# Cervical Pathology Monitoring in Pregnant Women

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***Summary.*** *Results of the examination, observation and management of 136 pregnant women with pathology of cervix uteri (CU) are presented. Malignant transformations epithelium of CU are more frequently found within patients who have failed to treat their background and pre-cancer diseases against concomitant papillomavirus infection. A thorough study of pregnant women with cervical pathology allows for a timely diagnosis to be made and an individual management plan to be developed. In the event of a combination of CIN III, CIS, CU and pregnancy, the treatment scheme is designed with consideration to pregnancy term, malignant process expansion level, and patient's willingness to have a baby.*
***Keywords:*** *cervix, pregnancy, papillomavirus infection, cervical intraepithelial neoplasms, CU cancer.*

## Introduction

Malignant tumours associated with pregnancy are an unusual and complex combination that requires a doctor and a patient to choose between the risk to the life of the mother or of the unborn child, when the clinical principle of obstetrics "to save a baby to the mother and a mother to the baby" cannot always be followed [2, 3, 15].

Cervix uteri (CU) cancer is the most common tumour during pregnancy that occurs during the reproductive period of a woman's life [3, 8, 13]. According to the literature, 5-year survival in the case of patients with CU cancer in combination with pregnancy in the initial stages (stages 1-11) is 68.2-77% of cases, in the advanced (III-IV stage) – 44-55% [3, 18].

Preventing CU cancer in pregnant women is the only chance of saving the life of the mother and the unborn child in such situations. The planned pregnancy should only take place with a healthy cervix uteri (CU) and cervical canal (CxC). In cases of their involvement and the onset of pregnancy, a thorough examination with clarification of the diagnosis, treatment and prevention of malignant process are indicated. The absence of oncological alertness contributes to untimely diagnosis of cervical background and precancerous diseases in pregnant women.

CU cancer in pregnant women occurs both on the CU outer surface, and in endocervix. Malignancy can involve stratified squamous (squamous cell carcinoma), transitional (metaplastic carcinoma) and glandular epithelium of the cervical canal mucosa (adenogenic cancer) [7, 9, 11, 16].

In the etiopathogenesis of CU cancer, the oncogenic strains of human papillomavirus (HPV) – 16, 18, 45, 31, 33, 52, 58, 35, 59, 56, 51, 73, 68 and 66 types play the leading role. These types of viruses are found in 90% of patients with CU cancer, as well as in patients with cervical dysplasia and carcinoma *in situ* [1, 4, 14, 17]. Most often, HPV infection occurs subclinically, usually against various gynaecological diseases, such as vulvovaginitis, cervical pseudo-erosion, endocervicitis. There is a combination of papilloma viral infection (HPV infection) with other sexually transmitted infections (STIs) – syphilis, gonorrhoea, chlamydia, genital herpes, trichomoniasis. With established oncological diseases, such as CU cancer, including postoperative relapses, vulvar cancer, endometrial cancer, ovarian cancer, HPV of high oncogenic risk were found in 57.9-97% of cases, with HPV of low oncogenic risk not reported or occurring rare [9, 15, 18].

In the practice of obstetricians and gynaecologists, HPV-associated genital disease remains one of the most important problems, because clinical manifestations, diagnosis and tactics for managing patients with different forms of PVI are contradictory and not standardized. The tendency towards unreasonable and sometimes aggressive treatment of women infected with HPV in recent years often leads to long-term complications, recurrence of diseases, especially during pregnancy [5, 9, 12].

Risk factors for CU cancer include long-term cervical (benign and precancerous) diseases, which, if left untreated, lead to CU cancer. In multi-stage carcinogenesis, in addition to HPV, a number of other co-carcinogenic agents of various nature participate. They include: early onset of sexual activity (up to 15 years), frequent change of partners (more than 5), smoking (more than 10 cigarettes a day), lack of sexual hygiene in both partners, history of anovulatory menstrual cycles before pregnancy, hyperestrogenism, primary infertility, exposure to radiation before and during pregnancy, cervical trauma in childbirth and abortions, STIs [5, 6, 13, 16, 18].

In the body of a pregnant woman, changes occur in all organs and systems, including the cervix. In the cervical stratified squamous epithelium (SSE), a large number of dividing cells can appear with impaired differentiation and hyperplasia. This contributes to PVI activation. The CxC mucous is hypertrophied due to increased size of the cylindrical epithelium cells and intensified mucous discharge in them. Due to hyperplasia of reserve subcylindrical cells, polypoid overgrowths are formed in the central canal. In some cervical areas, there is metaplasia of the cylindrical epithelium in SSE. In the cervical stroma during pregnancy, destruction of collagen fibers is observed, new blood vessels are formed, new cells appear, similar to decidual cells in their morphological characteristics. The stroma is infiltrated by lymphocytes, leukocytes, monocytes. The high incidence of background

and precancerous diseases, as well as the increased incidence of CU cancer in pregnant women, indicate the need to develop a methodology for diagnosis, monitoring and treatment of cervical pathology in this group of patients.

Given the above, the ***purpose*** of the study was to explore the CU condition in pregnant women and develop recommendations for timely diagnosis, treatment of cervical pathological conditions and prevention of CU cancer during pregnancy.

## Material and methods of the study

136 pregnant women were examined, upon referral by the oncology center with cervical dysplasia of varying severity and suspected CU cancer. The average age of patients is 27 ± 5.7 years. Primordial patients were 57 (42%), primiparous patients – 63 (46.3%), multipara patients – 73 (53.7%). A study of sexual history, bad habits, oncological anamnesis of first-degree relatives was performed in all the women consulted.

Colposcopy was performed with the colposcope "Scanner-MK-200", with conventional light filters, under 10-16-time magnification according to the International classification of colposcopic patterns (Rome, 1991).

Cytological smears from the surface of the cervical canal and transition zone were studied, which were obtained with cervical brushes. Cytological examination was performed after fixing in the Nikiforov mixture and Pap staining. Interpretation of cytological findings was carried out according to the classification developed in Bethesda (USA) in 1991 and supplemented in 2005. Cervical biopsy, followed by histological examination, was performed upon strict indications in the setting of a gynaecological inpatient department.

At the first stage, all pregnant women underwent vulvoscopy and colposcopy with targeted sampling with cervical brushes for cytological examination. All women were screened for Torch infections and underwent PCR examination for high and low oncogenic risk HPV DNA. After detection of STIs, all patients underwent ethiopathogenetic treatment. After detection of a viral infection, the pregnant women received the antiviral agent Proteflazid for 4 weeks starting from the second trimester. Proteflazid has a direct antiviral (inhibits virus-specific enzymes) and immunocorrecting (induces endogenous interferons, normalizes the parameters of cellular and humoral immunity), does not affect the foetus and course of pregnancy. Proteflazid was administered *per os* in the form of drops according to the scheme:

- Week 1: 5 drops x 3 times a day;
- Weeks 2-3: 10 drops x 3 times a day;
- Week 4: 8 drops x 3 times a day.

In addition, Proteflazid was administered topically on a tampon (1:5 dilution) for 10 days. The product does not cause complications, is well tolerated by pregnant women, has a pronounced antioxidant and anti-inflammatory effect [4, 5]. The efficacy of the treatment was assessed by clinical manifestations with colposcopic and cytological control every 2 weeks. Control PCR examinations for high and low oncogenic risk HPV DNA was carried out 2 months after childbirth.

## Results of the study and their discussion

In the study of sexual history, 12 (9%) women had a sexual debut before the age of 15, 96 (71%) – at the age of 16 to 20, 28 (20%) women – after 28 years. Before the onset of this pregnancy, 82 (60%) women had from 2 to 5 sexual partners, 23 (17%) had more than 5 partners in the past history and 31 (23%) had only 1 sexual partner.

The previous history of infections showed: gonorrhoea – 3 (2.2%) cases, syphilis – in 1 (0.7%), trichomoniasis – in 38 (28%), chlamydia – in 34 (25%), recurrent herpes – in 28 (20%) of the subjects. Each 3rd pregnant woman reported about repeated treatment of colpitis, cervical erosion, adnexitis without establishing the cause of the disease, prior to pregnancy. In the past, 8 patients underwent dermatological treatment of vulvar condyloma, which was removed by electrosurgical method. No patient was examined for HPV before pregnancy. After the PCR examination and DNA typing, high oncogenic risk HPV was detected in 61 (45%) pregnant women, 42 (31%) had low oncogenic risk HPV and 22 (16%) had HPV of both high and low oncogenic risk.

Complaints in pregnant women with cervical dysplasia were absent in 70% of cases, in 30% of patients there were pathological discharge from the genital tract (whites, spotting), itching of the external genital organs due to the presence of concomitant background pathology, and periodic pains in the lower abdomen.

Examination of 34 pregnant women identified isolated and multiple exophytic condylomas, which were located on the vulva, vaginal walls, cervix, but most often in maceration areas of the inguinal region, perineum and in the perianal region. Isolated condylomas were identified in small and large labia, in the outer opening of the urethra, in the region of the clitoris and introitus.

Vulvoscopy differentiated three main forms of exophytic condylomas: pointed, papillary, papular. Clinically, exophytic condylomas in some women were completely asymptomatic or caused psychological discomfort due to a cosmetic defect and even interfered with a normal sexual life. The psychological discomfort was manifested by a feeling of anxiety, guilt, decreased self-esteem, concern about the infection of the child and risk of developing cancer.

Complaints of the whites were present in 58.8% of pregnant women with exophytic condylomas, 29.4% suffered from itching, burning sensation in the vulva, and 17.6% experienced dysuric disorders. Almost every third pregnant woman did not present any complaints, small warts were diagnosed accidentally upon consulting a doctor.

An objective examination of patients with exophytic condylomas of external genital organs showed signs of concomitant inflammatory process, hyperaemia of mucous membranes and skin, cracks, ulceration. Each fifth woman with PVI of external genital organs was diagnosed with foci of infection in the vagina and on the cervix.

Cervical speculum examination of all pregnant women revealed areas of hyperaemia, swelling and various overgrowths. In 75 (55%) patients, the cervix was increased in size, softened, hypervascularized. A specific pattern of erosion, cervicitis, polyp, leukoplakia, condyloma, ectopia, deciduosis was determined. Dysplasias on unchanged CX (in the absence of background disease), as a rule, were not visualized with the naked eye. Upon a vaginal examination the cervix of soft consistency, increased in size was palpated with the presence of small exophyte formations or without them. The cervix sometimes bled when touched. A number of patients experienced the so-called "contact bleeding". A rectovaginal examination did not reveal pathological abnormalities.

A colposcopic examination showed that the cervix of pregnant women was pink with cyanosis, sometimes with a purple tint. Extended, full-blooded subepithelial vessels were defined, giving the cervix a marble appearance. Such changes, under a simple colposcopy, often resemble a malignant process. Ectopia of the cylindrical epithelium (ectopia gravidarum) was detected in 27 (20%) patients on the vaginal part of the cervix. It was represented by hypertrophied cylindrical epithelium with oedema and increased vascularization of papillae. SSE was oedematous, loose, with point elevations in some places. Schiller's test detected focal iodine negative regions, which is associated with uneven accumulation of glycogen in cells of hypertrophic SSE. In 35 (25.7%) pregnant women, cervical deciduosis was detected.

Exophytic overgrowths of decidual tissue on the cervix, vaginal vaults, cervical canal were difficult to distinguish from the exophytic form of CU cancer. Therefore, it is necessary to take smears from the surface of decidual overgrowth for cytological examination. Tumour-like deciduosis in the form of a pink or yellow isolated elevation with a number of vessels was detected in 12 (8.8%) pregnant women. The polypoid form of deciduosis, diagnosed in 23 (16.9%) patients, often originated from the cervical canal in the form of a whitish polyp with many small anastomosing vessels. Targeted biopsy in pregnant women with detected deciduosis was performed only in doubtful cases and when found in smears of severe dysplasia.

A targeted cytological and histological examination as indicated was performed upon detection of acetowhite epithelium, punctuations, mosaic, iodine negative zones, atypical vessels, exophytic condylomas, inflammation, cervical ulcers. The cytological examination detected coilocytes cells specific for PVI formed in tissues as a result of HPV cytopathic effect. There were cells with altered nuclei – dyskaryocytes. Dyskaryocytes are small cells of stratified squamous epithelium, with pyknotic nuclei of various shapes and sizes, with intense eosinophilic cytoplasm, which were located in complexes in the surface layers of the epithelium. Simultaneously, destruction of collagen fibers was observed in the cervical stroma, with simultaneous accumulation of the glycoprotein substance. The stroma was infiltrated by leukocytes, lymphocytes and monocytes.

Cytology revealed dysplastic changes in SSE, dyskaryosis of cells of different layers and disturbed nucleocytoplasmic ratio (depending on the degree of severity). In the presence of inflammatory changes in smears, the pregnant woman was examined for STIs – chlamydia, herpes, cytomegalovirus, trichomoniasis, vaginosis, ureaplasmosis, candidiasis. PCR was performed when koylocytes were detected in smear, for HPV typing.

To carry out a targeted biopsy, the pregnant woman was hospitalized. After a biopsy, one woman was prescribed with tocolytic therapy to preserve her pregnancy. Histological conclusion was final in making an accurate diagnosis. In histological preparations with dysplasia, there was impaired vertical anisomorphism and stratification of the lower layers of cells, due to total basal cell hyperreactivity. Hyperplastic cells of the lower layers had a narrow cytoplasm rim and a large nucleus. In the cells of the surface and intermediate layers, there was hyper- and parakeratosis, with the presence of signs of decidualization in the stroma due to pregnancy. Morphologically, dysplasias of I, II, III severity degrees were determined. At the same time, one patient had a different degree of dysplasia in different areas of the cervix or combination of a morphological picture of a benign background cervical disease with dysplasia of different severity degrees.

A complex examination detected benign background diseases in 39 (28.7%) pregnant women, mild and moderate dysplasia (CIN-I, CIN-II) in 75 (55.1%), severe dysplasia and cancer *in situ* (CIN-III and CIS) in 15 (11%) and stage I CU cancer in 7 (5.1%) patients. It was found that malignancy occurred against long-term untreated pseuderosion in 4 (26.7%) and CIN-I-III – in 11 (73.3%) patients.

An individual management plan for each pregnant woman with cervical pathology was developed after verification of the process on the cervix.

If a pregnant woman had a benign background cervical disease, she was followed up as usually in a maternity welfare center with mandatory colposcopic and cytological examination – once a trimester. Scheduled treatment of the cervix was carried out after childbirth.

In case of pre-cancerous cervical changes (CIN-I and CIN-II), 70% of women underwent conservative management with case monitoring until delivery. Full-term infants did not have any abnormalities in their health status. After delivery and repeated thorough examination, 6-8 weeks later, women received electro-, cryo-, laser surgical or radio-wave treatment upon indications. 12% of patients had spontaneous miscarriage, and another 18% of women had an artificial abortion at their request. Treatment of the cervix (destructive) upon indications was carried out 6-8 weeks after the termination of pregnancy.

When CIN-III and CIS were detected, all pregnant women underwent thorough examination in the oncologic dispensary to rule out an invasive process.

Thus, in most cases of benign and precancerous cervical pathology, the childbirth is carried out vaginally in accordance with the obstetrical situation.

Caesarean delivery was performed upon absolute or combined relative obstetric indications for the mother or intrauterine foetus. Certain situations may require choosing the amount of surgical intervention on the uterus in case of complications during vaginal childbirth or caesarean section (uterine atony, septic complications). In such cases, if the pregnant woman has CIN-III or CIS, total hysterectomy is indicated instead of supravaginal amputation.

In the presence of HPV-associated diseases in a pregnant woman (condylomatous overgrowths on the cervix, vulva, vagina), it is most advisable to perform caesarean delivery, to prevent laryngeal papillomatosis in an infant [1, 9, 17]. In other cases, the birth is carried out vaginally.

The delivery in women with detected herpetic cervical infection in subclinical and asymptomatic course was conducted vaginally, and in acute manifestation – by surgery [6].

With CIN-III or CIS, cytological and colposcopic monitoring of pregnant women was performed every month throughout the entire gestation period. None of the pregnant women showed any progression of the oncological process. Delivery is performed according to the obstetric situation in 12 (80%) – vaginally and 3 (20%) – by caesarean section. 6-8 weeks after delivery and thorough examination, radical organ-preserving treatment was performed – electro- or radio-wave conization of the cervix within healthy tissues.

When an invasive CU cancer (stage I) is detected, the treatment strategy depends on the gestational age of diagnosing [3,10,11]. At early terms (before weeks 12 of pregnancy) 5 pregnant women received a contact radiation therapy at a dose of 13.5 Gy, Wertheim hysterectomy and a remote radiation therapy of pelvic organs at a dose of 40 Gy. There were 2 cases of the first stage CU cancer in the later stages of pregnancy, when, at the insistence of the women, the pregnancy was prolonged until the terms of foetus viability, determined by ultrasound and other methods. When the foetus achieves viability (weeks 35-37), an integrated team of obstetricians, paediatricians, oncogynecologists and anaesthesiologists performed a surgical intervention in the form of corporal Caesarean section followed by Wertheim hysterectomy. Later, these patients received remote radiation therapy of pelvic organs at a dose of 40 Gy.

## Conclusions

The most common precancerous diseases and CU cancer in pregnant women occur and develop against long persistent PVI and pre-pregnancy background cervical diseases. Therefore, this pathology should be treated before the planned pregnancy.

Upon detection of clinical, subclinical forms of PVI and CIN I and II, abortion is not indicated, but it is recommended to perform case monitoring and antiviral treatment.

In pregnant women with PVI, who underwent antiviral treatment, there was no progression of precancerous diseases to invasive cancer, which gives grounds to perform postponed treatment, after the termination of pregnancy.

With CIN III and CIS diagnosed in early pregnancy, the patient should be offered to terminate pregnancy, carry out cervical treatment, and after treatment, pregnancy can be recommended.

When a pregnancy is combined with an invasive CU cancer, the method of treatment is determined based on the terms of pregnancy, when the diagnosis is first established, the stage of a pathological process and a desire of a woman to have a child.

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## Cervical Pathology Monitoring in Pregnant Women

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***Summary.*** *Results of the studies, observation and management of 136 pregnant women with cervix pathology (CP) are presented. Malignant transformations of the CP epithelium are more frequent to be found in the patients who have failed to treat their background and pre-cancer diseases on the backdrop of concomitant papillomaviral infection. An in-depth study of pregnant with cervix pathology allows for a timely diagnosis to be made and an individual management plan to be developed. In the event of a combination of CIN III, CIS, CP cancer and pregnancy, the treatment scheme is designed with consideration to pregnancy term, malignant process expansion level, and patient's willingness to have a baby.*

***Keywords:*** *cervix, pregnancy, papillomaviral infection, cervical intraepithelial neoplasms, cervical cancer.*