



Successful pregnancy and delivery following selective use of photodynamic therapy in treatment of cervix and vulvar diseases



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ABSTRACT

Background: Photodynamic therapy has been gaining popularity, particularly among young women. Therefore it is crucial to evaluate PDT for safety and its impact on fertility and delivery of healthy newborns.

Objective: The study analyzed the PDT treatment of 10 young women, who suffered from diseases of the vulva and cervix. The aim of the analysis was evaluating what impact PDT treatment had on their pregnancies and delivery.

Methods: 10 patients (22–32 years of age, 25.5 years of age on average) were treated with PDT in 2007–2014. 2 patients suffered from squamous cell hyperplasia, 2 patients from vulvar lichen sclerosis, 1 – genital warts, 1 – VIN I (current terminology: LSIL/Flat condyloma), 2 – CIN III (HSIL), 2 – CIN I (LSIL).

The patients underwent photodynamic therapy (PDT). In the course of PDT the 5% 5-aminolevulinic acid was used in gel form three hours before irradiation. The affected areas were irradiated with a halogen lamp PhotoDyn 501 (590–760 nm) during a 10-min radiation treatment. The treatment was repeated weekly for 10 weeks.

Results: The median observation time period between the end of therapy and delivery was 3.92 years (2–7 years). None of the patients suffered from infertility. All patients gave birth to healthy, full-term infants. In case of one pregnancy cervical cerclage was needed. Two patients were treated for hypothyroidism caused by the Hashimoto disease. One patient had gestational diabetes. Two patients had already given birth to 2 children. Five patients gave birth by caesarean section.

Conclusion: Topical PDT selectively used for treating the diseases of the female reproductive organs was applied in our group of patients and proved to be a safe method. It had no apparent negative impact on female fertility and allowed these women to give birth to healthy children.

1. Introduction

Photodynamic Therapy (PDT) is a non-invasive treatment method in gynecology. PDT makes it possible to destroy small clusters of cancerous and dysplastic cells without impacting healthy tissue [1]. PDT allows us to treat successfully multifocal, diffuse lesions. The treatment can be repeated without apparent induction of resistance presumably since DNA is not targeted and so there is no opportunity for treatment-induced mutation or selection) [2]. Recently, an increasing role is assigned to the influence of PDT on immune system, particularly on production and secretion of cytokines, with certainly further enhances the above mentioned mechanism. Immune – mediated inflammatory processes are delayed response, consisting in increased activity of

macrophages, neutrophils and lymphocytes, resulting in increasing secretion of interleukins. The photodynamic method is well tolerated by patients. Advantages that the method offers include preserving the correct structure of the organ, as well as the absence of scarring [1,2]. Most researchers have concluded that PDT is highly expedient in treating cervical intraepithelial neoplasia – CIN [3].

Likewise, research confirms that PDT is successful at treating epithelial diseases, such as vulvar lichen sclerosis and vulvar intraepithelial neoplasia (VIN) [4,5]. The most important proof of the safety of any therapy is preserving the organs and their functions. In the case of the female reproductive organs those functions are also preserving fertility and thus enabling women to give birth to healthy children.

Abbreviations: ALA 5, aminolevulinic acid; CIN, Cervical Intraepithelial Neoplasia; DMSO, dimethyl sulfoxide; HSIL, High grade squamous intraepithelial lesion; LED, light-emitting diode; LEEP, Loop Electrical Excision Procedure; LSIL, Low grade squamous intraepithelial lesion; LS, lichen sclerosis; PDT, photodynamic therapy; PpIX, protoporphyrin IX; VIN, Vulvar Intraepithelial Neoplasia

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2. Objectives of the study

The study analyzed the PDT treatment of 10 young women, who suffered from diseases of the vulva and cervix. The aim of the analysis was evaluating what impact PDT treatment may have had on their pregnancies and delivery.

3. Materials and methods

10 patients (22–32 years of age, 25.5 years of age on average) were treated with PDT. Each patients underwent colposcopy or vulvoscopy before biopsy and histopathological testing of cervical or vulvar sections, as well as HPV/DNA/PCR testing. All patients wished to have children in the future. In 2007–11, the patients were treated at the Chair and Department of Obstetrics, Gynaecology and Oncology II Faculty of Medicine, Medical University of Warsaw, Poland, and in 2013–14 they were treated at the Department of Female Genital Neoplasms of the Centre of Oncology in Warsaw. Both places used identical protocols for the PDT treatment.

The PDT treatment involved using 5% 5-delta-aminolevulinic acid (ALA) in gel form, with a 2% concentration of dimethyl sulfoxide (DMSO). The photosensitizer had been prepared by Prof. Alfreda Graczyk in the Department of Optoelectronics of the Military University of Technology, Poland, with the collaboration of the pharmaceutical company Farmapol. A thin layer of the gel was applied to cervical and vulvar lesions. Subsequently, after three hours the lesions were treated with light generated by a halogen lamp PhotoDyn 501 (590–760 nm), with the power density of 204 mW/cm², which emits 120 J/cm² in a 10-minute session. The treatment was repeated once weekly for 10 weeks. The distance between the lamp and the lesion was constant, about 27 cm. The 10 applications of PDT were applied to all patients. Check-ups were performed after 3 months, and following that, at 6-month intervals.

The PDT method of treatment was approved by the Bioethics Committee at the Warsaw Medical University (KB/57/2006) and by the Bioethics Committee at the Oncology Center at the Maria Skłodowska-Curie Institute in Warsaw (1/2012).

4. Results

Four patients underwent photodynamic therapy for cervical diseases – Table 1. Among them two patients (no. 6 and 8) suffered from a prolonged CIN 1 / current terminology LSIL lasting more than 2 years and high-risk Human Papilloma Virus: HPV HR 16 (no. 6), as well as 31 and 42 (no. 8). Histopathological testing via biopsy of the cervix, as well as HPV DNA testing, showed clearance of lesions and infections. Two other patients (no. 5 and 7) had been treated PDT prior to electroconization, due to CIN III/ HSIL and the HPV 16 infection. The patients underwent electroconization (LEEP - Loop Electrical Excision

Procedure - an excision of a cone-shaped sample of tissue from the cervix) and biopsy of the endocervical canal after 3 months of PDT. Following the end of treatment, in both patients less extensive cervical lesions were observed via colposcopy. The patients underwent electroconization these lesions and biopsy of the cervix. The CIN III/HSIL lesions were detected with the help of histopathological testing, and they were entirely removed. At the end of the all therapies the result of the HPV DNA test was negative. Two patients (no. 3 and 10) were treated with PDT for vulvar lichen sclerosus and for lack of clearance after treatment with Clobetazol. Both patients received PDT 10 treatments. In both cases a remission of the disease was observed, which lasted until the end of the observation. Patient no. 3, who was treated for vulvar lichen sclerosus, was also treated 10 times with PDT applied to the cervix because of the HPV 16 infection. Following treatment the HPV DNA test determined that the virus was absent. Two patients (no. 1 and 9) received 10 PDT treatments for squamous cell hyperplasia in the vulva and persisting discomfort. Remission was observed in both of these cases. One patient (no. 2) was treated for genital warts in the vulva and vagina, which were resistant to other forms of treatment, as well as for the HPV 16 infection. In this patient full recovery was observed; the HPV DNA testing did not detect the virus. Patient no. 4 was treated because of VIN 1/ LSIL/Flat condyloma and vulvar pain. In this case histopathological exam showed complete regression of the disease.

In the course of therapy three patients, who had vulvar lesions, reported temporary pain and burning, which were experienced only during the light application. No medications were needed. No adversary collateral impact of PDT was observed in the long run in any of the patients.

The median observation time period between the end of therapy and delivery was 3.92 years (2–7 years) – Table 2.

None of the patients suffered from infertility. All patients gave birth to healthy, full-term infants. In the case of one pregnancy (patient number 7), cervical cerclage was needed. This patient underwent conization after PDT. Two patients were treated for hypothyroidism caused by the Hashimoto disease (no. 2,6). One patient had gestational diabetes (no. 3). Two patients had already given birth to 2 children. Five patients gave birth to caesarean section: 1 - breech presentation (no.3), 2 - failure to progress in labor (no. 7, 8) 1 - cephalic pelvic disproportion (no. 10), 1 - fetal distress (no.4).

5. Discussion

Photodynamic therapy has been gaining popularity, particularly among young women. Therefore it is crucial to evaluate PDT for safety and its impact on fertility and delivery of healthy newborns.

This study discusses treatment of young female patients in the past. It is still an experimental method which requires constant calibration and improvement. It is important to remember that photodynamic therapy should be used as a last-resort method. In no case was it used as

Table 1
PDT treatment in patients.

Patient number no.	Age of patient at the time of PDT (years)	Reason for treatment with PDT (current terminology)	Year of treatment	Number of PDT treatments / Organ treated	Result of treatment
1	25	squamous cell hyperplasia	2007	10 / vulva	clearance
2	22	genital warts, HPV 16	2009	10 / vagina	clearance
3	23	vulvar lichen sclerosus, HPV 16	2010	10 / vulva 10 / cervix	HPV neg LS – remission
4	24	VIN I (LSIL/Flat condyloma)	2010	10 / vulva	clearance
5	25	CIN III (HSIL), HPV 16	2010	10 / cervix	clearance
6	28	CIN I (LSIL), HPV 16	2013	10 / cervix	clearance
7	32	CIN III (HSIL), HPV 16	2013	10 / cervix	clearance
8	27	CIN I (LSIL), HPV 31, 42	2013	10 / cervix	clearance
9	27	squamous cell hyperplasia	2014	10 / vulva	clearance
10	22	vulvar lichen sclerosus	2014	10 / vulva	clearance

Table 2
Pregnancies and labor in PDT-treated patients.

Patient number (no.)	Time difference between therapy and delivery (years)	Course of pregnancy	Weight of the newborn (gram – g) S – son D – daughter	Vaginal delivery – VD or cesarean section – CC (indications for CC)	Child development
1	5	Physiological	S 2950 g	VD	Normal
2	2	Physiological	D 2870 g	VD	Normal
		Hashimoto disease	D 3340 g	VD	Normal
3	5	Hashimoto disease	S 3610 g	VD	Normal
		Gestational diabetes treated with diet	S 3200 g	CC (breech presentation)	
4	8	Physiological	D 3300 g	CC (fetal distress)	Normal
5	4	Physiological	S 3050 g	VD	Normal
		Physiological	D 3000 g	VD	Normal
6	2	Hashimoto disease	S 3140 g	VD	Normal
		Hashimoto disease	D 3500 g	VD	Normal
7	2	Cervical cerclage	S 3300 g	CC (failure to progress in labor)	Normal
8	3	Physiological	D 3800 g	CC (failure to progress in labor)	Normal
9	2	Physiological	S 3200 g	VD	Normal
10	2	Physiological	D 3800 g	CC (cephalic pelvic disproportion)	Normal

an initial course of treatment. It is a final option that can be used when other methods are ineffective.

Patients, who suffered from vulvar lichen sclerosus, had been ill for 1.5–2 years. During the first stage of the treatment, patients were given clobetazol, but there was no improvement (patients' main complaint was pruritus). Due to the steroid treatment being ineffective, patients decided to try the photodynamic therapy.

No patient in the described group was treated for an HPV infection but because of diseases and symptoms caused by that infection.

Patients who have been diagnosed with squamous cell hyperplasia suffered mainly from a burning sensation and issues related to intercourse. We did not observe any clinical correlation with a specific disease of the vulva. There was no improvement regardless of treatment method used. They underwent PDT. Remission was observed on the basis of absence of clinical symptoms, as well as regular results of vulvoscopy. During observation there was no return of symptoms.

The basis of photodynamic therapy are photocytotoxic reactions resulting from the influence of light on cells which have accumulated molecules of a photosensitizer [6]. Cytotoxic and cytolethal effect of PDT associated with formation of free radicals by excited photosensitizer [7].

The most frequently used photosensitizer in gynecology is aminolevulinic acid (ALA). In our study the 5% 5-delta aminolevulinic acid (ALA) was used in gel form. It is a natural precursor of endogenous photosensitizer – protoporphyrin IX (PpIX). It is classified as a C category medication to be avoided in pregnancy. However, category C means that ALA's teratogenic or embryotoxic properties have not been determined by controlled clinical studies on pregnant women. ALA can be used in pregnant women only when its benefits are greater than the risk of ALA harming the fetus. Hence photodynamic therapy is not used in pregnant women [8].

A separate issue is using PDT in treating diseases of reproductive organs and the impact of PDT on the reproductive functions of a woman in the future.

As the author of this study argue, only multi-year observations of diverse aspects of PDT treatment can prove that PDT, used for treating the diseases of the female reproductive organs, is a safe method that does not have a negative impact on female fertility and allows women to give birth to healthy infants. There are few research studies on this topic.

Ahn TG et al. described 2 cases of full term pregnancies and deliveries that followed treatment combining chemotherapy and photodynamic therapy in the case of cervical cancer Ib1 and Ib2 [9]. The authors used for PDT intravenous injection of photosensitizer (hematoporphyrin derivative: Photogem® 2.5 mg/kg or Photofrin® 2 mg/kg). All patients demonstrated remarkable results, preserving their fertility.

Yang YG et al. used photodynamic therapy in the case of 5 pregnant

patients who suffered from genital warts [10]. The clearance rate of genital warts was 100%. No recurrence was found during the follow-up period. It demonstrated high clearance rate of warts, was well-tolerated by patients, and showed no adverse effects on mothers and fetuses. All patients gave birth to healthy children. Pregnancies and deliveries were non-eventful [10]. ALA hydrochloride powder for topical use and an XD2635AB photodynamic laser was used for treatment.

Choi MC et al. used photodynamic therapy (PDT) with or without loop electrosurgical excision procedure /conization to preserve fertility in 59 young patients with cervical intraepithelial neoplasia (CIN 2: 4, CIN 3: 22, carcinoma in situ: 31, adenocarcinoma in situ: 2) [11]. Surface photoillumination with red laser light at a wavelength of 630 nm was applied to the uterine cervix and endocervical canal of patients 48 h after an intravenous injection of 2 mg/kg of photosensitizer. Among 29 patients who tried to be pregnant, 18 patients achieved 25 pregnancies (6 abortions, 1 ectopic, 1 preterm, 15 term, and 2 ongoing pregnancies) [11].

Park YK et al. reported that they have performed PDT on 22 cases (CIN 2 were 4 cases, CIN 3–15 and invasive cervical cancer – 3). The authors used for therapy photosensitizer 2.0 mg/kg injected intravenously. CR was 95% in CIN group and was 67% in invasive cancer group. Three patients had 4 successful pregnancies and delivered 4 healthy live births [3].

The standard therapeutic methods of cervical neoplasia were based on the focal destruction; conization, loop electro surgical excision procedure, laser ablation, cryotherapy, electrosurgery. These conventional therapeutic modality have many disadvantages; cervical stenosis, the possibility of incompetent cervix, premature rupture of membrane or preterm delivery [3].

In agreement with the results of the abovementioned studies, as well as observations of other researchers, PDT is an important alternative to the surgical treatment of VIN and CIN, particularly in young women, since PDT allows for preserving the correct structure of the vulva and cervix [12]. PDT is effective in treating epithelial diseases, such as the vulvar lichen sclerosus [4,5]. PDT offers excellent cosmetic results since it does not cause scarring [1,5]. These benefits are of utmost importance to young women who wish to give birth.

For a young patient undergoing photodynamic therapy is important whether it will have a negative impact on having children in the future. In search of the answer to this question, many years of observation were carried out.

Today's medicine and PDT can help women who desire to have children despite being diagnosed with the female reproductive system diseases.

6. Conclusions

Topical PDT selectively used for treating the diseases of the female reproductive organs was applied in our group of patients and proved to be a safe method, it had no negative impact on female fertility and allowed these women to give the birth of healthy children.

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Declaration of Competing Interest

The author has no conflict of interest to declare.

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