, and will not be accumulated in tissues for a long period nor increase the phototoxic reaction after multiple treatments [15,16]. In recent years, some scholars have studied that PDT can activate local specific immunity for the purpose of treatment [17]. PDT's light wave lengthen is 635 nm, with the penetrability of 6mm [18]. When the light irradiates on the vaginal mucosa, it would not cause any adverse effect on the fetus in the uterus in theory. In treatment for non-pregnancy cases, we found that PDT can significantly reduce the recurrence of CA [19]. Previously, our treatment team had reported 3 cases of CA in pregnancy treated with ALA-PDT [20]. However, due to the small sample sizein the report, our department conducted this prospective study on the clinical efficacy of PDT and cryotherapy in treating 36 cases of CA in pregnancy. In the PDT treatment group, 15 cases showed a complete clearance of warts after 3 treatments; 1 case had a recurrence at the vaginal orifice due to vaginal co-infection with candida albicans, which was later treated with topical antifungal therapy combined with PDT and then clinically cured (Table 1).

During treatment for the two groups of CA in pregnancy, pain is the

Table 1
Comparison in clinical efficacy between two groups of CA in pregnancy (%) $\chi^2 = 4.674$, $p = 0.031 < 0.05$.

Group	Number of cases	Inefficient	Efficient	Cured	Cure rate	Recurrence	Recurrence rate
PDT	16	0	1	15	93.8	1	6.3
Cryotherapy	22	0	6	16	72.7	8	36.4

main adverse reaction. Pain is a complex subjective feeling that varies from case to case. In practice, pain is obvious at the first treatment, in the case of co-infection with candida albicans and at the first 3 min of irradiation. Any unbearable pain can be relieved by local cooling and irradiation suspension. During cryotherapy, because the cases suffered from sharp pain, the treatment was often suspended for a while and continued after pain relief. After treatment, edema can be relieved by cold compress and dressing change with iodophor; 1 case of co-infection with candida albicans suffered from significant edema after treatment. The principle of cryotherapy for CA is based on the destructive effect of low temperature on cells. However, low temperature and ultra low temperature can be used to remove only visible warts, but not viruses in sub-clinically infecting areas around the warts; therefore, new warts would grow from latent virus. It was for this reason that CA is easy to relapse. We found that warts were easy to blood after repeated freezing and thawing cycles during cryotherapy, while the light irradiation of PDT caused neither direct damage to warts nor bleeding. A shortage of cryotherapy is high recurrence rate. At six months follow-up after cryotherapy, 25 (69%) interferon and 27 (73%) placebo recipients experienced recurrences [21]. In another study, the recurrence rates in the ALA-PDT combined with cryotherapy group and cryotherapy group were 3.6% (5/137) and 31.5% (35/111) in the external genitals ($P < 0.05$) [22].

During treatment for CA in pregnancy, more cares from clinicians were also beneficial for treating and reducing adverse reactions. After the 1-month postpartum follow-up period, the newborns grew and developed well, without any abnormality in physical examinations; and after the 1-year postpartum follow-up period, none case reported neonatal infection with CA. In conclusion, treatment for CA in pregnancy can reduce both the infectivity of affected lying-in women at childbirth and the risk of neonatal infection with CA. On the basis of the findings, ALA-PDT has a definite therapeutic efficacy on CA in pregnancy, and any case of CA in pregnancy shall be diagnosed and treated as early as possible.

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