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EFFICACY OF PHOTODYNAMIC THERAPY IN THE TREATMENT OF CERVICAL PRECANCEROUS CONDITIONS CAUSED BY HUMAN PAPILLOMAVIRUS

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Abstract

Relevance: PDT is a high-tech treatment that uses a combination of a photosensitizer, light and molecular oxygen. The method is based on the mechanisms of free radical oxidation, disruption of the vascular stroma of tumors and elimination under the influence of immune cells. It is a non-invasive, effective and safe treatment that damages and destroys structures in the affected area. However, to normalize the immune response, ensuring a stable regression of carcinogenesis, prolonged elimination of HPV is necessary.

Aim: to assess the status of various levels of tissue damage in cervical dysplasia in combination with PVI, using PDT as the main method of treatment.

Search strategy: In this study, indicators of the state of the organ, tissue, cellular and molecular levels are used to assess the course of PVI of the cervix. The role of the immune response in HPV-associated precancerous diseases of the cervix is considered. The article presents work on the treatment of dysplasia of varying degrees associated with HPV in 92 patients over a two-year period using PDT.

Results: The use of photodynamic therapy in women with HPV-associated cervical precancerous disease is a promising area of research. The results of the work link the role of TLRs with the development of squamous intraepithelial lesions (SIL). Further clinical studies are needed to evaluate efficacy, safety and optimal timing.

Key words: *photodynamic therapy, human papillomavirus infection, squamous intraepithlial lesion, cervix.*

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Резюме

ЭФФЕКТИВНОСТЬ ФОТОДИНАМИЧЕСКОЙ ТЕРАПИИ В ЛЕЧЕНИИ ПРЕДРАКОВЫХ СОСТОЯНИЙ ШЕЙКИ МАТКИ, ВЫЗВАННЫХ ВИРУСОМ ПАПИЛЛОМЫ ЧЕЛОВЕКА

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Актуальность: Фотодинамическая терапия (ФДТ) представляет собой неинвазивный высокотехнологичный метод лечения, основанный на взаимодействии фотосенсибилизатора, света определённой длины волны и молекулярного кислорода. Механизм действия ФДТ включает индукцию свободнорадикального окисления, нарушение сосудистой стромы опухоли и активацию иммунного ответа, направленного на элиминацию патологических клеток. Метод отличается высокой селективностью и безопасностью, обеспечивая прицельное разрушение поражённых тканей с минимальным повреждением здоровых структур. В то же время, при лечении опухолей, ассоциированных с вирусом папилломы человека (ВПЧ), для достижения стабильной регрессии патологического процесса требуется длительная и эффективная элиминация вируса, способствующая нормализации иммунного ответа и снижению риска рецидива.

Цель: оценка показателей состояния различных уровней тканевого поражения при дисплазиях шейки матки в сочетании с ПВИ, с использованием ФДТ, в качестве основного метода лечения.

Стратегия работы: В настоящем исследовании ФДТ применялась для терапии шейки матки при вирус-ассоциированных предраковых изменениях. Стратегия оценки эффективности лечения включала анализ показателей на органном, тканевом, клеточном и молекулярном уровнях. Особое внимание уделено роли иммунного ответа при ВПЧ-ассоциированных предраковых заболеваниях. Представлены результаты наблюдения за 92 пациентками с цервикальными дисплазиями различной степени тяжести в течение двух лет, получавшими лечение с использованием ФДТ.

Результаты: Применение фотодинамической терапии (ФДТ) у женщин с ВПЧ-ассоциированными предопухолевыми заболеваниями шейки матки представляет собой перспективное направление клинических исследований. Полученные результаты свидетельствуют о потенциальной взаимосвязи между экспрессией Toll-подобных рецепторов (TLRs) и развитием плоскоклеточных интраэпителиальных поражений (SIL). Дальнейшие масштабные клинические исследования необходимы для уточнения эффективности, безопасности и оптимальных сроков применения ФДТ в данной категории пациентов.

Ключевые слова: *фотодинамическая терапия, папилломовирусная инфекция, плоскоклеточное интраэпитлиальное поражение, шейка матки.*

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Түйіндеме

HPV ТУДЫРҒАН ЖАТЫР МОЙНЫНЫҢ ІСІК АЛДЫ ЖАҒДАЙЛАРЫН ЕМДЕУДЕГІ ФОТОДИНАМИКАЛЫҚ ТЕРАПИЯНЫҢ ТИІМДІЛІГІ

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Өзектілігі: ФДТ – фотосенсибилизатор, жарық және молекулалық оттегінің комбинациясын пайдаланатын жоғары технологиялық емдеу. Әдіс бос радикалды тотығу, ісіктердің тамырлы стромасының бұзылуы және иммундық жасушалардың әсерінен жойылу механизмдеріне негізделген. Бұл зақымдалған аймақты инвазивті емес, тиімді және қауіпсіз емдеу әдісі. Дегенмен, иммундық жауапты қалыпқа келтіру, канцерогенездің тұрақты регрессиясын қамтамасыз ету, HPV-ны ұзақ жою қажет.

Мақсаты: емдеудің негізгі әдісі ретінде ФДТ қолдана отырып, жатыр мойны дисплазиясында тіндердің зақымдануының әртүрлі деңгейлерінің күйін PVI біріктірілімінде бағалау.

Жұмыс стратегиясы: Бұл зерттеуде жатыр мойнының PVI барысын бағалау үшін органның, тіннің, жасушалық және молекулалық деңгейлердің күйінің көрсеткіштері қолданылады. Жатыр мойнының HPV-ассоциацияланған ісік алды ауруларында иммундық жауаптың рөлі қарастырылады. Мақалада ФДТ көмегімен екі жыл ішінде 92 пациентте HPV-мен байланысты әртүрлі дәрежедегі дисплазияны емдеу бойынша жұмыс жүргізілген.

Нәтижелер: HPV-мен байланысты жатыр мойны обыры алды ауруы бар әйелдерде фотодинамикалық терапияны қолдану зерттеудің перспективалық бағыты болып табылады. Жұмыстың нәтижелері TLR рөлін жалпақ эпителий ішілік зақымданулардың (SIL) дамуымен байланыстырады. Тиімділікті, қауіпсіздікті және оңтайлы уақытты бағалау үшін қосымша клиникалық зерттеулер қажет.

Түйінді сөздер: *фотодинамикалық терапия, адам папилломавирустық инфекциясы, скамозды интраэпителиальды зақымдану, жатыр мойны.*

Дәйексөз үшін:

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Introduction

The cervix is an important part of the female reproductive system, and diseases related to its pathology significantly affect health and quality of life. One of the most common causes of precancerous changes in the cervix is infection with the human papillomavirus (HPV). HPV infection can lead to the development of dysplasia and cervical carcinoma, which in turn increases the risk of cervical cancer [12,22]. Cervical cancer ranks second in prevalence among oncological diseases in women in the Republic of Kazakhstan. According to data from the National Cancer Registry monitoring the epidemiological situation in the country, 1,952 new cases of cervical cancer were registered in 2020. This accounts for 7.3% of all newly diagnosed malignant neoplasms in women. The highest incidence rate is observed in the age group of 45 to 49 years [1].

In recent decades, there has been an increase in HPV-associated diseases, making the search for effective treatment methods a pressing issue. HPV is a leading risk factor for the development of cervical dysplasia and its progression to cancer; therefore, timely diagnosis and treatment of precancerous conditions are crucial [4,11,31].

Modern treatment methods for precancerous cervical diseases include surgical interventions such as cervical conization, cryotherapy, and laser therapy. However, these methods have several limitations, including high invasiveness, long recovery periods, and the risk of recurrence [3,15]. In this context, photodynamic therapy (PDT) has attracted attention in recent years as an alternative treatment method for precancerous conditions.

PDT is a non-invasive method that uses photosensitizers activated by light of a specific wavelength. When the photosensitizer acts on pathological cells, it causes their destruction, enabling effective treatment of precancerous states [2,16]. Importantly, photodynamic therapy not only contributes to tumor mass reduction but also stimulates the body's immune response. This, in turn, promotes a higher level of remission and reduces the risk of disease recurrence. Lee et al. confirmed in their study that PDT significantly influences the management of HPV-associated cervical cancer by stimulating the immune response and improving long-term therapeutic outcomes [18].

Photodynamic therapy is based on mechanisms involving free radical oxidation, disruption of tumor vascular stroma, and activation of immune responses that lead to the elimination of pathologically altered cells. The method is characterized by high selectivity, non-invasiveness, effectiveness, and safety, providing localized damage and destruction of affected tissues with minimal impact on healthy structures. An additional component of therapy is systemic photobiomodulation with laser blood oxygenation (SPLBO), whose mechanism of action is based on photobiological effects. Under light radiation, physicochemical rearrangements of protein structures occur in tissues, accompanied by changes in enzyme system activity and the structural-functional properties of cell membranes.

As a result of SPLBO:

- **Erythrocytes:** membrane permeability and deformability increase, aggregation ability decreases, and ATP and 2,3-diphosphoglycerate levels rise, improving the oxygen-transport function of blood.
- **Leukocytes:** activity of membrane receptors is enhanced, DNA synthesis is activated, phagocytic activity increases, secretion of bactericidal cationic proteins and production of interleukins and growth factors intensify, DNA repair enzyme systems are activated, and the reactivity of immunocompetent cells changes.

• **Platelets:** structural changes in membranes occur, and rheological activity is stimulated.

• **Blood plasma:** bactericidal, antioxidant, and proteolytic properties are enhanced; activity of complement, lysozyme, natural and immune antibodies increase; coagulation, anticoagulation, and fibrinolytic properties normalize. A sharp decrease in lipid peroxidation products is also observed.

The complex of these changes indicates the development of a pronounced systemic immunological response, which may contribute to prolonged elimination of human papillomavirus (HPV) and reduce the risk of disease recurrence.

Photodynamic Therapy (PDT) has recently been actively considered as an innovative alternative to traditional methods for treating cervical dysplasia, especially in cases associated with human papillomavirus (HPV) infection. Accumulated clinical data confirm the high efficacy of this approach. According to several studies, PDT contributes to significant improvement in the condition of women with precancerous cervical lesions (Goodman et al., 2024) [10].

A systematic review conducted by Goodman and colleagues highlights the organ-preserving potential of the method: PDT demonstrates favorable outcomes in the regression of cervical intraepithelial neoplasia (CIN) and HPV infection clearance (Goodman et al., 2024) [10].

Furthermore, significant contributions to the evaluation of PDT efficacy were made by Sharma et al., who presented clinical trial results confirming the safety and minimal invasiveness of this method in treating cervical pathologies (Sharma et al., 2023) [24].

Additionally, clinical observations report a complete remission rate of up to 90% three months after PDT, with HPV elimination observed in 75% of patients after 12 months (Van der Zee et al., 2005) [27].

Despite these promising prospects, experts emphasize the need for further randomized studies aimed at elucidating the mechanisms of PDT action, investigating long-term outcomes, and assessing recurrence risk.

The aim of the present study was to determine the efficacy of photodynamic therapy in treating HPV-associated precancerous cervical conditions. To achieve this goal, a review of the existing scientific literature and an analysis of clinical observations were conducted.

Materials and Methods

This study analyzed data on the use of photodynamic therapy (PDT) in women with HPV-associated precancerous cervical lesions. The study included both retrospective and prospective components.

The retrospective analysis was based on medical records of patients treated between 2022 and 2024, diagnosed with cervical intraepithelial neoplasia (CIN). Clinical characteristics, examination results, treatment regimens applied, and the dynamics of the pathological process during follow-up were analyzed. Data sources included archival materials from the Medical Center UDP Hospital and the gynecological department of MedInService LLC (Moscow).

The prospective observation covered the period 2023–2024 and included patients who provided written informed consent. These women underwent PDT treatment under both outpatient and inpatient care. The study evaluated not only immediate clinical efficacy but also recurrence rates and therapy tolerability.

For the retrospective component, the following parameters were collected and analyzed:

• **Clinical-epidemiological data:** age, gynecological history, information on HPV vaccination and prior treatments;

• **Virological data:** virus type, presence of condylomas, viral load measured by PCR;

• **Immunological data:** mRNA expression levels of Toll-like receptors TLR2, TLR3, TLR4, and TLR8, assessed by quantitative real-time RT-PCR.

For a more in-depth assessment of the patients' condition, a leukocyte differential blood count analysis was used to evaluate the immune responses accompanying the disease progression.

The study was conducted at the Department of Obstetrics and Gynecology No. 1 of the non-commercial joint-stock company "Astana Medical University," as well as at specialized institutions in Moscow, including Guta Clinic and the I.M. Mechnikov Research Institute of Vaccines and Sera.

Participants and Grouping

The study included 92 women (age range: 18–50 years, median 31.3 years, IQR = 27–39), divided into three groups:

1.Control group – 13 patients without cervical pathology;

2.LSIL group – 13 women with low-grade squamous intraepithelial lesions;

3.HSIL group – 66 patients with high-grade intraepithelial lesions.

Inclusion Criteria:

- Age 18–65 years;
- Confirmed intraepithelial lesions;
- Available data on the expression of at least one TLR;
- Absence of current inflammatory infections;
- Voluntary consent to PDT and participation in the study.

Exclusion Criteria:

- Pregnancy or lactation;
- Negative results of RT-PCR;
- Contraindications to PDT;
- Ongoing antitumor therapy.

Sample Collection and Processing

A total of 92 samples of ectocervical and endocervical epithelial cells were collected from patients at the gynecological department of the Hospital of the Presidential Administration in Astana. Samples were delivered to the Molecular Immunology Laboratory at the I.M. Mechnikov Research Institute of Vaccines and Sera for analysis of TLR (Toll-like receptor) gene expression. Cervical smears were collected following strict protocols (patients refrained from local medications and hygienic procedures prior to sampling). TLR expression was quantified using the DT-96 instrument (DNA-Technology LLC). GAPDH mRNA was used as the control gene. mRNA isolation employed affinity chromatography methods, and primers were designed with Vector NTI Advance software.

Photodynamic Therapy (PDT) Procedure

Photodynamic therapy was performed after the completion of the patients' menstrual cycle to avoid any influence of menstruation on treatment effectiveness.

The PDT protocol consisted of three main stages:

Photosensitizer (PS) administration:

Patients received an intravenous injection of a chlorin e6-based photosensitizer over 30 minutes. The dose ranged from 1 to 1.2 mg per kilogram of body weight to achieve optimal PS concentration in target tissues.

Darkness period:

Following the injection, patients observed a dark period of 24–48 hours to minimize light exposure and ensure complete elimination of the photosensitizer from healthy tissues. This step was crucial to reduce phototoxicity risk and improve treatment efficacy.

Medicinal products used:

PHOTOLON (PN015948/01, Belmedpreparaty RUE, Belarus) was used as an adjunct to promote more effective accumulation of the photosensitizer in pathological tissues.

Accumulation of PS in affected tissues and its clearance from healthy tissues occurred within three hours after injection, providing optimal conditions for subsequent light exposure.

Second Stage: Photodiagnostics (PD)

At the second stage, photodiagnostics was performed to assess the accumulation of the photosensitizer (PS) and to map the tumor area. A LED light source (Polironic LLC, Russia) emitting light at 400 nm was used for this purpose. The source was equipped with a yellow optical filter mounted on a video colposcope (Kernel KN-2200A-HD, China). This filter blocked ultraviolet radiation and allowed detection of red fluorescence, indicating the localization of the PS in the target tissue.

Third Stage: Targeted Irradiation

At the third stage, targeted irradiation was performed on the cervical canal and the vaginal part of the cervix. Photoirradiation was directed at the surface of the cervix, which activated the PS and destroyed pathological tissues.

The photoirradiation time (T, minutes) was calculated using the established formula (Formula 1). To determine the areas of the cervical canal and the cervical surface, formulas 2 and 3 were used, allowing precise dosing of the light exposure depending on the size of the irradiated area.

Target Photoirradiation Doses (Es):

- 334 J/cm² for the cervical canal.
- 290 J/cm² for the cervical surface.

For photoirradiation of the cervical canal, a flexible cylindrical diffuser with a working length of 4 cm (l) and radius of 0.1 cm (r) was used. The power of photoirradiation (P) was 1 W.

The cervical surface was irradiated using macro- or microlenses for external exposure. The procedure was performed remotely and perpendicular to the target area. The irradiation spot diameter was 2.5 cm (d), and the photoirradiation power (P) was 1.7 W, ensuring a dose of Es = 290 J/cm².

Formulas for Calculating Photoirradiation Time (T):

1. Total irradiation time was calculated by the formula:

T=Es×S60×P(Formula 1)T = \frac{Es \times S}{60 \times P} \quad \text{(Formula 1)}T=60×PEs×S(Formula 1)

Where:

- Es — photoirradiation dose (J/cm²)
- P — photoirradiation power (W)
- S — irradiated surface area (cm²)

2. The irradiated area for the cervical canal was calculated as:

Scc=6.28×r×l(Formula 2)S_{cc} = 6.28 \times r \times l \quad \text{(Formula 2)}Scc=6.28×r×l(Formula 2)

Where:

- r — diffuser radius (cm)
- l — diffuser length (cm)

3.The irradiated area for the cervical surface was calculated as:

Scs=0.785×d2(Formula 3)S_{cs} = 0.785 \times d^2 \quad \text{(Formula 3)}Scs=0.785×d2(Formula 3)

Where: d — irradiation spot diameter (cm)

Power density control was performed using a laser irradiation indicator PDI-01 (Alcom Medica LLC, Russia), ensuring accurate dosing of photoirradiation. A laser device “LAHTA-MILON” 662-2, emitting light at 662 nm, was used to activate the photosensitizer.

Darkness Protocol Before and After the Procedure

After photodynamic therapy (PDT), patients were required to strictly follow the darkness protocol to minimize light exposure and ensure safety during photosensitizer elimination from tissues.

1. **Wearing sunglasses:** Patients were advised to wear sunglasses for 24–48 hours post-procedure to protect their eyes from light exposure and prevent phototoxic reactions.

2. **Limiting use of phones and tablets:** The use of mobile devices and tablets was restricted, with screens set to minimum brightness to reduce light exposure.

3. **Room lighting:** In rooms where patients stayed, illumination levels were kept below 50 lux to prevent photosensitization and ensure safe elimination of the photosensitizer.

4. **Applying sunscreen:** Patients were recommended to apply sunscreen with SPF 50 when going outdoors in sunny weather to protect their skin as needed.

Investigated Parameters

To evaluate clinical-epidemiological, immunological, and digital features in each group, the following parameters were used:

- **Age (years):**
- Mean ± standard deviation (M ± SD) and median (Me).

The control group patients had a mean age of 30 years (95% confidence interval [CI]: 29–38).

The mean age of patients with cervical intraepithelial lesions of varying severity differed by group. In the group with low-grade intraepithelial lesions (LSIL), the mean age was 27 years (95% CI: 27–31), whereas in the group with high-grade lesions (HSIL), the mean age was 37 years (95% CI: 30–39).

- **Menarche (years):**
- The age of menarche was the same across all groups, with a median age of 13 years at first menstruation.
- **Age at sexual debut (years):**

The mean age of onset of sexual activity also did not differ between groups and was 18 years.

- **Number of sexual partners:**

This differed depending on lesion severity. The median number of sexual partners was 3 in the control and LSIL groups, whereas it was 5 in the HSIL group, potentially indicating a relationship between a higher number of sexual contacts and more severe intraepithelial changes.

Duration of Primary Viral Infection (PVI), months:

- In the LSIL group, the mean duration of PVI was 22.35 months (95% CI: 6.35–61.82).
- In the HSIL group, the mean duration was 13.8 months (95% CI: 3.08–30.83).

Immune response parameters and viral load:

- **Leukocyte count in cervical secretion:**
  - Control group: mean 8 cells per field of view.
  - LSIL group: mean 5 cells.
  - HSIL group: mean 13 cells.
- **Viral load (Log(10^5)):**
  - LSIL group: mean 5.55 (95% CI: 4.8–6.62).
  - HSIL group: mean 5.8 (95% CI: 5.1–6.6).
- **Acetowhite epithelium area (%):**
  - Control group: mean 18.06% (95% CI: 10.13–25.98).
  - LSIL group: mean 36.4% (95% CI: 25.5–47.37).
  - HSIL group: mean 32.13% (95% CI: 27.86–36.39).

5. Leukocyte responses and immunological indicators

- **Types of leukocyte immune responses:**

Blood analysis revealed differences in predominant types of leukocyte response among the studied groups.

- In the control group, the second type of leukocyte response predominated (66.7%).
- In the LSIL group, the first type of response was more frequent (38.5%).
- In the HSIL group, the third type predominated (37.9%).

Expression of Toll-like receptors (TLRs)

The gene expression levels of immune receptors TLR2, TLR3, TLR4, and TLR8 were assessed by quantitative reverse transcription PCR (qRT-PCR). The results are presented in Table 1.

Table 1.

Efficacy of photodynamic therapy in the treatment of cervical precancerous conditions caused by human papillomavirus.

Parameter	Statistics	Control (n = 13)	LSIL (n = 13)	HSIL (n = 66)
TLR2 (OE)	M ± SD / Me	0.95	2.26	1.54
95% CI / Q_1–Q_3	0.73–1.27	1.19–43.8	1.04–2.18	
TLR3 (OE)	M ± SD / Me	0.89	1.24	1.27
95% CI / Q_1–Q_3	0.8–1.23	0.69–2.32	0.30–2.49	
TLR4 (OE)	M ± SD / Me	0.84	2.14	1.36
95% CI / Q_1–Q_3	0.72–0.41	1.19–60.28	0.9–2.87	
TLR8 (OE)	M ± SD / Me	0.9	2.15	1.3
95% CI / Q_1–Q_3	0.72–1.29	0.90–2.56	0.94–2.02	

Note: M — mean; SD — standard deviation; Me — median; Q_1–Q_3 — interquartile range; CI — confidence interval

Analysis of TLR Expression. The analysis of TLR expression between Group I and the other groups prior to photodynamic therapy (PDT) revealed only minor differences. Group II exhibited a trend toward increased TLR4 expression compared to the other groups (P = 0.066); however, the absolute expression level of TLR4 in this group remained the lowest when compared to Groups I and III, which was statistically significant (P = 0.035).

Regarding TLR3, a trend toward decreased expression was observed in the control group compared to the other groups (P = 0.099), although the differences did not reach statistical significance.

TLR8 expression was significantly reduced in Groups I and II compared to Group III (P = 0.032).

In the studied cohort, TLR4 and TLR8 expression levels showed a significant decrease—by 7% and 13%, respectively—two hours after cervical PDT (P = 0.03 and P < 0.001). In contrast, the expression levels of TLR2 and TLR3 did not show significant changes two hours post-PDT (P = 0.968 and P = 0.701, respectively).

Changes in TLR Expression in Patients with LSIL (Group III). A statistically significant 1.3-fold decrease in TLR8 expression was observed two hours after photodynamic therapy (PDT) in patients with low-grade squamous intraepithelial lesions (LSIL) (P = 0.003). Expression levels of TLR2 and TLR4 remained slightly elevated compared to the control group, with increases of 74.7% and 42.7%, respectively (P = 0.144 and P = 0.069). Expression levels of TLR3 and TLR8 decreased to values comparable to those observed in the control group.

Changes in TLR Expression in Patients with HSIL (Group III). A 1.1-fold decrease in TLR8 expression was recorded two hours after PDT in patients with high-grade squamous intraepithelial lesions (HSIL), with the difference reaching statistical significance (P = 0.042). Among patients with cervical intraepithelial neoplasia grade 3 (CIN3), a trend toward increased TLR3 expression was observed (P = 0.067), although the change did not reach statistical significance. A modest increase in TLR2 expression by 36.8% was also noted (P = 0.231), while expression levels of TLR3, TLR4, and TLR8 decreased to levels comparable to those in the control group.

Categorical Parameters and Their Distribution Among Study Groups

Presence of Subjective Complaints: In the control group, 23.1% of participants reported subjective complaints. In the subgroup with low-grade squamous intraepithelial lesions (LSIL), such symptoms were observed in 15.4% of women, while in the group with high-grade lesions (HSIL), the rate was 16.7%.

History of Therapeutic Intervention: Analysis of medical history revealed that 76.9% of women in the control group had previously undergone therapeutic treatment. This parameter was lower in the LSIL and HSIL subgroups—61.5% and 42.4%, respectively.

Gynecological History: The prevalence of gynecological conditions in medical history was comparable across groups: 69.2% in both the control and LSIL groups, and 72.7% among women with HSIL.

History of Human Papillomavirus (HPV) Infection:

HPV infection was documented in 46.2% of patients in the control group. In the LSIL group, this proportion was 23.1%, whereas in the HSIL group, it reached 53.0%.

Type of HPV Infection Identified:

In the LSIL group, HPV co-infection (multiple HPV types) predominated, accounting for 53.8% of cases. In contrast, women with HSIL more frequently had mono-infections, with a rate of 57.6%.

Table 2

HPV Infection Characteristics Among Study Groups.

HPV Infection Characteristic	Group I(Control, n = 13)	Group II(LSIL, n = 13)	Group III(HSIL, n = 66)	P-value
Absence of active HPV infection	13 (100%)	2 (15.4%)	7 (10.6%)	<0.001
HPV mono-infection	0 (0%)	4 (30.8%)	38 (57.6%)	—
HPV co-infection (multiple types)	0 (0%)	7 (53.8%)	21 (31.8%)	—

Detection of Acetowhite Epithelium During Colposcopy

Diagnostic colposcopic examination revealed the presence of acetowhite epithelium in 15.4% of patients in the control group. A substantially higher detection rate was observed in patients with LSIL (92.3%) and HSIL (80.3%).

Statistical Analysis

Statistical analysis was performed using Visual Studio Code 2 (v.1.66.2) with Python 3.12.X, employing statistical packages including pandas, scipy, matplotlib, and seaborn.

The Shapiro–Wilk test was used to assess the normality of quantitative variables. Variables with a normal distribution were described using the mean (M), standard deviation (SD), and 95% confidence interval (95% CI). For variables that did not follow a normal distribution, the median (Me) and interquartile range (IQR), defined by the 25th and 75th percentiles, were reported.

Categorical variables were presented as absolute (n) and relative (%) frequencies. Comparisons of independent quantitative variables with normal distribution were conducted using one-way analysis of variance (ANOVA), followed by Tukey's post hoc test, provided that homogeneity of variances was confirmed. For independent variables with non-normal distribution, the Kruskal–Wallis test was applied, followed by Dunn's test with Holm's correction for multiple comparisons.

The strength and direction of the association between two variables were assessed using Spearman's rank correlation coefficient (r□). For paired samples, comparisons of quantitative variables were performed using the Wilcoxon signed-rank test.

Statistical significance was defined as $P < 0.05$.

Results

TLR8 may serve as a potential early molecular immunological marker for the progression of HPV infection, given its highest expression levels across all groups and the pronounced suppressive effect of photodynamic therapy (PDT) observed in our study.

Our study has several limitations, including the absence of a comparative treatment method, lack of a standardized approach to HPV testing, and variability in HPV types and viral load among patients.

Nevertheless, the study is based on data obtained from real-world clinical practice, which represents a valuable contribution to evaluating the impact of PDT on TLR expression in HPV-associated cervical lesions and understanding its potential as a prognostic factor for treatment efficacy.

Additionally, we did not assess TLR expression in biological material obtained via liquid biopsy, which may influence the results considering TLR expression in the stroma. However, one of the advantages of PDT as a treatment method lies in its ability to modulate TLRs: activating them in suppressed conditions or suppressing their overexpression, as demonstrated in our study. This dual regulatory effect highlights PDT's potential as a promising therapeutic approach for HPV-associated cervical lesions.

The study demonstrated that photodynamic therapy is highly effective in treating precancerous cervical conditions. Most patients showed significant clinical improvement, including regression of atypical cells and normalization of cytological findings. Approximately 75% of women exhibited no signs of atypia six months after completing the treatment course.

Complete regeneration of cervical tissues without scar formation was observed in 15% of cases, confirming the low invasiveness of PDT. These results may indicate the development of a positive systemic immune response that contributes to prolonged elimination of human papillomavirus.

However, it should be noted that the efficacy of PDT may vary depending on the photosensitizer used and the stage of the disease. Therefore, decisions regarding the use of PDT for treating women with HPV-associated precancerous cervical lesions should be made on an individual basis, considering all risk factors and in close consultation between the patient and her healthcare provider.

Among the TLRs analyzed in our study, the most significant changes were observed for TLR8, which decreased in all groups two hours after photodynamic therapy (PDT). The greatest reduction was recorded in patients with severe dysplasia (HSIL/CIN III), potentially indicating modulation of the inflammatory response accompanied by correction of the immune response in the damaged tissues.

Our results confirm that PDT effectively reduces TLR4 expression, which may reflect modulation of inflammatory factors and alteration of the local immune microenvironment in cervical lesions. These changes suggest that PDT exerts a systemic effect on the immune response, contributing to reduced inflammation and normalization of tissue condition.

The study also noted a phenomenon of TLR3 overexpression in the group with low-grade cytological diagnosis (LSIL), as well as a decrease in TLR3 expression in the group with severe dysplasia (HSIL/CIN III). However, these changes were not statistically significant ($p = 0.099$), indicating the need for further research to better understand the impact of PDT on TLR3 expression depending on disease stage.

Furthermore, no significant changes in TLR2 expression were found two hours after PDT, which may be related to the diversity of HPV types among patients, potentially influencing the immune response. These observations highlight the necessity for further studies to identify the precise mechanisms by which PDT affects TLR expression and the associated immune responses.

Discussion

The conducted study aligns with both national and global strategies for the prevention, diagnosis, and treatment of clinical manifestations of human papillomavirus infection (HPV) of the cervix, supporting the World Health Organization's goals to reduce the incidence and mortality of cervical cancer.

Photodynamic therapy (PDT) has established itself as a promising treatment modality for malignant neoplasms due to its minimally invasive nature, low systemic toxicity, and potent immunomodulatory effects. Unlike conventional treatment methods such as surgery and radiotherapy, PDT targets pathological tissues directly with minimal damage to healthy structures. This facilitates cervical tissue restoration with minimal scarring and improves the overall clinical condition of patients.

Moreover, PDT stimulates the body's immune response, which is crucial for treating HPV-associated infections. As noted in a recent review by Fan et al. (2024), photodynamic therapy exerts not only a local cytotoxic effect on tumor cells but also modulates the immune response by activating various molecules and receptors, including Toll-like receptors (TLRs), potentially promoting long-term viral clearance and preventing disease recurrence [8].

Our study demonstrated that PDT can significantly influence the expression of TLR molecules, confirming the method's capacity to modulate the immune response in cervical tissues. This is particularly relevant in the context of HPV-associated diseases, where modulation of inflammatory and immune processes is critical for achieving sustained remission and preventing disease progression.

Nevertheless, despite promising results, this study has several limitations. Notably, the absence of a comparative analysis with alternative treatment methods limits the direct assessment of PDT's advantages. Additionally, the heterogeneity of HPV types among included patients may influence treatment outcomes. These factors underscore the need for further research involving larger, more homogeneous cohorts and inclusion of control groups to objectively evaluate the efficacy and safety of PDT in treating HPV-associated cervical lesions of varying severity.

One of the key advantages of PDT is its high antiviral efficacy. The mechanism is based on the targeted action of activated photosensitizers on the viral genome, promoting viral DNA destruction and subsequent elimination from the body. The effectiveness of this mechanism is supported by PCR analysis results demonstrating a high rate of HPV DNA clearance following treatment. Due to this capability, PDT represents a particularly promising approach for treating HPV-associated diseases such as cervical intraepithelial neoplasia (CIN), especially at early stages before progression to invasive cancer [26].

Furthermore, the combination of minimal tissue damage, strong antiviral activity, and restoration of cervical structural functions justifies the use of PDT as a highly pathogenetically grounded treatment method. These characteristics contribute to a reduced recurrence rate, which is especially important for young women concerned about preserving reproductive function. Studies such as those by *Hussain et al*. [13] confirm PDT's superior efficacy compared to other treatments like cryotherapy and highlight its advantage in maintaining patients' reproductive potential.

Photodynamic therapy offers unique opportunities for the treatment and prevention of cervical diseases, including CIN and cervical cancer. According to research by Ishchenko A.I., one of the key features of PDT is its minimal invasiveness and the lack of need for prolonged rehabilitation post-procedure, which significantly reduces costs and enhances economic efficiency. This is particularly relevant when patients can quickly return to their normal activities without downtime [14].

The application of PDT is not limited to cervical cancer treatment; it can also serve as an important component of preventive programs, particularly for women with prior cervical lesions.

Following organ-preserving treatment of the cervix with PDT, thorough dynamic follow-up is necessary for early detection of potential recurrences. Recommended surveillance includes regular cytological examinations of exocervical and endocervical scrapings and PCR testing for HPV presence and types. Colposcopy remains an essential tool for visual monitoring of cervical status in the post-therapeutic period, enabling timely identification of pathological changes and informing further patient management.

However, recurrence of cervical intraepithelial neoplasia (CIN) and cervical cancer remains a significant challenge despite modern treatment methods, including PDT. According to data published in the *European Journal of Obstetrics & Gynecology and Reproductive Biology* [17], recurrence rates range from 5% to 25%, with most recurrences diagnosed within the first 24 months after treatment. This underscores the necessity for ongoing research to evaluate the long-term efficacy of PDT in treating and preventing cervical diseases.

Studies such as those by *Park J. et al.* (2019) and *Prakash S.* et al. have demonstrated that PDT is a safe and effective alternative to conventional treatments for cervical dysplasia. These studies particularly highlight PDT's ability to treat precancerous cervical conditions without surgical intervention, thus reducing the risk of postoperative complications and restoring cervical structure with minimal functional impairment [20,21].

Special attention should be given to the use of PDT in patients unable to undergo traditional surgery due to contraindications, desire to preserve fertility, or preference for less invasive treatment. In such cases, PDT represents an optimal alternative, effectively eliminating pathological changes while preserving the natural cervical anatomy.

A notable study by *M.C. Choi et al.* compared the efficacy of PDT combined with loop electrosurgical excision procedure (LEEP or conization) in young women diagnosed with CIN II and III. The results showed that 98.1% of patients achieved complete remission one year post-treatment, indicating high efficacy in preserving fertility and preventing recurrence [5]. Thus, PDT is a promising method

for treating dysplasias, offering high effectiveness with minimal risk and preserving reproductive function [9].

A 2018 systematic review on the efficacy and safety of PDT for treating CIN and HPV infection highlighted both the beneficial effects and potential adverse reactions of the method. The main side effects included mild to moderate pain and edema in the treated area, which are generally transient, indicating relatively low trauma compared to surgical treatments [29].

Studies have also shown that photodynamic therapy (PDT) exhibits efficacy comparable to electrosurgery in the treatment of precancerous cervical lesions. For instance, a study published in Gynecologic Oncology in 2015 found no significant differences in clinical effectiveness between PDT and electrosurgical methods, confirming the high competitiveness of PDT in managing cervical intraepithelial neoplasia (CIN) [16,32].

Moreover, as highlighted in a systematic review by *Zepeda et al.,* PDT represents a promising approach for both precancerous lesions and cervical cancer. In particular, the use of the photosensitizer AlPcSmix demonstrated high efficacy in eradicating differentiated tumor cells as well as resistant cancer stem cells (CSCs). Application of PDT induced pronounced phenotypic changes in cells, including reduced proliferative activity and increased cytotoxicity, making the method especially promising for treating more advanced disease forms [30,31].

Nonetheless, to achieve optimal therapeutic efficacy, further studies on dose-dependent responses are needed. This is essential to precisely determine the maximum antitumor activity while minimizing effects on healthy tissues, thereby further improving the safety and effectiveness of the method.

Research conducted by *Della Fera A.N., Warburton A.,* and *Coursey T.L.* supports the potential of PDT using methyl aminolevulinate in patients with HPV-associated precancerous cervical lesions. Methyl aminolevulinate is one of the most commonly used photosensitizers for treating precancerous cervical conditions, offering good activation under specific conditions and selective destruction of atypical cells [7,25].

The study by *Lee et al.* emphasizes that for precancerous cervical lesions such as CIN I, a watchful waiting approach is acceptable, whereas active treatment is recommended for more severe forms, CIN II and III. Standard treatment options include PDT, cryotherapy, thermal ablation, and focused ultrasound. The choice of therapy should depend on the severity and extent of lesions, as well as the clinical context and patient condition [19,23].

The present study, conducted in Kazakhstan, is the first to evaluate the impact of PDT on the expression of TLR2, TLR3, TLR4, and TLR8 in cervical epithelial cells with HPV-associated lesions of varying severity. This represents an important contribution to understanding the molecular mechanisms of PDT, particularly regarding its effect on immune receptors such as TLRs, which play a crucial role in the immune response to viral infections and neoplastic changes.

However, it should be noted that this study involved a limited patient sample and a follow-up period of only one year. This restricts the ability to obtain long-term data on recurrence rates and potential delayed consequences of PDT application. To gain a more comprehensive understanding of the long-term effectiveness of PDT, further studies with extended follow-up and larger patient cohorts are needed. Such research will help clarify the role of PDT in preventing recurrences and maintaining long-term cervical health in women with HPV-associated lesions.

Conclusions

TLR Expression Levels and Clinical Indicators. The mRNA expression levels of TLR2, TLR3, TLR4, and TLR8 can serve as important biomarkers for assessing the severity of HPV-associated lesions. This opens new avenues for molecular diagnostics, enabling not only the determination of dysplasia degree but also the evaluation of the body's response to treatment. Additionally, lymphoid and neutrophilic infiltration, as well as leukocyte count in cervical secretions, are important indicators of inflammation and immune response to infection, which may aid in predicting therapy effectiveness and monitoring disease progression.

Efficacy of Photodynamic Therapy (PDT). The most pronounced effect of PDT was observed in cases of severe cervical dysplasia, highlighting the importance of an individualized treatment approach. Despite certain limitations in PDT use for milder cases, its high efficacy in severe lesions is confirmed by clinical and virological outcomes. This suggests the potential of PDT as a first-line therapy in advanced stages of the disease, particularly for women wishing to preserve reproductive function.

Role of Immunological Markers. Integration of immunological markers with clinicopathological data and digital diagnostic tools (such as colposcopy and PCR) significantly improves diagnostic accuracy and enables more precise monitoring of treatment effectiveness. This is especially important for assessing parameters like viral load, inflammation level, and immune response, which influence prognosis.

HPV Eradication and Prevention of Malignant Transformation. There is strong evidence that PDT contributes to the eradication of human papillomavirus and prevents malignant transformation of cells. This supports the use of PDT as a highly effective, minimally invasive treatment approach consistent with modern oncology trends emphasizing tissue preservation and minimization of intervention while maintaining high therapeutic efficacy.

In conclusion, our findings confirm the promising future of photodynamic therapy for treating HPV-associated cervical dysplasia. However, further studies are needed to evaluate the long-term efficacy and safety of the method, as well as to advance technologies ensuring broader accessibility and improved quality of treatment.

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