MINISTRY OF HEALTH OF THE REPUBLIC OF UZBEKISTAN

SAMARKAND STATE MEDICAL UNIVERSITY

TUGIZOVA DILDORA ISMOILOVNA

CERVICAL CANCER IN PREGNANCY

Monograph

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CERVICAL CANCER IN PREGNANCY

(Monograph)

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Improving methods of early diagnosis and tactics of management of pregnant women with cervical cancer. **Monograph /** Tugizova D.I. – Samarkand, 2025.- *p.

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Annotation.

Management of oncological diseases in pregnant women includes one of the key points – preserving pregnancy and minimizing the teratogenic effect while maintaining anti – cancer effectiveness no lower than in the population of non – pregnant women. The monograph presents problematic aspects of diagnosis and treatment cervical cancer in pregnant women, based on a literature analysis of sufficiently large scientific works, as well as on the results of our own research. Methods for the comprehensive diagnosis and treatment of cervical cancer during pregnancy using neoadjuvant polychemotherapy are proposed. The use of polychemotherapy in pregnant patients with cervical cancer is associated with tumor dynamics and general health comparable to those in non-pregnant women, according to subjective and objective assessments.

The monograph is intended for oncologists, obstetricians and gynecologists, and residents of the master's program and clinical interns in the specialty of oncology and obstetrics and gynecology. The materials of the monograph can be used in the educational process of the departments of oncology and obstetrics and gynecology of medical universities.

INTRODUCTION

RELEVANCE OF THE PROBLEM. According to GLOBOCAN, in 2018, there were 569847 new cases of cervical cancer registered worldwide (the 4th most common cancer in women worldwide) and 61072 new cases in Europe (the 8th most common cancer in women in Europe). The mortality statistics are also depressing: in 2018, there were 311365 deaths registered worldwide (the 4th most common cause of cancer death in women) and 25829 new cases in Europe (the 10th most common cause of cancer death in women in Europe) [8, "Fan" Publishing House, 2020; 27, pp. 1215-1230; 102, pp. 667-673].

Work on the study of cervical cancer in the world began back in the distant 1950s of the twentieth century. However, significant progress in diagnosis and treatment was achieved closer to the end of the twentieth century. In the United States, entire cooperative groups were created to study cervical cancer in pregnant women. The main ones are The Gynecologic Oncology Group (GOG) and NRG Oncology focused on improving the results of cervical cancer treatment. The most important contribution of GOG/NRG Oncology was a series of clinical trials that led to the landmark announcement of the National Cancer Institute in 1999 regarding the use of chemoradiation therapy in patients receiving radiation as a therapeutic method for various clinical scenarios of cervical cancer [Keys H 1999, Whitney C 1999, Huh W 2017] [65,78].

Cervical cancer is one of the most common malignant neoplasms among pregnant women and occurs with a frequency of 1/1000–2000 pregnancies [Roxana Schwab, 2021] [13.50]. Although cervical cancer in pregnant women is quite rare, social factors such as an increase in the average age of motherhood, frequent change of sexual partners, etc., lead to an increase [Maggen, C 2020] [87]. In 2021, 1827 patients with cervical cancer were identified in the Republic of Uzbekistan, of which stage I - 12.0%, stage II - 54.1%, stage III - 23.6%, IV - 5.0% (Tillyashaykhov M.N. et al. 2022). Tashkent city was in first place in terms of detection – 292 cases, Andijan was in second place – 187 cases, and Fergana was

in third place – 179 cases. The least number of cases were detected in Syrdarya – 37, Navoi – 45, and Jizzakh – 67 cases. 141 cases were detected in Samarkand. Of these, 11.3% were at stage I, 48.9% at stage II, 36.9% at stage III, and 2.8% at stage IV. The mortality rate was 1.3% [8]. According to WHO, cervical cancer is the eighth most common malignant neoplasm and is common in developing regions. For example, according to statistics for 2018, 311365 deaths were registered out of 569847 new cases. According to the Monitoring of Cancer Incidence in Japan (MCIJ), the incidence of cervical cancer in Japan increased from 11053 [60] in 1975 to 34120 in 2017. The average age was 35 years. In Brazil, cervical cancer ranks 3rd in incidence and, according to research in 2016, the incidence rate was 15.85 new cases per 100000 women [da Silva ERP. 2017] [25, 50, 54].

In India, according to WHO estimates, 122844 new cases and 67544 deaths were caused by cervical cancer, accounting for almost 1/3 of all cervical cancer deaths in 2014 [Prajakta Adsul. 2017] [106]. The prevalence of cervical cancer in pregnant women in Africa also has its own characteristics. For example, high-risk regions are East and West Africa (more than 30 per 100 000), Southern Africa (26.8 per 100 000), Middle Africa (23.9 and 23.0 per 100000, respectively) [Ahmed Ibrahim MD. 2013] [65]. In East, South-Central Africa and Melanesia, cervical cancer among pregnant women remains the most frequently diagnosed malignant neoplasm [Globocan, 2008] [96].

In Russia, the standardized incidence rate of cervical cancer in 2016 was 13.70 per 100 thousand female population. [Saevets V.V. 2016] [2,7]. In South Korea, by 2016, cervical cancer accounted for 2.2% of all diagnosed malignant neoplasms and 2.6% of cancer deaths among women, and 3013 new cases and 755 deaths were identified [Yumi Lee, 2016] [86,91]. The incidence rate per 100000 population was 11.7 new cases and 7.5 deaths [Kyu-W J. 2016]. As for Western Asia (including Egypt), the incidence of cervical cancer is relatively low. Estimated age-standardized incidence rates range from 2 to 9.5 with a mean of 3,

which is below the global average and amounts to 7.9 per 100000 people per year (Table 2) [Ghazi A. 2018]. According to the International Network on Cancer, Infertility and Pregnancy, the most common malignant neoplasm among pregnant women is breast cancer (39%), followed by cervical cancer (13%), lymphoma (10%), ovarian cancer (7%) and leukemia (6%) [de Haan J, 2018] [89]. In particular, the spread of human papillomavirus (HPV) has caused an increase in precancerous and cancerous lesions of the cervix, especially in younger women of childbearing age [Lynge E., 2014] [14,77]. Due to the above – mentioned factors, cervical cancer has recently become the most common gynecological malignancy in pregnant women (4 per 100000 births) [Hecking T, 2016] [30]. In China, from 2009 to 2015, 98900 new cases of cervical cancer were detected in pregnant women, and 30500 of them unfortunately died [Chen W. 2015, Di J. 2015, Wang B. 2015]. In the United States, studies have shown that among an average of 4000000 pregnant women, 2% to 7% (i.e. 80000-320000) will have an abnormal Pap test during pregnancy [Arias E. 2002, Morimura Y. 2002, Douvier S. 2003, Cheng X. 2000]. Of these, pregnancy is complicated by neoplasia (including carcinoma in situ and invasive carcinoma) in about 1.5 to 12 pregnancies per 1000000 women [Smith LH. 2001, Smith LH. 2003, Demeter A 2002]. By 2018, 13240 new cases and 4170 deaths were diagnosed in the United States [Patti Olusola, 2019].

CHAPTER I

INDIVIDUAL APPROACH TO CARE OF PREGNANT WOMEN WITH CERVICAL CANCER

Cervical cancer is a malignant neoplasm whose substrate can be both squamous epithelial cells and glandular epithelium, and is the fourth most common malignant pathology and the fourth cause of cancer mortality in women. Although the tumor is potentially preventable by vaccination against the human papillomavirus (HPV) and an effective screening strategy, the peak incidence coincides with the childbearing period in a population in which these preventive

strategies are not used sufficiently [68]. Also, cervical cancer is the third most common oncological pathology in pregnant women (4 cases per 100000 pregnancies [62]. Various data indicate that detection of cervical cancer in pregnant women is not associated with a negative impact on survival. However, limited literature data do not allow us to state the reliability of these statistics [64]. Treatment of cervical cancer in pregnant women is a complex task, which includes two main aspects – optimal anti-cancer treatment and prolongation of pregnancy. The treatment strategy may include conservative methods and surgical procedures, depending on the tumor size, involvement of regional and distant lymph nodes, gestational age and the woman's desire to continue the pregnancy [58,76]. Despite the fact that in recent years the incidence of cervical cancer has been decreasing due to the described preventive strategies, the increase in the age of pregnant women contributes to the frequency of cervical cancer diagnosis in pregnant women [62].

Pregnancy complicated by cervical cancer is defined in the case of primary diagnosis of cervical cancer during pregnancy or 6-12 months after delivery [3,6]. The number of pregnancies complicated by cervical cancer is small. In 1-3% of women suffering from cervical cancer, the oncology was first diagnosed during pregnancy [48,49]. Of these, about half were pregnant at the time of diagnosis of the disease, the rest – 6-12 months after delivery.

It is unknown whether pregnancy increases the risk of developing or progressing cervical cancer. However, it is assumed that elevated estrogen levels and human chorionic gonadotropin activate the procarcinogenic effect of human papillomavirus (HPV) infection. Other researchers believe that increased blood flow and lymphatic circulation in early pregnancy with a simultaneous decrease in specific immunity and cervical dilation may contribute to the development of cervical cancer [93].

Today, therapeutic strategies for cervical cancer in pregnant women are limited to cervical conization and polychemotherapy. The choice of patient management tactics also includes tumor monitoring during pregnancy or

termination of pregnancy for the purpose of conducting therapeutic anti-cancer measures [94]. The choice of patient management tactics depends on the gestational age at the time of primary diagnosis of the pathology. Termination of pregnancy is the most common choice in case of tumor diagnosis before 20 weeks of pregnancy. In case of the first detection of a tumor, the concept of active surveillance is more typical. The gestational age also determines the time and method of delivery. However, various treatment strategies do not negatively affect maternal survival, but take into account the risk of negative effects on the fetus, including theratogenesis, malformations, underdevelopment and survival of the fetus.

Gunther and co-authors developed an algorithm for the management of patients with cervical cancer diagnosed during pregnancy (Fig. 1) [76,84,85].

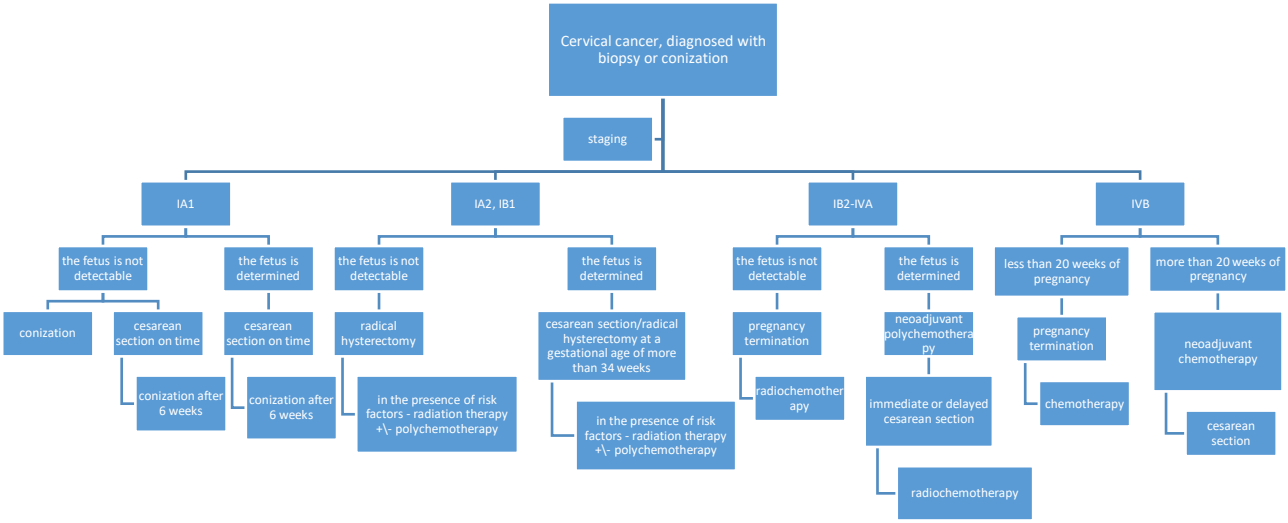


Figure 1. Algorithm for managing pregnant women with cervical cancer

(Hunter MI et al. 2018)

Prolongation of pregnancy in the early stages of cervical cancer and delay of treatment in the early stages of the pathology can be quite safe [64]. Diagnostic conization, although associated with a significant risk of hemorrhage, allows to establish the actual depth of invasion in case of a microinvasive tumor [23]. Involvement of lymph nodes can be diagnosed by MRI, which is safe for the mother and fetus. An alternative is laparoscopic lymphadenectomy, which is also an effective and informative procedure acceptable during pregnancy [84].

Neoadjuvant polychemotherapy in the gestational period is possible in certain groups of patients - with an advanced stage of the disease or high-risk cervical cancer. Polychemotherapy methods are being developed that allow the fetus to mature. However, the choice should be individualized, balanced, taking into account the risk of antenatal toxicity versus the risk of disease progression in case of choosing active surveillance tactics.

The drug of choice for PCT is platinum drugs [105] due to the detection of a low concentration of the active substance in the fetal blood, which indicates effective placental filtration. The timing of delivery is a critical point in the management of pregnant women with cervical cancer: according to modern guidelines, premature delivery is a safe and optimal compromise between the maximum possible maturation of the fetus and the possibility of active anti-cancer therapy for the mother [20].

Some studies have described the safety of delayed anti-cancer treatment for cervical cancer from 1 to 32 weeks, which allows the fetus and placenta to mature in the case of IA-IB1 cervical cancer [32,99,101,105].

The use of CO2 laser conization of the cervix in cases of minimally invasive cervical cancer is safe if the length of the conization site is less than 2 cm [103]. A series of 4 pregnant women with cervical cancer who underwent laser conization at 16-23 weeks was also reported. In all cases, the pregnancy ended in term delivery. Three patients subsequently underwent radical hysterectomy and lymphadenectomy. In none of the cases was recurrence of cervical cancer observed during 2-13 years of observation [35].

Postpartum extrafascial hysterectomy is recommended for patients with stage IA1 cervical cancer without lymphovascular invasion and negative margins determined by biopsy. If the patient insists on preserving the reproductive function, serial regular monitoring with cytological examination is possible.

Patients with minimally invasive cervical cancer usually do not undergo cesarean section. However, in case of a large node, vaginal delivery is contraindicated due to the risk of tumor dissemination. In case of cesarean section,

a vertical uterine incision is recommended to preserve the lower portion of the uterus for pathological examination.

For patients with cervical cancer stage IA1 LVSI, IA2, IB1, radical hysterectomy with bilateral lymphadenectomy is recommended during cesarean section or 6-8 weeks after delivery [42].

For stage IA2-IB2 cervical cancer, radical hysterectomy with bilateral lymphadenectomy is performed at any gestational age. Also, radical bilateral tracheolectomy through vaginal or abdominal access reduces the risk of cervical cancer metastasis with satisfactory obstetric outcomes. Thus, in a series of 10 vaginal and 11 abdominal tracheolectomies at 5-22 weeks of pregnancy, spontaneous abortions were observed in 6 cases within a week after surgery, while all other pregnancies were resolved at 29-39 weeks [42].

Undoubtedly, the most optimal strategy against cervical cancer in pregnant women is participation in preventive screening programs. Unfortunately, most pregnant women do not undergo regular gynecological screening in the pregestational period. Since the Pap test is an integral part of early antenatal screening, it allows detecting changes in the cervical epithelium in the target population, as well as diagnosing the tumor at an early stage [68]. In case of detection of cells suspicious for cervical cancer, especially taking into account the initially altered epithelium (hormone-dependent epithelial changes in cervical cancer in pregnant women), a biopsy is recommended, preferably during colposcopy [29]. Colposcopic biopsy during pregnancy is a safe and informative procedure that can be complicated by delayed bleeding, but this complication is successfully resolved by tamponade [61].

Women whose regular gynecological screening revealed changes in the Pap test indicating dysplasia of the cervical epithelium should be advised to postpone pregnancy planning until the dysplasia is cured. Pregnant women with a suspicious Pap test result should be referred for colposcopy, provided that the procedure is performed by a specialist familiar with the specific physiological changes of the cervix during pregnancy. During colposcopy, a biopsy of the altered tissue is

performed to verify the diagnosis, stage the pathology and develop an individual plan for patient management.

The incidence of cancer in pregnant women has increased in recent decades, making the issue of solving interdisciplinary problems increasingly urgent – choosing patient management tactics aimed at controlling cancer while maintaining pregnancy and minimizing the risk to the mother and fetus. Today, 1 in 1000 is complicated by malignant pathology [97]. National and international registries have been established, including the International Network on Cancer, Infertility and Pregnancy, which combines many clinical cases. The results of small cohort studies have also been conducted and published, indicating the possibility of conducting anti-cancer treatment [95].

Cervical cancer is the third most common oncological pathology in pregnant women. The complexity of studying the problem is associated with both ethical aspects and individual differences in clinical situations, which complicates the conduct of trial studies and limits our knowledge of the optimal tactics of patient management. The incidence of cervical cancer in pregnant women is 8-15 cases per 100 thousand pregnancies [58,92]. Probably, the increase in the incidence of the disease in pregnant women compared to non-pregnant women is also associated with the fact that women who are not regularly monitored come to the attention of gynecologists during pregnancy [69]. Pregnancy does not affect the survival rate of patients with cervical cancer [34,69,90,106]. The tactics of patient management depend on the stage of the disease, tumor size, macroscopic and histopathological characteristics of the formation, gestational age, age of the patient and her desire to prolong the pregnancy.

Cervical cancer diagnosed at a late stage is associated with a less favorable prognosis, while early detection of the disease allows for surgical procedures to be performed while preserving pregnancy (lymphadenectomy for lymph node examination, conization, or tracheolectomy) or to postpone treatment until the end of pregnancy, which is impossible when diagnosing an advanced stage of the disease [19,47,88]. According to the latest recommendations, radical

tracheolectomy during pregnancy is not a procedure of choice, especially in the case of progressive disease, since it is associated with a high risk of miscarriage (up to 60%) [19,47,91,94]. Termination of pregnancy in case of progressive cervical cancer allows for the use of standard approaches to the treatment of pathology, however, modern progress in oncology allows for the consideration of anti-cancer treatment in pregnant women. Without interrupting it, and selecting gentle therapy regimens. Data on neoadjuvant chemotherapy allow for the use of therapy to inhibit the progression of the disease and to postpone termination of pregnancy until the fetus matures.

Standard therapy for cervical cancer includes polychemotherapy and radiation therapy [47], but neoadjuvant polychemotherapy allows to postpone the use of radiation therapy and radical surgical treatment and to provide an opportunity to complete pregnancy at least until the maturation of the fetal lungs. The effectiveness of this approach compared to the standard therapy regimen has been studied for the last 20 years. A meta-analysis comparing neoadjuvant polychemotherapy followed by radiation therapy with isolated radiation therapy in patients with advanced stage cervical cancer showed the advantage of polychemotherapy over surgical treatment only in the group of patients receiving high doses of cisplatin and in patients with short intervals between courses [105]. The same study showed better survival of patients in the polychemotherapy + surgical treatment group compared to the radiation therapy group (OR 0.65, advantage - 14% five-year survival) [105]. In a randomized study, Gupta et al. found better relapse-free survival in patients with locally advanced cervical cancer in the chemotherapy + radiation group compared to patients with chemotherapy + surgery. However, in the group of patients with stage IIB2/IIA, chemotherapy showed an advantage, but statistical significance of the results was not achieved due to the small number of patients. The authors also indicated that patients with no response to therapy or disease progression despite chemotherapy had a significantly worse prognosis compared to the rest [67].

PCT + surgery compared with isolated surgery is described in a Cochrane review, which showed better survival, relapse-free survival, metastasis to regional lymph nodes, and a lower frequency of parametric invasion in patients who received PCT [87]. Zhao et al. did not find an association between PCT and better relapse-free survival, but in an analysis of 8 studies that included 1544 patients, PCT + radical surgery improved overall survival, reduced the risk of local and distant recurrences, metastasis to lymph nodes, and the degree of parametric invasion compared with surgical treatment alone [108]. Also, chemotherapy followed by surgery reduced the need for adjuvant radiotherapy compared with isolated surgery by reducing tumor size, the severity of lymphovascular and stromal invasion, metastasis to regional lymph nodes and distant metastasis [82,99].

Based on the available data, chemotherapy followed by surgery does not worsen the prognosis of patients compared to isolated surgery [57,82,99,101,107,108]. The EORTC55994 trial, conducted between 2002-2014, in which chemotherapy followed by hysterectomy was performed in 311 patients and chemotherapy and radiotherapy in 309 patients. Analysis of 12-year follow-up (mean 8 years) did not reveal any significant differences between the groups. A trend towards the advantage of chemotherapy and radiotherapy was noted in women over 50 years of age. According to the authors' conclusion, the morbidity associated with therapy and the quality of life of patients require additional analysis due to chemotherapy-associated toxicity [81].

Today, there is no reliable data on the effectiveness of PCT in patients with progressive cervical cancer during pregnancy, so this treatment option is largely experimental. However, the role of this method of anti-cancer therapy is promising, since it allows postponing the use of more radical methods that require termination of pregnancy. The goals of PCT in pregnant women:

1. tumor stabilization and prevention of dissemination until completion of pregnancy;

2. reduce the volume and spread of the tumor, while maintaining its operability and accessibility to radiation therapy;
3. reducing the risk of metastasis to lymph nodes and distant regions during pregnancy [92].

Safety of chemotherapy during pregnancy

Since 1948, when the first chemotherapy agent was used during pregnancy [49], the experience of using PCT in this period has expanded significantly. However, the issue of safety and outcomes for the fetus remains open. Organogenesis, which occurs mainly during the 6-10th week of pregnancy, is the most vulnerable process to the influence of exogenous substances, especially cytostatic molecules. Such exposure can cause congenital malformations and termination of pregnancy if carried out during this period. The estimated risk of theratogenesis with the use of one chemotherapy drug in the first trimester is 7.5-17%, and increases to 25% when using 2 or more drugs [73]. According to generally accepted recommendations, PCT should not be used before the 10th week of gestation, and optimally - before the 14th week of gestation. The use of PCT after the 1st trimester is not associated with an increased risk of congenital malformations [40]. The use of PCT in the 2nd and 3rd trimesters is associated with fetal growth restriction, low birth weight, and preterm birth [40,43]. Taking these patterns into account, regular obstetric monitoring with attention to fetal development, intrauterine growth, and the risk of preterm birth can improve pregnancy outcomes. Since the central nervous system and gonads are still developing at this time, the late effects of PCT on cognitive function, carcinogenesis, fertility, and possible effects on subsequent generations of children who received the drugs in utero require further study.

Several studies have examined the effects of PCT on late development, cognitive, and cardiovascular outcomes in children exposed to the drugs in utero. These studies have shown that outcomes in this group of children are comparable to those in the general population [15,22,43]. In one study, Amanth et al. showed a high rate of preterm birth among 70 children exposed to PCT in utero. After 22

months, the group of children born preterm had more severe cognitive impairment compared to children born at term [15]. A study by Chardonik et al. also found an increased rate of preterm birth in the case of PCT during pregnancy, but without a negative effect on cognitive function [43]. Iatrogenic preterm birth should be excluded, since cognitive decline is associated with preterm birth, but not PCT. It is recommended to plan delivery at least 3 weeks after the last course of PCT to allow the bone marrow to recover from the negative cytostatic effect of PCT and to minimize the risk of iatrogenic suppression of hematopoiesis (anemia, hemorrhagic syndrome, infectious complications) in the mother and fetus [17]. Also, since the liver and kidneys of the fetus are not yet mature, the ability of the fetus to eliminate chemotherapeutic agents is reduced and the post-PCT period allows the drug to be excreted through the placenta. The last cycle of PCT should be performed no later than 35 weeks of pregnancy to reduce the risk of hematopoietic suppression of the fetus in case of premature delivery [17].

Pharmacokinetics and transplacental transport of drugs are also of interest. Transplacental transport of active molecules of cytostatic drugs is carried out mainly by passive diffusion. This process depends on such characteristics of the drug as the ability to dissolve in fats (lipophilicity), ionization, molecular weight and protein binding [82]. The most widely used drugs for neoadjuvant chemotherapy are platinum drugs, isophosphamide and taxanes. Kohler et al. [83] measured the concentration of platinum in amniotic fluid and cord blood and found concentrations of 11-42% and 23-65% of the concentration in maternal blood, respectively. Interestingly, a mouse model demonstrated a concentration of carboplatin in fetal blood of 117% of the maternal concentration, while in baboons it was 57.5% [94,101]. Studies of taxane concentrations have not revealed the drug in the blood of mouse embryos, while in a baboon model the concentration of taxanes in fetal blood was 1.4% of the concentration in maternal blood [67,79]. However, it is assumed that taxanes are deposited in fetal tissues to a greater extent than other chemotherapeutic agents due to their physicochemical properties [87,99]. Isophosphomide should be avoided during pregnancy due to its toxicity

profile, insufficient information on fetal safety, and suspected nephrotoxic and gonadotoxic effects [101]. Low concentrations of some molecules in fetal tissues due to the placental barrier allow their relatively safe use during pregnancy.

Physiological changes associated with pregnancy, such as increased plasma and extracellular fluid volume, changes in plasma protein concentrations, their binding capacity, increased glomerular filtration rate, and changes in liver function affect the pharmacokinetics of cytotoxic drugs in pregnant women. Since most drugs do not correspond to long-term therapy between therapeutic and toxic concentrations, changes in pharmacokinetics affect the efficacy and safety of drugs. Van Carlsten reported a decrease in the maximum plasma concentration and area under the curve of all tested drugs in maternal blood, which is probably due to an increase in clearance and volume of distribution [28,54]. This finding limits the extrapolation of standard chemotherapy regimens for cancer in pregnant women by analogy with non-pregnant women.

Management of oncological diseases in pregnant women includes one of the key points - preserving the pregnancy and minimizing the teratogenic effect while maintaining anti-cancer efficacy no lower than in the population of non-pregnant women. In this situation, systemic therapy plays a significant role. Termination of pregnancy is considered in the case of rapidly progressing or complicated course of the disease. Induction of premature labor in order to begin anti-cancer treatment should be avoided if possible, due to adverse effects on the fetus [55].

Large national and international registries have been created to determine the effectiveness of gestational anti-cancer therapy [52]. It has been established that obstetric outcomes have improved significantly in recent decades, with a simultaneous decrease in the incidence of premature termination of pregnancy and induction of preterm labor [52]. Changes in obstetric tactics are associated with an increase in knowledge about the natural history of cancer during pregnancy, as well as a trend towards reducing drug treatment during the gestational period. A recent Italian single-center study showed that in the last decade there has been a decrease in the incidence of premature cesarean sections and an increase in the

incidence of induction of labor in order to initiate full-fledged anti-cancer therapy [39]. Neonatal outcomes in terms of cognitive and cardiovascular status in the first 6 years of age in children who were exposed to chemotherapeutic drugs during the prenatal period did not differ from children in the control (general) population [58,79]. However, if it is necessary to use polychemotherapy, it is necessary to take into account that use during the gestational period can affect fetal growth, and earlier use can cause the development of congenital defects [52].

An important factor is the choice of diagnostic procedures, which can also adversely affect the fetus. The use of ionizing radiation should be minimized during pregnancy [103]. Although the radiation dose used during diagnostic procedures is minimal, its effect on the fetus can be fatal - effects on mental development, malformations, growth disorders and even death have been reported [80]. The risk of stochastic carcinogenic effects of ionizing radiation depends on the gestational age and the radiation dose used. The total dose in case of pregnancy should be less than 100 mGy [103] and it is recommended to conduct the study only in case of a decisive influence of the study result on the determination of the treatment tactics [74]. The lifetime risk of developing malignant neoplasms in case of exposure of the fetus to ionizing radiation at a dose of 50 mGy at the age of more than 12 weeks of pregnancy is about 2%, although exact calculations are unreliable [104]. In recent years, due to the development of medical technologies, the dose of radiation to which the fetus is exposed in utero has been significantly reduced. However, in each specific case, the decision to use a diagnostic method based on ionizing radiation must be made separately.

Non-ionizing imaging techniques such as ultrasound and magnetic resonance imaging (MRI) can be safely used in pregnant women for staging of pathology. Due to insufficient knowledge of the effects on the fetus, the use of gadolinium, a contrast agent used in MRI, is recommended to be minimized, weighing the risk-benefit ratio [98].

In non-pregnant women, the use of positron emission tomography integrated with computed tomography is a valuable informative diagnostic intervention used

for the detection and staging of various types of cancer (especially hematological and breast tumors). However, in pregnant women, due to the high dose of radiation exposure to the fetus (up to 50 mGy), this method is not recommended [23]. Whole-body MRI is an alternative method that allows detection of both the primary tumor and metastatic foci and can be used during pregnancy [24]. Pineapple juice can be used as an oral contrast agent during MRI [71,72].

Scintigraphy can also be used in pregnant women, provided that a low dose of radioisotope is used, so that the exposure dose to the fetus does not exceed 5 mGy [63,70,103]. The minimum possible dose of technetium is administered locally 2 hours before scanning. In this case, 90% of technetium is absorbed in the area of the tumor and there is minimal systemic distribution and risk to the fetus. Indocyanine green is a dye used for visualization of formations in infrared light, characterized by minimal placental transport and can also be used during pregnancy [9,12,19]. Blue dye is not recommended due to some risk of anaphylactic reactions (0.1%) [31].

Surgical treatment of oncological diseases in pregnant women is possible in the shortest possible time, provided that the impact on the uterus is minimal [56]. Cervical cancer – in individual cases can be operated on with intact myometrium and parametrium [10]. In case of contractile activity of the myometrium, tocolytics are administered during the operation. Tocolytics can also be used in the first 48 hours of the postoperative period [1,13].

The decision to use chemotherapy is made taking into account the gestational age, physiological changes in pregnant women, and the pharmacokinetic characteristics of the drugs. Transplacental transport occurs primarily by simple diffusion. Most chemotherapeutic agents are small-molecule drugs that are not subject to conversion and protein binding, so they easily cross the placenta. In baboons, the passage of chemotherapy drugs across the placenta varies from insignificant for docetaxel to 0.58 for carboplatin [15]. The consequences for children born to women from women who received chemotherapy were monitored up to 6 years of age and did not reveal a significant

negative effect. Later outcomes have not been studied. The use of targeted drugs and hormonal drugs is not recommended until convincing data on their safety for the fetus are obtained.

PCT is contraindicated before 12-14 weeks of pregnancy due to its negative impact on organogenesis. After this period, most cytotoxic drugs can be used relatively safely [44]. Standard treatment regimens are used based on the current weight of the pregnant woman. After 35 weeks of pregnancy, PCT treatment is recommended to be stopped to provide the necessary sufficient time window for the restoration of the hematopoietic function of the bone marrow of the mother and fetus.

The following patterns apply to biological and targeted therapy: large molecules such as monoclonal antibodies cross the placenta by active transport, which is possible after 14 weeks of gestation; small molecules such as tyrosine kinase inhibitors cross the placenta throughout pregnancy [89]. The use of biological and targeted drugs is associated with fetal cytopenia, skeletal and visceral malformations, and premature intrauterine fetal death [26,101,133]. These drugs are contraindicated during pregnancy due to their anti-angiogenic properties, with the exception of imatinib and rituximab [38,111].

Maintenance therapy – antiemetic drugs – metoclopramide and serotonin receptor antagonists as part of anti-cancer treatment are safe during pregnancy [19], except for neurokinin-1 inhibitors [36]. Corticosteroid hormones such as betamethasone and dexamethasone are not recommended, as they are characterized by 100% placental permeability. The drugs of choice are molecules metabolized in placental tissue – prednisolone and methylprednisolone, hydrocortisone. There is no consensus regarding stimulating hematopoietic growth factors such as erythropoietin, but if necessary, they can be used with dose adjustment based on weight and hematological picture [45].

Radiation therapy of malignant tumors during pregnancy is possible, except for tumors of the pelvic localization. Thus, in relation to cervical cancer, radiation therapy is contraindicated due to the lethal effect on the fetus.

Obstetric management includes prenatal diagnostics of the fetus's condition – screening for fetal aneuploidy (study of cell-free DNA in the blood of pregnant women at 10-20 weeks, origin – placental cells) [37]. The informativeness of the method in relation to fetal pathology is controversial [16,33,37,96,100].

An informative method of prenatal screening of the fetus's condition is ultrasound. It is recommended to conduct the examination every 2 weeks in order to detect delayed fetal development, possible developmental defects, malformations, and contractile activity of the myometrium. Also, given that PCT is associated with the risk of premature birth, it is recommended to conduct ultrasound measurement of the length of the cervix every 2-4 weeks [93].

Delivery in pregnant women with oncological pathology is planned taking into account the balance of two factors: to minimize the duration of the period free from chemotherapeutic agents in order to reduce the risk of tumor progression in the mother, and at the same time to optimize the time to provide a sufficient time window for the regeneration of hematological stem cells of the fetus. Surgical delivery by cesarean section in cancer patients is 30%, which is higher than 21% in the general population [92]. This is due to both the planning of the next stage of anti-cancer treatment and the goal of reducing psychological and emotional stress in women. However, vaginal delivery is preferable. In patients with cervical cancer, the decision on the method of delivery is made individually, since there is a risk of insemination of tumor cells into the sites of rupture of the mucous membrane of the birth canal or episiotomy.

Delivery is recommended to be planned no earlier than 4 weeks after the end of the course of PCT to provide sufficient time for the cytostatic agent to be metabolized in the placenta and the myelosuppressive effect to be reduced. Thus, it is reported that with delivery 4 weeks after PCT, the incidence of neutropenia is 20-33% [88,106], more than 4 weeks later - only 5.5%. Neutropenia at birth is associated with the risk of nosocomial infection.

After delivery, placental examination is a necessary step. Histological examination is performed to determine whether metastasis has occurred (the villi

are mainly examined, since metastasis occurs through them). Detection of placental metastasis indicates a risk of fetal metastasis [104]. Fetoplacental metastasis is more often observed in melanoma and lung cancer [12]. The characteristics of placental development and maturity are also studied, since this aspect is directly related to short stature of the fetus [39,107]. Studying placental tissue will also provide future data on the impact of various anti-cancer treatment regimens on the placenta and fetus.

Lactation in patients undergoing cancer treatment may be reduced both due to the action of drugs and due to psychoemotional stress [59,85]. However, recommendations for breastfeeding are limited by the high concentration of cytotoxic agents in breast milk and the high risk of milk infection due to cytostatics [66,103]. Moreover, platinum drugs are determined more than 3 weeks after the last course of PCT [102]. In children who are breastfed by mothers who received PCT, complications include gastrointestinal infection and neutropenia [79].

The consequences of the use of PCT in women during pregnancy include cardiotoxicity in children, especially against the background of anthracycline therapy, with the development of heart failure [59], growth retardation [24], cognitive impairment [21], and hematological toxicity [17].

Thus, the analysis of published data shows that, despite the available experimental and clinical data on the information content and safety of individual diagnostic and therapeutic methods used in oncology in pregnant women, there is no single algorithm for the tactics of managing pregnant women suffering from cervical cancer.

CHAPTER II

MATERIAL AND METHODS OF THE RESEARCH

In a study of 102 women of reproductive age diagnosed with cervical cancer, the main group consisted of 66 pregnant women, 36 women of whom cervical cancer was detected outside of pregnancy (Table 1).

The majority of patients included in the study were residents of the Andijan and Samarkand regions (29% each, Fig. 2), the intergroup difference depending on the region of residence of women was insignificant (Fig. 3). The majority of women included in this study lived in rural areas (60%, Fig. 4), according to this indicator the groups were comparable (Fig. 5).

Table 1

Characteristics of study groups

Indicator	Main group (n=66)	Comparison group (n=36)	Reliability of intergroup differences
Age, years	33.67±1.78	33.28±0.73	Nd
Region of residence			
Andijan	30.30%	25.0%	Nd
Namangan	3.03%	13.89%	Chi square=4.03, $p<0.05$
Fergana	9.09%	22.22%	Nd
Navainskaya	24.24%	19.44%	Nd
Samarkand	33.33%	19.44%	Nd
Urbanization Index	26/40	15/21	Nd
Live in the city	39.39%	41.67%	Nd
Live in rural areas	60.61%	58.33%	Nd

Figure 2. Distribution of patients by regions of residence

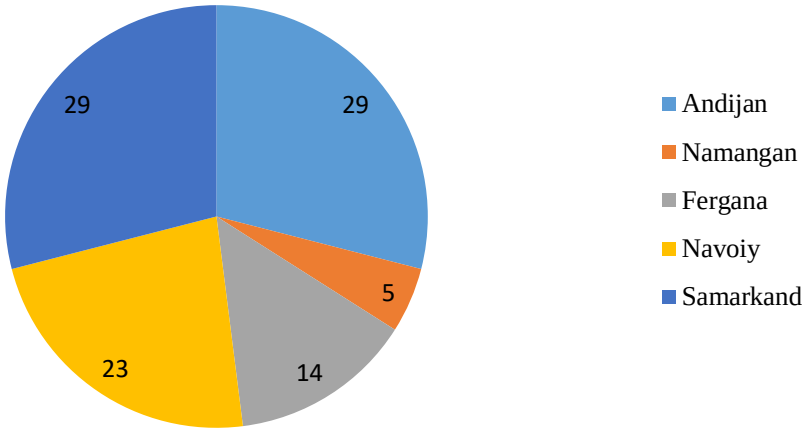


Figure 3. Distribution of patients into groups based on their area of residence

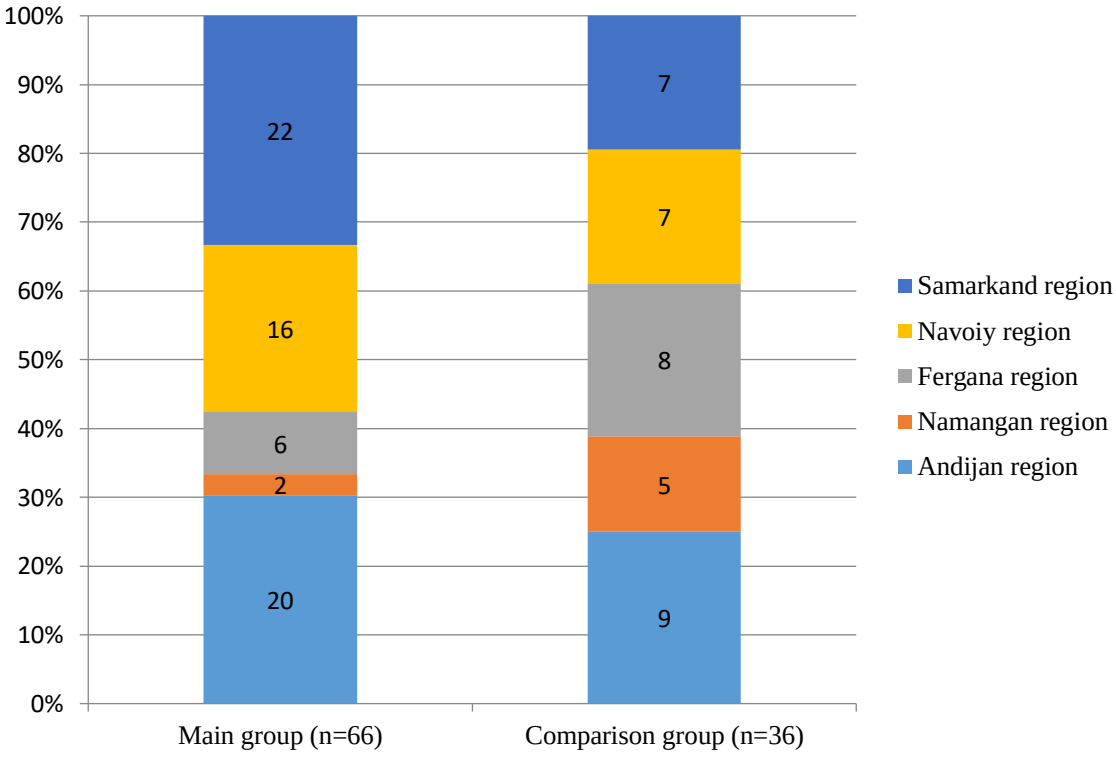


Figure 4. Distribution of patients by urbanization indicator

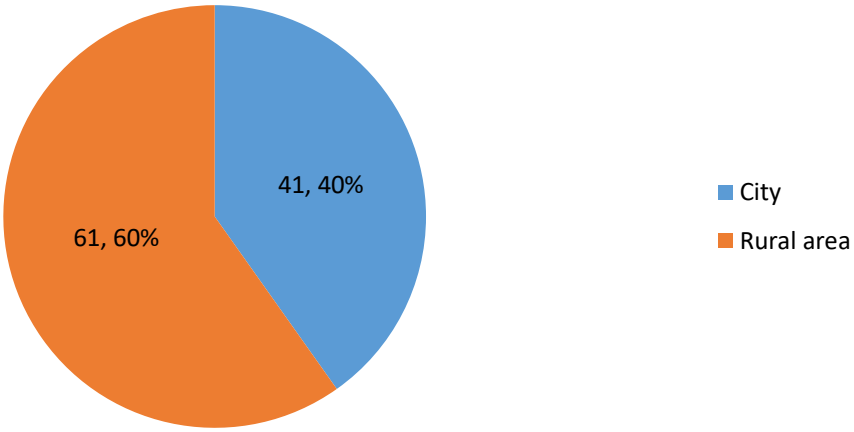
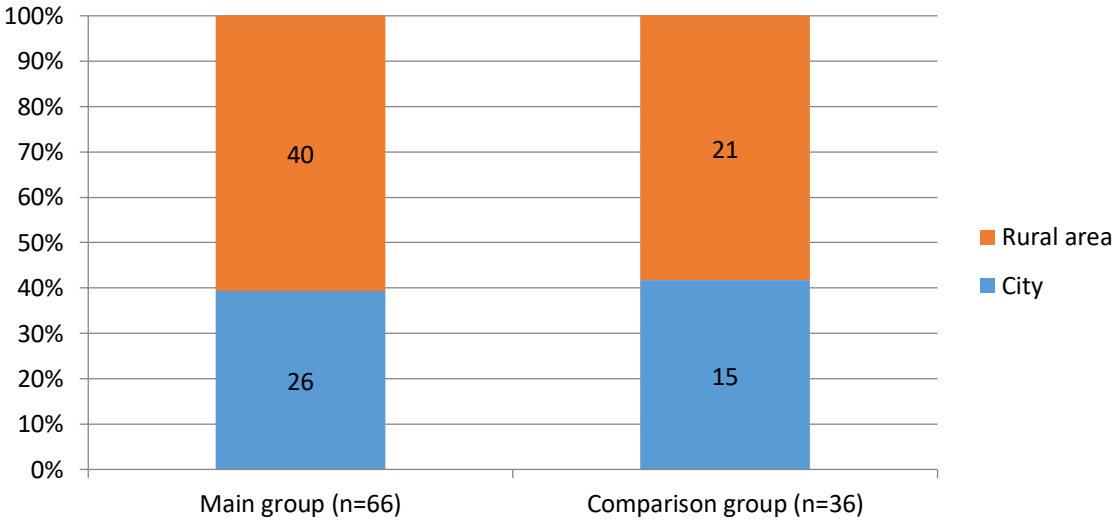


Figure 5. Distribution of patients in the study groups by urbanization indicator



Inspection in the mirrors

During the examination, the tumor mobility, localization (cervical, vaginal, cervical type transformed after childbirth into the vaginal type, cervical-parametric, vaginal-parametric), and growth pattern (ulcerative, exophytic, endophytic, infiltrative, ulcerative-eroded, mixed) were determined.

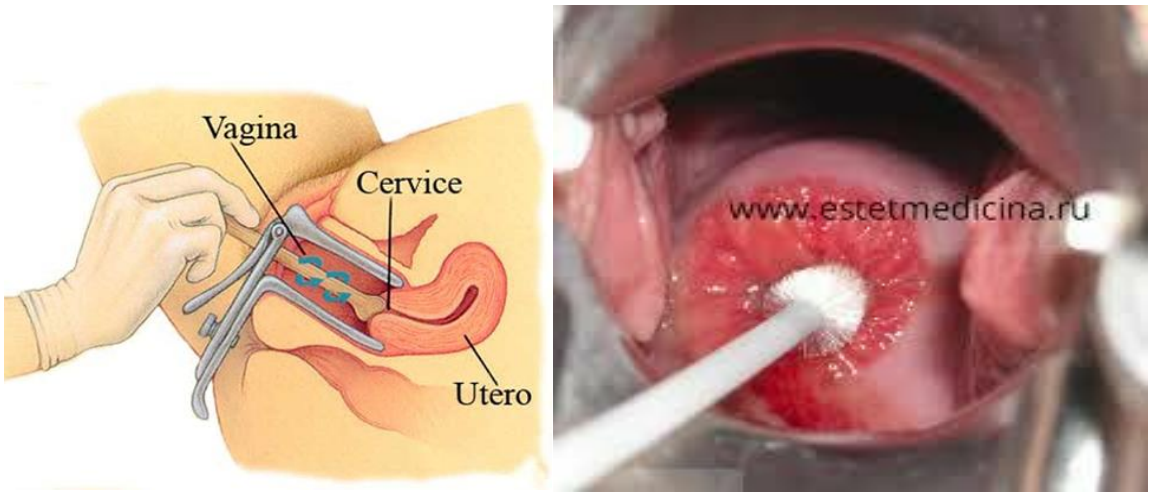


Figure 6. Technique for taking a smear from the cervical canal

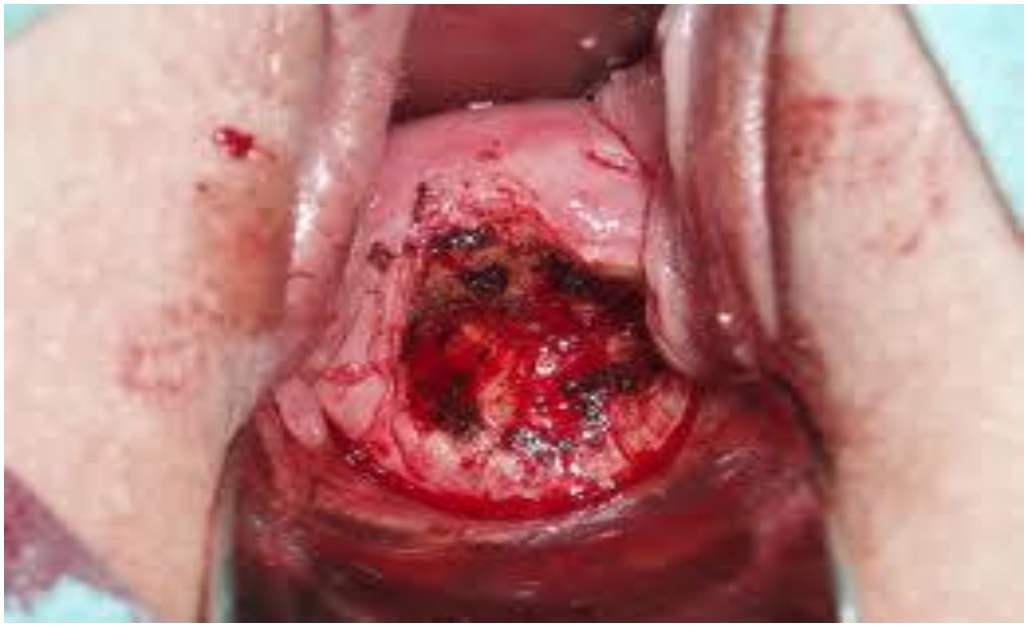


Figure 7. Cervical cancer as seen in speculums

Biopsy and histocytological examination

The biopsy was performed under visual control, the biopsy was placed in a formalin solution, and diagnostic preparations were subsequently prepared from the biopsy on glass, stained hematoxylin and eosin, van Gieson method, Congo red. The finished slides were examined in the pathological anatomy department by a pathologist and the tumor type was determined: squamous cell nonceratinizing, endometrioid invasive and epidermoid carcinoma, as well as the degree of

differentiation - poorly differentiated (G-3), moderately (G-2) and highly differentiated (G-1).

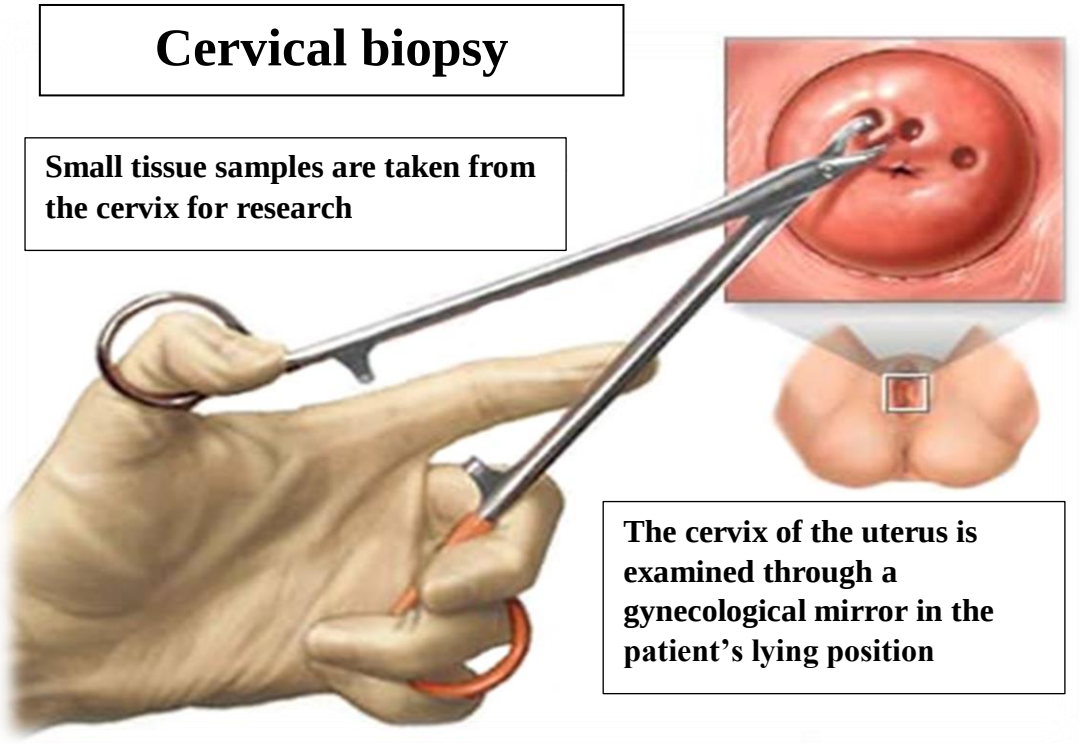


Figure 8. Technique for taking a biopsy from the affected area of the cervix

Ultrasound examinationwere performed on a color Doppler device "Sonoscape S22" with 4D images (Shenzhen, Guangdong, China). To perform a transabdominal ultrasound examination, it is necessary that the bladder is full at the time of the examination. This is necessary so that the cervix is as clearly visible as possible. The advantage of a transabdominal examination is that the doctor can see the pelvis as a whole and assess the size of the tumor. The examination is carried out as follows: using a special sensor with a frequency of 3.5 MHz, applied to the woman's abdomen, the doctor sees certain data on the computer monitor, according to which he determines the condition of the cervix, the presence or absence of a cancerous tumor. The transvaginal sensor is an elongated tube with a scanning head. The length is 12-14 cm, the diameter is 3 cm. The scanning frequency of the sensor is in the range of 4-7 MHz, which is optimal for examining the pelvic organs and the uterus itself. Transvaginal ultrasound requires an empty bladder. A

special sensor is inserted into the woman's vagina, transmitting information to a computer. After the examination, the doctor will be able to assess the condition of the organ and make a diagnosis.

Colposcopy

The procedure was performed using a video colposcope model: "Kernel KN - 2200". Colposcopy is an optical microscopic examination that uses stereoscopic a magnifying glass for increasing the tissue surface from 4 to 40 times, this technique is part of standard diagnostics, especially for practicing gynecologists. Patients are asked to sit on a chair,Afterwards, a speculum is gently inserted to spread the vaginal walls and create a "clear view." The doctor then places a colposcope in front of the vagina to illuminate the vulva, vagina, and the transition from the cervix to the vagina (portio vaginalis uteri).Women were given the Vinegar test, the effect of which lasts up to 3-4 minutes, and the Schiller test.(Lugol's method) which is based on the interaction between iodine and glycogen: flat epithelium is uniformly stained dark brown, altered epithelium does not absorb iodine, columnar epithelium does not contain glycogen and therefore there is no iodine absorption. The colposcopic lesion can take on all shades from brown-red (normal flat epithelium) to a lighter color due to the charge of glycogen. Yellow color is characteristic of atypical or immature epithelium. This test helped us to determine the boundaries between the epithelium and the lesion.

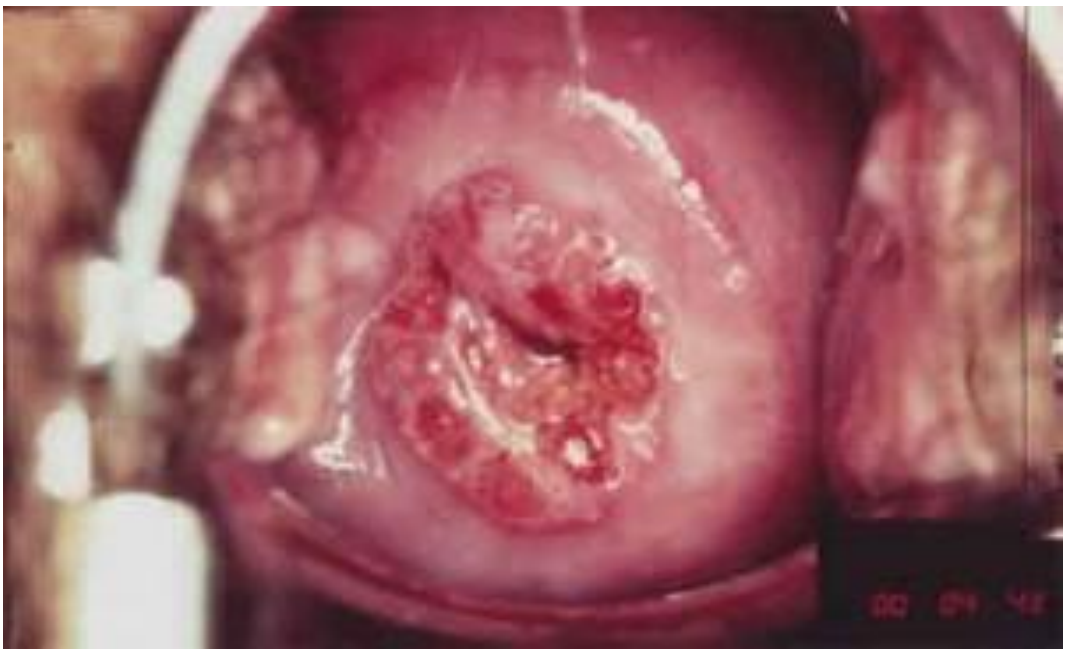


Figure 9. Colposcopic picture of cervical cancer

Computer tomography was performed on a 3rd generation SOMATOM AR.TX "Siemens" (Germany) device, with a tomography step of 5 mm. All generally accepted conditions were observed during the CT scan. Before the study, all patients underwent a topogram, where the level of the beginning of the CT scan was determined. Scanning was performed at the height of a shallow breath - from the level of the upper edge of the liver to the level of VL3. Scanning time is 5 seconds.

MRI of the pelvis

MRI was performed in polyprojection in coronary, sagittal and axial projections in T1 spin-echo (SE) mode. It was performed on the MagnetomOpen/Viva device, Siemens (Germany) with a magnetic field strength of 0.2 T. Patients were asked to lie on their backs. In all projections, the following were determined: slice thickness (SL) 3-5 mm, distance between slices (SP) 1-2 mm, number of slices 12-16. The total examination time was 20-25 minutes.

Apgar scale –was used for rapid assessment of the newborn's condition. A scale of 5 criteria was used (skin color, heart rate, reflex excitability, muscle tone, breathing), each of which was assessed in the range of 0-2 points. The maximum

score was 10 points. In the case of an assessment of 8-10 points, the condition of the newborn was assessed as satisfactory (normal), 6-7 points - moderate (mild asphyxia), 4-5 points - severe (moderate asphyxia), 1-3 - extremely severe (severe asphyxia), 0 points - stillborn.

Karnofsky scale-EGOS –was used to assess the general health status and functional capacity in patients with cervical cancer before and after chemotherapy. Based on a scoring system of 0-5 points: 0 points -The patient is fully active, able to do everything as before the illness (90-100 points on the Karnofsky scale); 1 point - The patient is unable to do heavy work, but can do light or sedentary work (for example, light housework or office work, 70-80 points on the Karnofsky scale); 2 points - The patient is treated on an outpatient basis, is capable of self-care, but cannot do work. Spends more than 50% of his waking time actively in an upright position (50-60 points on the Karnofsky scale); 3 points - The patient is capable of only limited self-care, spends more than 50% of his waking time in a chair or bed (30-40 points on the Karnofsky scale); 4 points - Disabled, completely unable to take care of himself, confined to a chair or bed (10-20 points on the Karnofsky scale); 5 points - death.

Evaluation of complications of chemotherapy –The toxicity of PCT was assessed by degrees of severity. Hematological, renal, cardiovascular and gastrointestinal symptoms were determined.

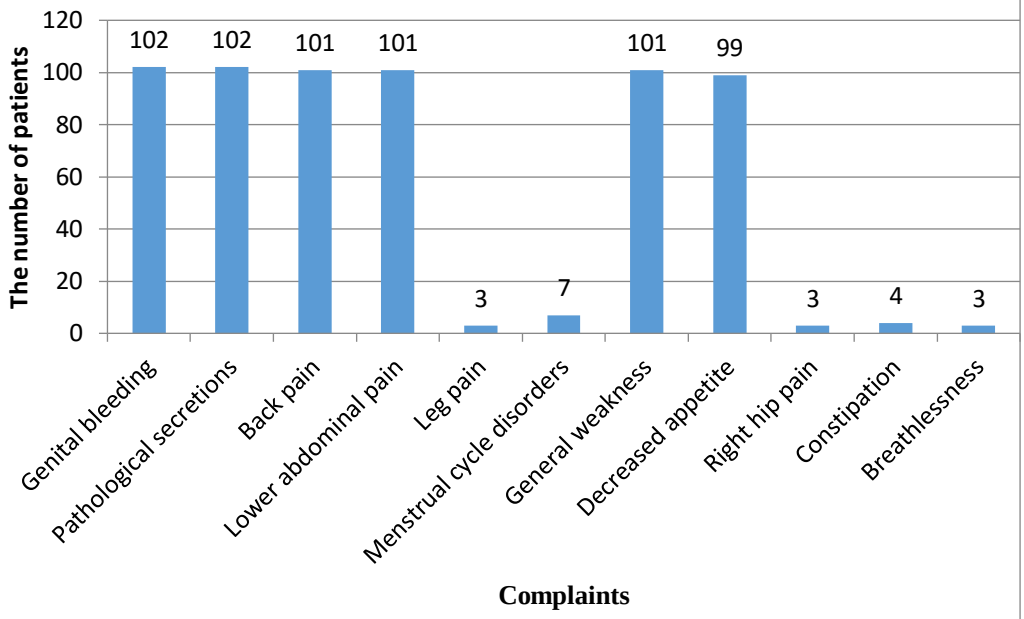
CHAPTER III

DIAGNOSTIC ASPECTS OF CERVICAL CANCER IN PREGNANT WOMEN

All women were referred for hospitalization to the branches of the RSSPMCOiR from primary health care institutions; hospitalization was planned, in order to verify the diagnosis and determine the management tactics. In 2 women in the main group (3.03%) and 1 woman in the comparison group (2.78%), hospitalization, during which the patient was included in this study, was repeated, while in the remaining overwhelming majority it was primary (chi square = 0.41, ND). In 10 patients in the main group (15.15%) and 9 patients in the comparison group (25.0%), cervical cancer was detected earlier, while in the remaining women, inclusion in the study was associated with the primary diagnosis of oncopathology (chi square = 1.44, ND).

In 8 patients in the main group (12.12%) and in 3 patients in the comparison group (8.33%) cervical cancer was diagnosed during examination and treatment of another pathology (incidental detection); in the remaining patients, cervical cancer diagnostics was initiated upon seeking medical attention due to complaints suspected of cervical pathology (chi square=0.55, ND). However, retrospective analysis revealed that all patients had complaints that could reflect the presence of cervical cancer (or other oncopathology); the prevalence of complaints is shown in Fig. 10 and Table 2. The overwhelming majority of women complained of bleeding from the genitals and pathological discharge (100%), pain in the segments associated with genital lesions – lower abdomen and lower back (99.02%), general symptoms – weakness (99.02%) and decreased appetite (98.02%). Complaints such as pain in the legs, pain in the right hypochondrium, menstrual irregularities, constipation, and shortness of breath occurred in less than 7% of patients and cannot clearly indicate pathology of the cervix, as they are nonspecific.

Figure 10. Frequency of detection of various complaints in women with cervical cancer.



Such regional complaints as leg edema and urination disorders were not observed in any case, which is probably explained by the detection of pathology at early stages, before metastasis to the urinary system and metastatic blockade of the inguinal lymph nodes. Also, such general symptoms as impaired sexual desire, hyperthermia, weight loss were not observed, which is also associated with early diagnosis of the tumor, before the development of severe cancer intoxication and cachexia. An additional argument in favor of the insignificant severity of cancer intoxication is the fact that in all women complaining of decreased appetite (99 people), the severity of this symptom was insignificant.

Table 2

Prevalence of complaints in patients

Complaints	Main group (n=66)	Comparison group (n=36)	Chi square
Bleeding from the genitals	66 (100%)	36 (100%)	
Pathological	66 (100%)	36 (100%)	

discharge			
Lower back pain	66 (100%)	35 (97.22%)	2.13, nd
Pain in the lower abdomen	66 (100%)	35 (97.22%)	2.13, nd
Pain in the legs	2 (3.03%)	1 (2.78%)	0.41, nd
Menstrual irregularities	6 (9.09%)	1 (2.78%)	1.87, nd
General weakness	66 (100%)	35 (97.22%)	2.13, nd
Decreased appetite	66 (100%)	33 (91.67%)	5.23, $p<0.05$
Extragenital pain (right hypochondrium)	0 (0%)	3 (8.43%)	5.23, $p<0.05$
constipation	2 (3.03%)	2 (5.56%)	0.50, nd
dyspnea	2 (3.03%)	1 (2.78%)	0.41, nd

In terms of bleeding, in most patients the bleeding was minor and detected only during a gynecological examination; in 1 patient in the comparison group (2.78%) the bleeding was severe and was the reason for visiting a gynecologist (chi square=2.13, nd).

In most patients, discharge from the genital tract was of a contact-bloody nature (58%, Fig. 11). The distribution of women depending on the presence of pregnancy showed that in the main group, contact-bloody discharge was more common than in the comparison group (chi square = 12.92, $p < 0.01$, Fig. 12).

Figure 11. Distribution of patients with cervical cancer based on the characteristics of vaginal discharge.

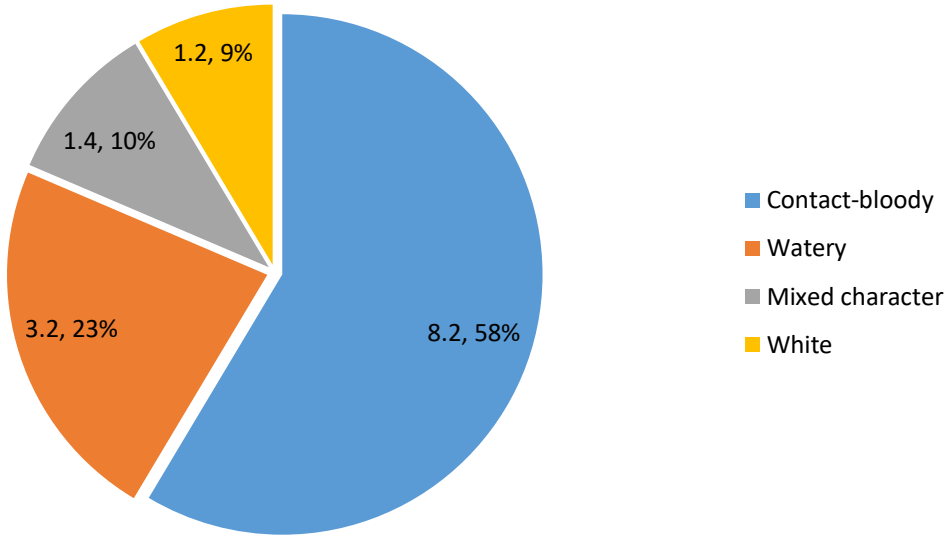
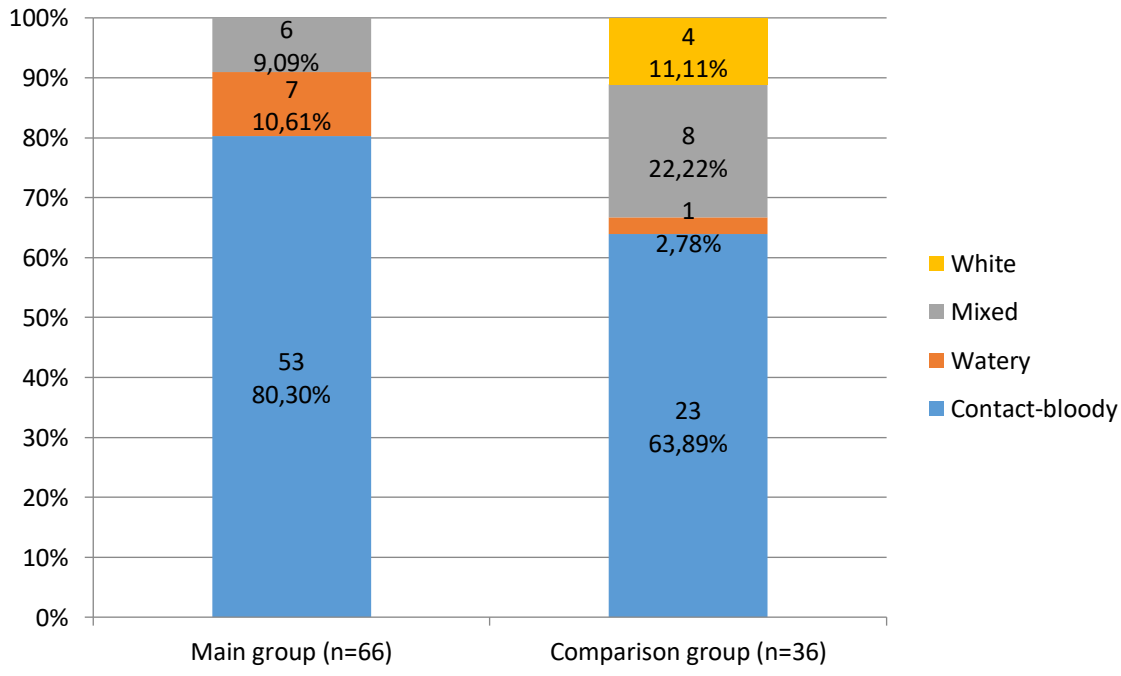
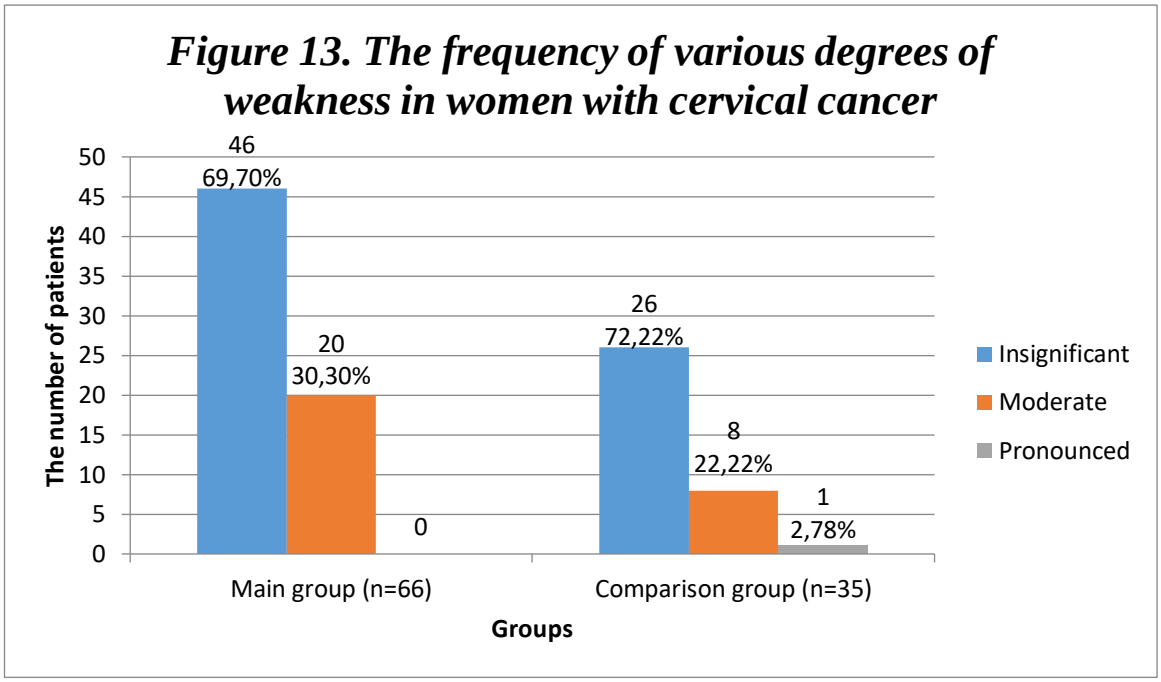


Figure 12. The nature of pathological discharge in women with cervical cancer.



General weakness was slightly expressed in most patients (81.37%), moderately expressed in the rest (27.45%) and significantly expressed in one patient (0.98%). The differences between the main group and the comparison

group in the frequency of different severity of the symptom were insignificant (Fig. 13).



Obstetric and gynecological history: average age of onset of menstrual cycle was 12.88±0.12 years (12.97±0.16 years in the main group and 12.72±0.18 in the comparison group, ND), average age of onset of sexual activity was 20.54±0.14 years (20.64±0.62 years and 20.36±0.21 years, respectively, ND). Regular sexual activity was observed in 101 patients, irregular in 1 patient.

In the main group, on average, women had 4 pregnancies (2-12) and 2 abortions (0-7), in the comparison group – 3 (0-7, $p<0.001$) and 0 (0-4, $p<0.01$), respectively.

In the main group, which included women diagnosed with cervical cancer during pregnancy, the tumor was most often diagnosed in the 2nd trimester of pregnancy.

Thus, the study showed that cervical cancer first detected during pregnancy was more often associated with contact-bloody nature of discharge, compared to cervical cancer detected outside the gravid period, which is probably due to increased blood filling and cervical edema during pregnancy. All patients with cervical cancer had symptoms suspicious for cervical neoplasm. An increase in the

frequency of pregnancies naturally increases the risk of diagnosing a tumor during pregnancy.

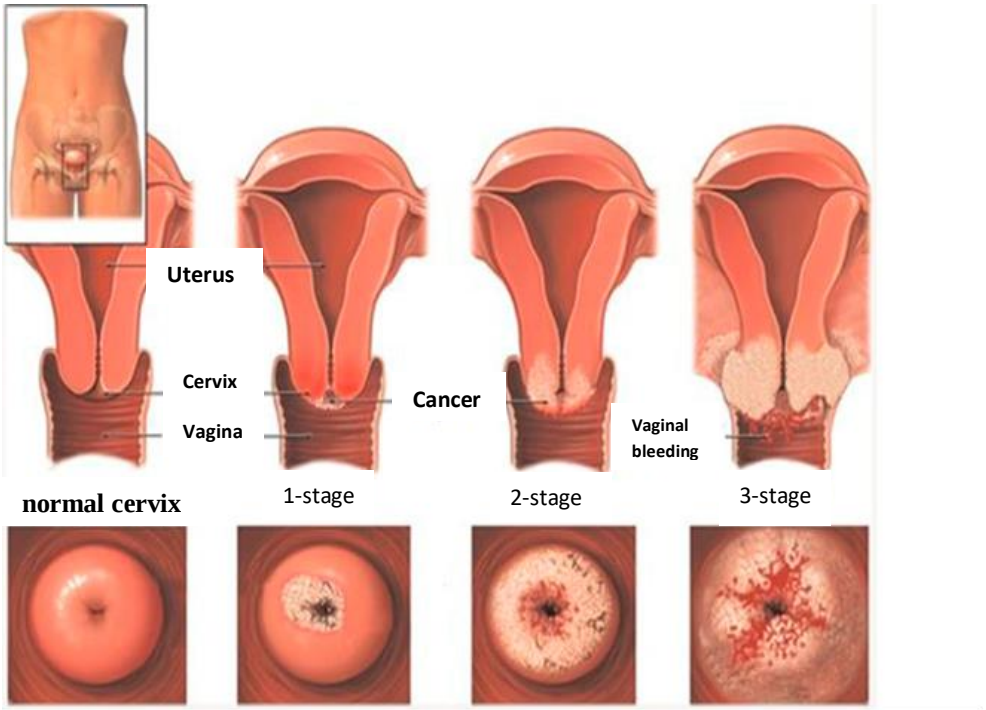
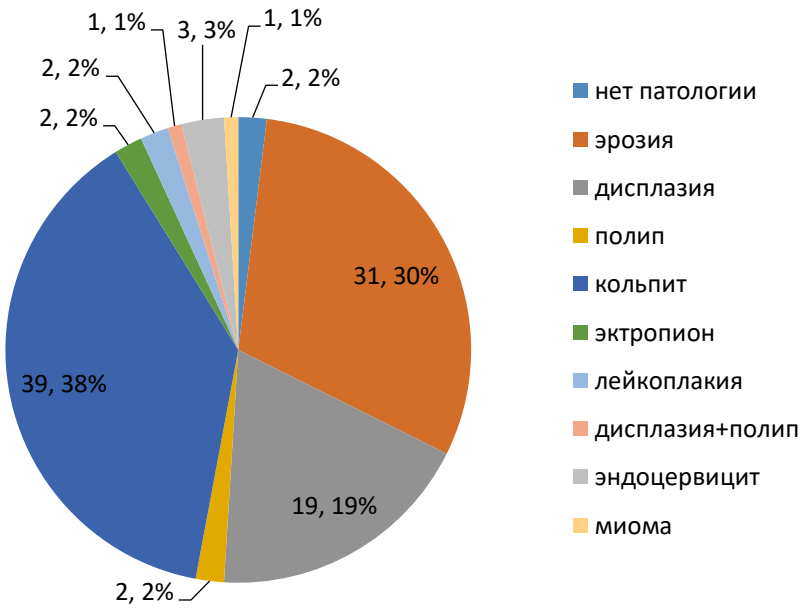


Figure 14. Stages of cervical lesions

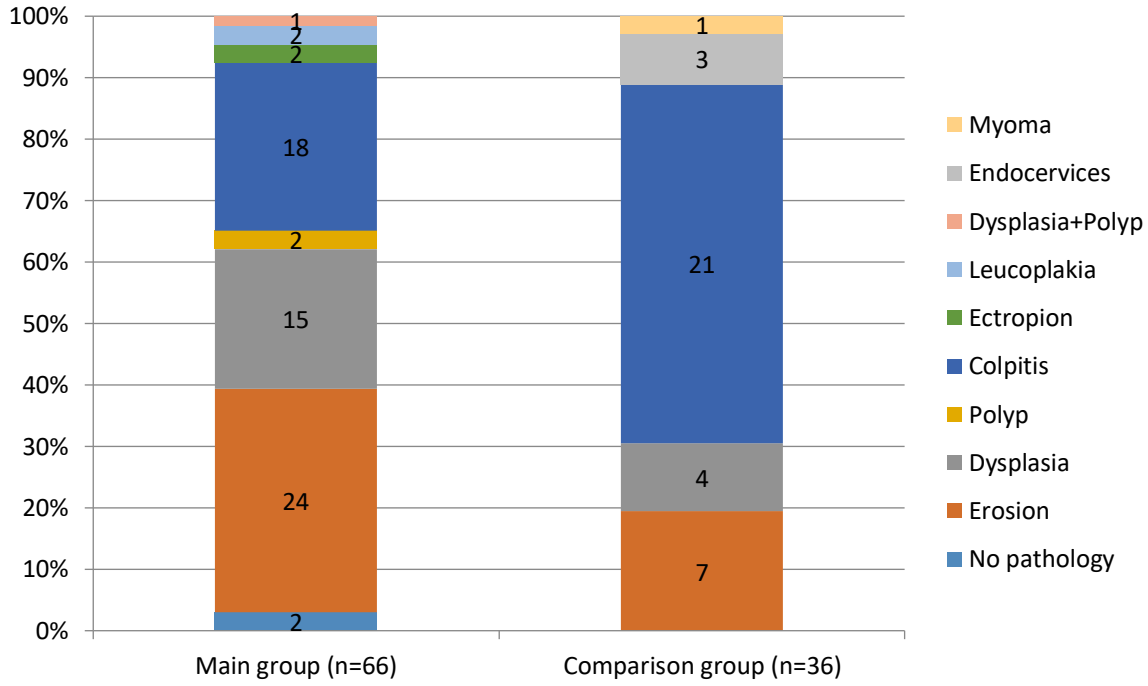
The gynecological anamnesis revealed various variants of cervical pathology in 98% of women included in the study, which can be considered as a background for the development of oncopathology (Fig. 15).

Figure 15. The frequency of background cervical pathology in patients with cervical cancer



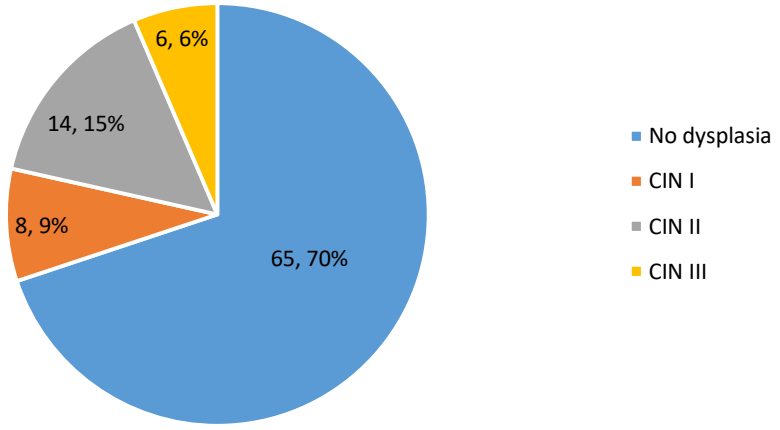
The distribution of patients by study groups (Fig. 16) revealed that in the comparison group, a significant proportion of background conditions was colpitis, which is not a potentially carcinogenic pathology (21 women - 58.33% versus 18 women - 27.27% in the main group, chi square = 9.27, $p < 0.01$), while in the main group, potentially carcinogenic background pathology of the cervix was diagnosed in 69.70% (40 women).

Figure 16. The frequency of occurrence of various types of background cervical pathology in women of childbearing age with diagnosed cervical cancer, depending on the presence of pregnancy



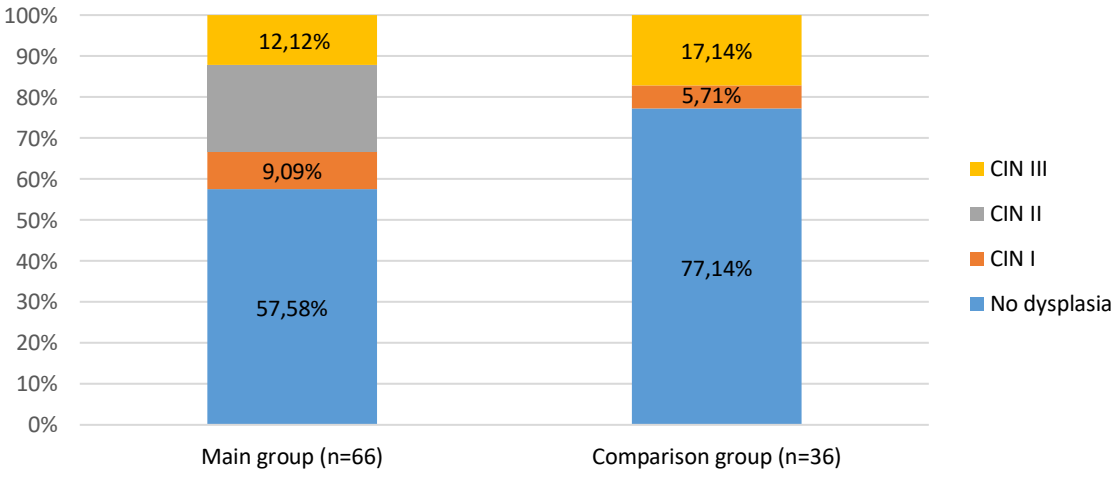
All women were assessed for the degree of cervical epithelial dysplasia using the CIN system (Fig. 17). Only 30% of patients had a history of cervical epithelial dysplasia, which may indicate insufficient primary oncological screening.

Figure 17. The frequency of cervical epithelial dysplasia in patients with cervical cancer



Distribution of patients into comparison groups showed that pregnant women were significantly more likely to have underlying pathology of the cervical epithelium (chi square=9.53, $p<0.05$), in particular CIN II dysplasia (Fig. 18), although the detection rate of dysplasia was insignificantly higher in the representatives of the main group (42.41% versus 25%, chi square=3.17, nd), in general.

Figure 18. Previously detected cervical epithelial dysplasia in patients with cervical cancer, depending on the comparison group



Accordingly, the detection rate in the anamnesis of patients included in the study were procedures to limit cervical pathology: in total, procedures were performed in 37 patients (36.63%): in the main group, various procedures were performed in 48.48% of patients (32 women), in the comparison group - only in 14.28% (5 women, chi square = 11.69, $p < 0.001$). The procedures included: diathermoconization (15 patients of the main group and 4 comparison groups), cryodestruction (12 women of the main group), simple coagulation (4 patients of the main group and 1 patient of the comparison group) and removal of the cervical polyp (2 women of the main group).

In the comparison group, 1 patient had a history of surgery to remove a tumor of the posterior lip, 1 patient had a unilateral cystectomy, and 1 patient underwent Wertheim's operation during the present study - a radical intervention for cervical cancer. In the main group, Wertheim's operation was performed in 4 patients (chi square = 0.92, nd).

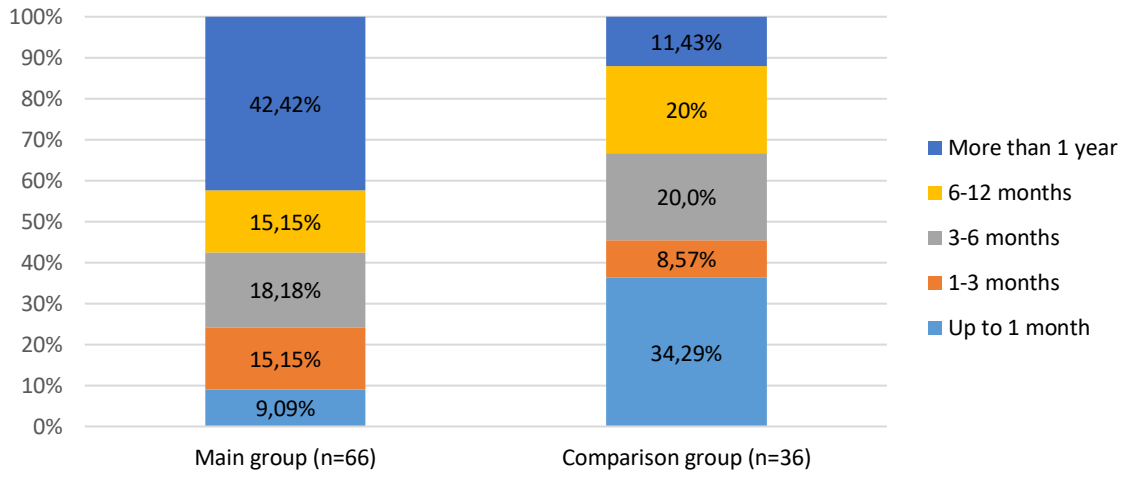
34 patients in the main group and 12 patients in the comparison group (52.52% and 33.33%, chi square = 3.17, nd) received anti-inflammatory and symptomatic treatment of the background pathology of the cervix.

Thus, the described stage of the study showed that 98% of women of fertile age with diagnosed cervical cancer had a history of background cervical pathology, including 59.80% with precancerous pathology. Precancerous conditions, including cervical epithelial dysplasia, are more often diagnosed in pregnant women.

The present study included the study of the time of women's appeal for cervical cancer. It was revealed that 18 women (17.82%) were included in the present study within a month from the appearance of the first complaints, in the remaining patients the time from the first manifestations of the disease to inclusion was more than a month, and in 32 patients (31.68%) - more than a year. The selection of comparison groups showed that in the main group of women, there were significantly more women included in the study at a later stage than in the comparison group (chi square = 16.44, $p < 0.01$, Fig. 19), which indicates both the

late appeal of women and the insufficient alertness of primary health care physicians regarding the risk of cervical cancer in pregnant women.

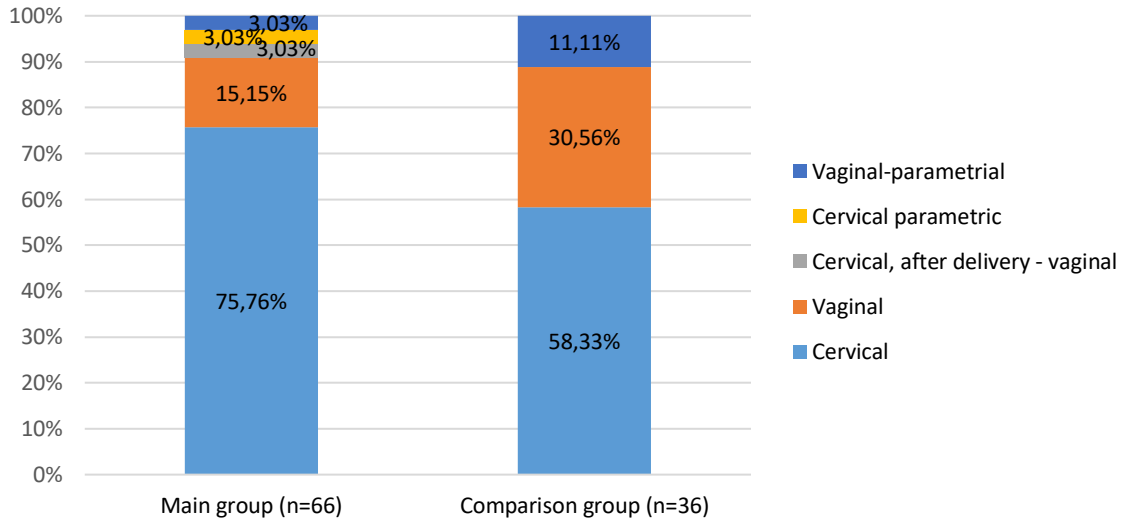
Figure 19. Distribution of patients by referral time from the appearance of cervical cancer symptoms depending on the study groups



Six women in the main group and two women in the comparison group had been diagnosed with cervical cancer earlier, and for this reason, before the start of this study, the patients were hospitalized, systemic polychemotherapy was performed in all cases, and brachytherapy in 2 cases. The remaining patients were diagnosed with cervical cancer for the first time before inclusion in the study.

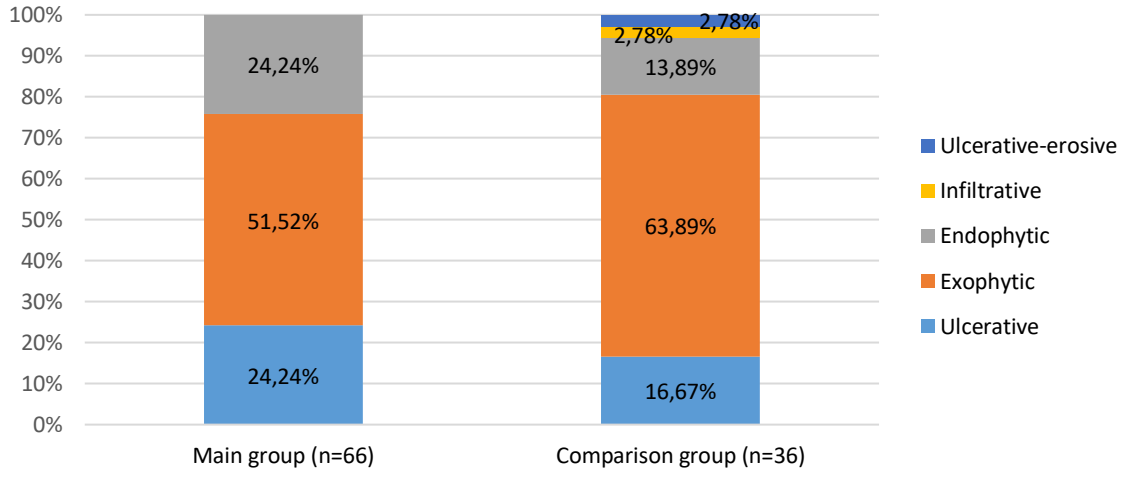
According to the localization of the primary tumor, the cervical type was observed in most women (71 people, 69.61%), and less often - vaginal (21 people, 20.59%). There were no significant differences between pregnant and non-pregnant women in the localization of the primary lesion (Fig. 20). However, the distribution of women by the primary involvement of the cervix or vagina showed that cervical involvement is more typical for pregnant women (81.82%), while in non-pregnant women the frequency of cervical involvement is slightly more than half of the cases (58.33%) and the frequency of primary vaginal involvement increases (41.67%, chi square = 6.49, $p < 0.05$).

Figure 20. Frequency of various variants of cervical cancer localization in the study groups



In terms of tumor growth pattern, most women had exophytic growth (57 women - 55.88%), while the rest had ulcerative (21.57%) and endophytic (20.59%) growth, with no significant difference between the study groups (Fig. 21).

Figure 21. Distribution of patients with cervical cancer depending on the nature of tumor growth in the study groups



The palpation characteristics of the tumor were dense in most cases (88 patients, 86.27%), while in the rest it was ulcerated (14 patients, 13.13%) without significant differences between the groups (in the main group, 54 and 12 patients, in the comparison group, 34 and 2 patients, respectively, chi square=3.45, ND). According to the sign of displacement relative to the underlying tissues, the tumor

was immobile in 97 women (95.10%), and mobile in 5 (4.90%), also without intergroup differences (in the main group, 64 and 2, in the comparison group, 33 and 3 patients, respectively, chi square=1.33, ND).

Staging of cervical cancer (Table 3) showed that the tumor was most often diagnosed at stage 2b (57 women – 55.88%), comparable in the study groups (chi square = 1.55, ND), while in the group of pregnant women, tumors diagnosed at stage 2b were more common than in the comparison group (chi square = 4.03, $p < 0.05$) and less common – at the in-situ stage (chi square = 8.11, $p < 0.01$). In general, the frequency characteristics of the study groups depending on the stages of cervical cancer were comparable (chi square = 13.19, $p < 0.05$).

Table 3

Frequency of cervical cancer stages at primary tumor diagnosis in women of childbearing age depending on the study group

Stage	Main group (n=66)	Comparison group (n=36)	All patients (n=102)	χ^2	p<0.05
In situ	2 (3.03%)	5 (13.89%)	7 (6.86%)	4,297	0.038
1a	0 (0.00%)	1 (2.78%)	1 (0.98%)		
1v	16 (24.24%)	1 (2.78%)	17 (16.67%)	7,727	0.005
2a	10 (15.15%)	4 (11.11%)	14 (13.73%)	0.321	0.571
2v	34 (51.52%)	23 (63.89%)	57 (55.88%)	1,447	0.229
3a	0 (0.00%)	1 (2.78%)	1 (0.98%)		
3v	4 (6.06%)	1 (2.78%)	5 (4.90%)	0.539	0.463

According to the TNM system, the most common tumors were those with the characteristics T2 (71 patients, 69.61%), N0 (77 patients, 75.49%), and M0 (99 patients, 97.06%). The groups were comparable in terms of the frequency distribution of variants of this classification (Table 4). There were 54 women (52.94%) with the characteristic T2N0M0 CC: 34 in the main group and 20 in the comparison group (chi square=0.20, ND). In 3 women with the characteristic M1,

distant metastases were found in the lungs (1 case) and in the lungs and liver (2 cases).

Table 4

Occurrence of different variants of cervical cancer according to the TNM system categories in the study groups

Groups	T1	T2	T3
Main group (n=66)	18	44	4
Comparison group (n=36)	7	27	2
Main group, %	27,27	66,67	6.06
Comparison group, %	19.44	75	5.56
Chi square	0.82, nd		
	N0	Nx	N1
Main group (n=66)	48	18	0
Comparison group (n=36)	29	6	1
Main group, %	72,73	27.23	0
Comparison group, %	80.56	16, 67	2.78
Chi square	3.14, nd		
	M0	M1	
Main group (n=66)	64	2	
Comparison group (n=36)	35	1	
Main group, %	96,97	3.03	
Comparison group, %	97.22	2.88	
Chi square	0.41, nd		

Histologically, squamous cell nonkeratinizing cancer was predominant (88 patients – 86.27%), epidermoid carcinoma was diagnosed in 12 patients (11.76%), and only in 2 cases – endometrioid invasive cancer (1.96%, Fig. 22). In terms of the frequency of detection of various histological types of cervical cancer, both study groups were comparable (Fig. 23).

Figure 22. The histological structure of cervical cancer in women included in the study

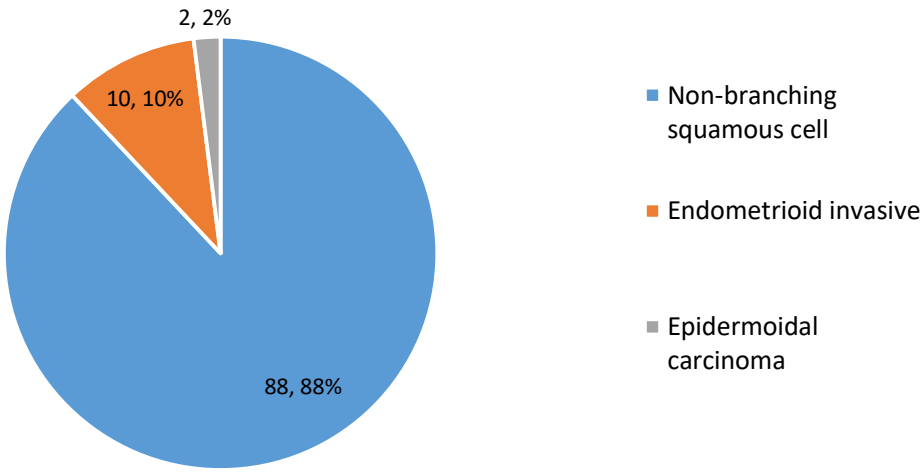
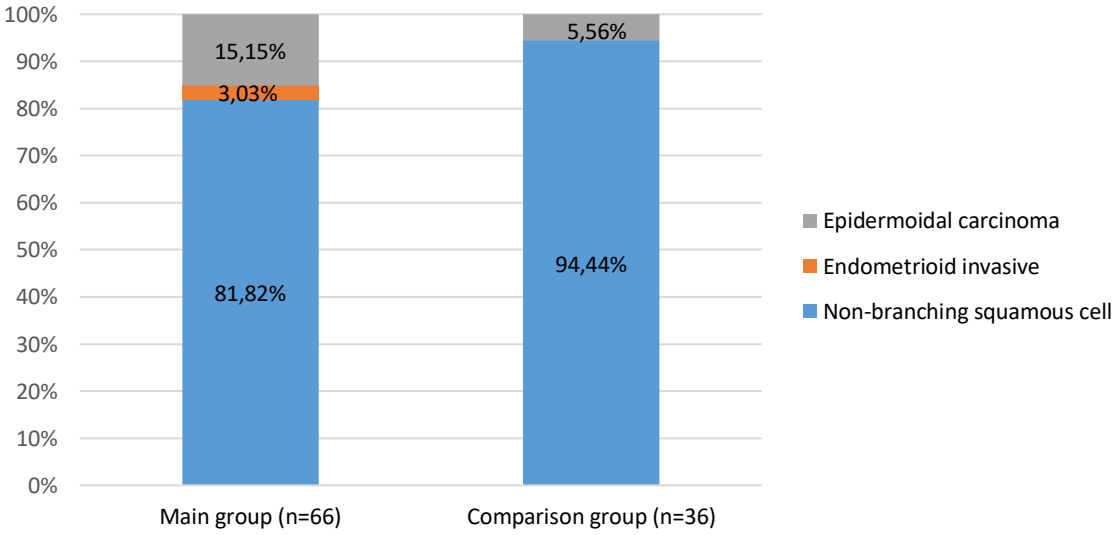


Figure 23. Frequency of occurrence of various histological variants of cervical cancer in the study groups



Cytological examination revealed G2 degree of differentiation (moderate) in the majority of women included in the study (Fig. 24) without significant differences between study groups in the frequency of occurrence of tumors with different degrees of differentiation (Fig. 25).

Figure 24. The incidence of cervical cancer of various cytological characteristics in women of childbearing age

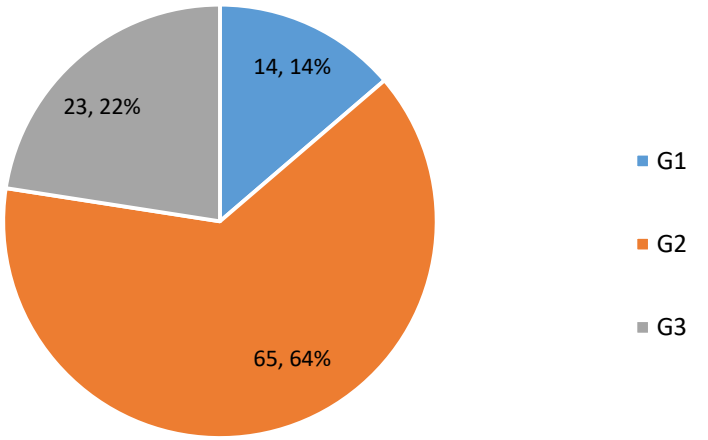
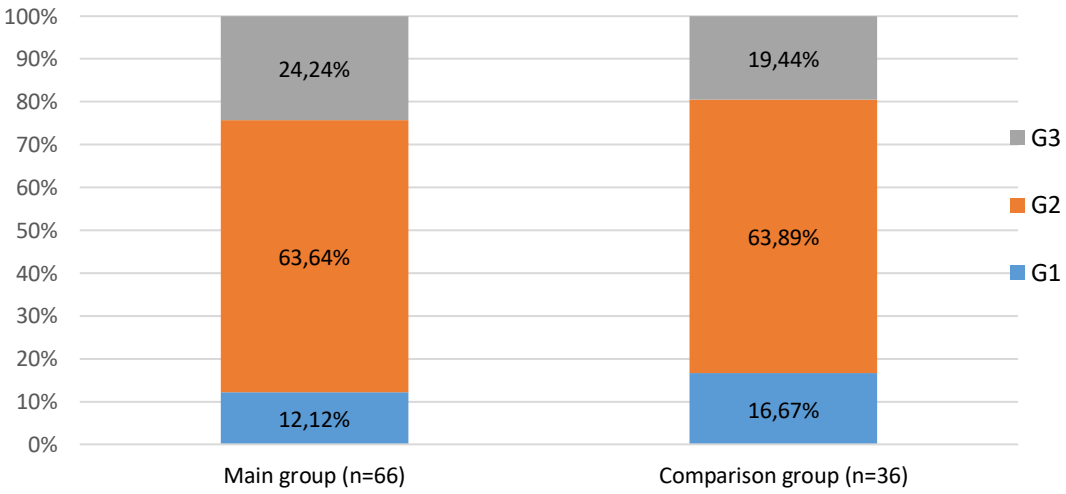
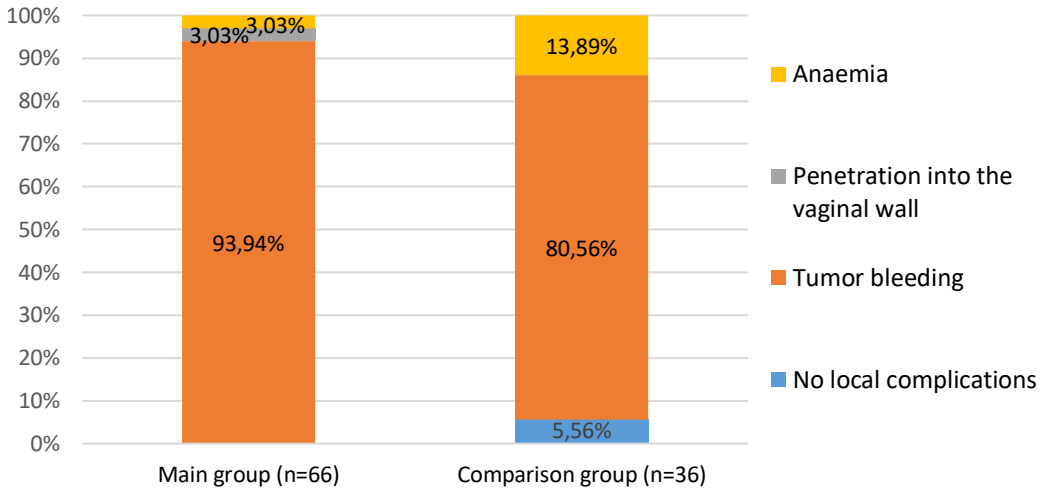


Figure 25. Different degrees of differentiation of cervical cancer cells in women of childbearing age depending on the presence of pregnancy



The most frequent local complication of cervical cancer was bleeding (91 patients – 89.22%), its frequency was comparable in both clinical groups (93.94% in the main group versus 80.56% in the comparison group), however, the frequency of hemorrhagic anemia caused by bleeding was higher in the comparison group (13.89% versus 3.03% in the main group, Fig. 26). Invasion into the vaginal wall was observed only in 2 patients (1.96%).

Figure 26. Local complications of cervical cancer in women of childbearing age depending on the clinical group



Thus, this branch of the study showed that cervical cancer is detected in pregnant women at a later stage compared to non-pregnant women of the same age group. Most women have a cervical location of the primary lesion, especially pregnant women. The tumor growth is predominantly exophytic, the consistency is dense, immobile. The tumor is most often diagnosed at stage 2b and T2N0M0. Pathomorphological examination most often reveals moderately differentiated non-keratinizing squamous cell carcinoma. A characteristic local complication of cervical cancer in women of childbearing age is bleeding from the tumor, which is associated with the development of anemia (more often in non-pregnant women).

Diagnosis of cervical cancer is based on a gynecological examination of the cervix in mirrors, colposcopic examination, MRI of the pelvic area and other regions.

Gynecological examination of the cervix in mirrors (Table 5) in all patients allowed us to detect cervical pathology, comparable in both clinical groups of the study.

Table 5

Frequency of occurrence of signs indicating cervical cancer, detected during examination in speculums, in women of childbearing age, depending on the study group

	Main group (n=66)	Comparison group (n=36)	All patients (n=102)
Inspection			
Deformed	48	23	71
Eroded	16	10	26
Eroded and deformed	2	3	5
Chi square	1.71, nd		
Consistency			
Rocky	0	2	2
Dense	64	32	96
tight elastic	2	2	4
Chi square	4.21, nd		
Mobility			
Sedentary	38	20	58
Movable	16	10	26
stiff	12	6	18
Chi square	0.16, nd		
Painfulness			
Painless	36	21	57
Painful	30	15	45
Chi square	0.18, nd		
Parametrium			
Infiltrated to the bone	18	8	26
Not infiltrated to the bone	20	16	36
Rigid	2	1	3
Free	26	11	37

Chi square	2.06, nd		
Vaults			
Fit	26	17	43
Rigid	12	8	20
Free	28	11	39
Chi square	1.39, nd		
Discharge			
Watery	2	2	4
Watery-bloody	22	13	35
Bloody	38	16	54
Bloody	4	1	5
Whites	0	4	4
Chi square	9.04, nd		
Number of discharges			
Abundant	48	26	74
Moderate	18	10	28
Chi square	0.05, nd		

Of the 7 signs determined during examination in mirrors, all patients had at least 2, and in 30 patients (29.41%) all 7 signs indicated the presence of cervical cancer (Fig. 27). Intergroup comparison revealed differences on the verge of statistical significance in the number of patients with different numbers of positive signs in the aspect of cervical cancer (Table 6); however, the clinical significance of this finding is not obvious.

Figure 27. Distribution of patients with cervical cancer by the number of signs indicating pathology detected in mirrors

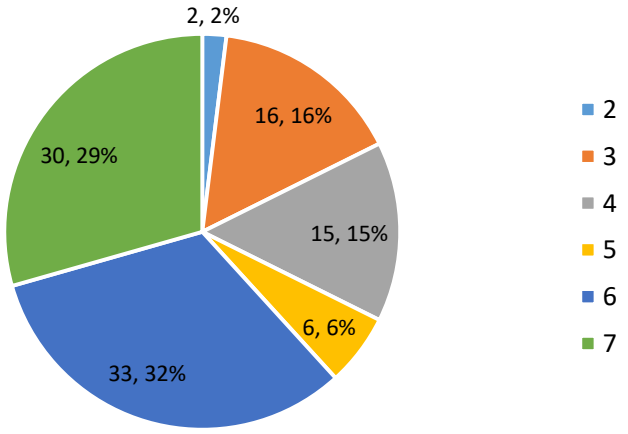


Table 6

Distribution of patients in clinical groups depending on the number of signs indicating cervical cancer, determined during examination in mirrors

Group	Number of features, positive for cervical cancer						χ^2	p<0.05
	2	3	4	5	6	7		
Main group (n=66)	0	9	13	6	20	18	6,649	0,010
Comparison group (n=36)	2	7	2	0	13	12		

All patients included in the study underwent colposcopy, according to the results of which 62 patients of the main group were diagnosed with carcinoma, 2 - severe dysplasia and 2 - leukoplakia of the cervix, in the comparison group carcinoma was detected in 31 patients, severe dysplasia - in 5 patients (chi square = 1.67, ND). However, the biopsy performed during colposcopy allowed us to verify the diagnosis of cervical cancer in all patients. According to the results of colposcopy, in 54 patients in the main group and 30 patients in the comparison group, the tumor size was determined to be more than 2 cm, in the rest - 1-2 cm (chi square = 0.13, ND).

Transvaginal ultrasound is a mandatory examination. In the main group, in addition to the presence of pregnancy in the uterine cavity, the conclusion included a description of the cervical tumor - in all patients, except for 2 patients with tumor invasion into the uterine cavity, in 2 patients - into the wall of the lower third of the ureter with the development of ureterohydronephrosis, in 2 patients - compression from the outside of the tumor of the bladder and rectum. In the comparison group, one patient was diagnosed with a cervical canal polyp, the remaining patients - a cervical tumor, complicated in 1 patient by invasion into the uterine cavity, in 2 patients - into the wall of the bladder and in 1 patient - into the wall of the lower third of the ureter with the development of ureterohydronephrosis (the intergroup difference in the frequency of tumor invasion into the uterus, adjacent organs and compression of adjacent organs according to transvaginal ultrasound data is chi square = 2.44, nd). Transvaginal ultrasound allows not only to diagnose the tumor, but also to specify its size (Fig. 28). Intergroup comparison showed that 1-2 cm cervical cancer is more often detected in pregnant women compared to non-pregnant patients (18.18% versus 5.56%), and tumors of 6 cm or more in size are more often detected in non-pregnant women (Table 7).

Figure 28. Frequency of detection of various sizes of cervical cancer using transvaginal ultrasound examination

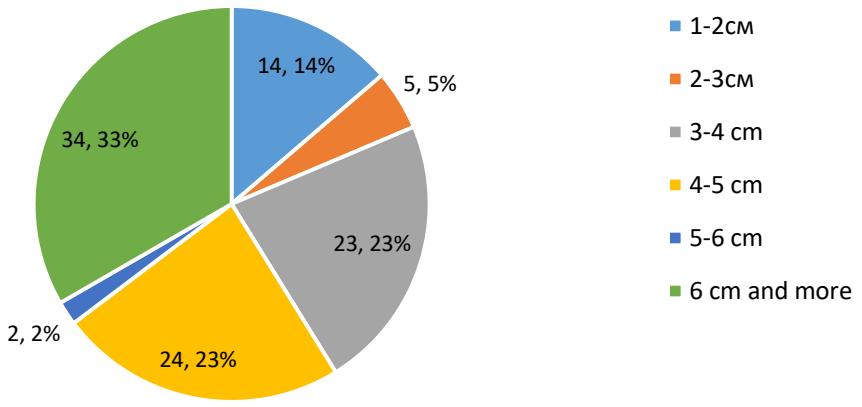


Table 7

Frequency of detection of cervical cancer of different sizes using transvaginal ultrasound depending on the clinical groups of the study

Groups	1-2cm	2-3cm	3-4cm	4-5cm	5-6cm	6 cm and more	χ^2 3,136 3,091	p<0.05 0,077 0,079
Main group (n=66)	12	2	16	18	0	18		
Group comparisons (n=36)	2	3	7	6	2	16		
All patients (n=102)	14	5	23	24	2	34		
Main group %	18.18%	3.03%	24.24%	27.27%	0.00%	27.27%		
Group comparisons %	5.56%	8.33%	19.44%	16.67%	5.56%	44.44%		
All patients %	13.73%	4.90%	22.55%	23.53%	1.96%	33.33%		

MRI was used as an additional visualization method to clarify the localization and prevalence of cervical cancer, as well as the involvement of surrounding organs and tissues and the presence of distant metastases. The study was conducted on all patients included in the study. Based on the MRI results, patients with metastatic lesions of the lungs and liver, lesions of distant lymph nodes, involvement of the pelvic lymph nodes, the spread of cervical cancer to the body of the uterus, surrounding tissues, the wall of the ureter, bladder, rectum were identified, while the frequency of complicated cervical cancer did not differ in both study groups (Table 8). The study is safe for both the pregnant woman and the fetus, has no teratogenic effect and can be used as a diagnostic and verification method during pregnancy.

Table 8

Frequency of MRI findings in patients with cervical cancer depending on the clinical study group.

Sign	Main group (n=66)	Group comparisons (n=36)	All patients (n=102)	χ^2	p<0.05
Education cervix	66 (100%)	36 (100%)	102 (100%)		
Defeat body of the uterus	4 (6.06%)	3 (8.33%)	7 (6.86%)	0.188	0.664
Defeat walls of the ureter	2 (3.03%)	2 (5.56%)	4 (3.92%)	0.394	0,530
Defeat walls bladder	2 (3.03%)	1 (2.78%)	3 (2.94%)	0.005	0.942
Defeat walls rectum	0 (0%)	1 (2.78%)	1 (0.98%)		
Damage to surrounding tissue	3 (4.55%)	2 (5.56%)	5 (4.90%)	0.051	0.821
Pelvic LAP	5 (7.58%)	3 (8.33%)	8 (7.84%)	0,018	0.892
Distant metastases (distant lymph nodes, liver, lungs)	2 (3.03%)	2 (5.56%)	4 (3.92%)	0.394	0,530

Thus, the described branch of the study showed that a thorough gynecological examination allows detecting cervical cancer in 100% of cases, in particular, examination of the cervix in mirrors and assessment of the consistency of the cervical tissue did not show a false negative result in any case, and 61% of women with cervical cancer were found to have 6 and 7 signs of pathology.

Additional diagnostic methods – colposcopy, transvaginal ultrasound and MRI – allow us to clarify the type of tumor and its prevalence with the involvement of nearby and distant organs and tissues.

All women included in the study underwent neoadjuvant polychemotherapy after cervical cancer verification and disease staging. The following treatment regimens were used: 1) Paclitaxel 175 mg/m2 on day 1 + carboplatin 300-400 mg/m2 intravenously by drip over 15-60 minutes on days 1-3 with an interval of 21 days and 2) Paclitaxel 175 mg/m2 on day 1 + topotecan 0.75 mg/m2 on days 1-3 with an interval of 21 days.

In both clinical groups, the majority of patients were administered the paclitaxel + carboplatin regimen, less frequently – paclitaxel + topotecan. In 17 cases, patients were administered 2 courses of paclitaxel + carboplatin followed by replacement with paclitaxel + topotecan. The frequency of application of various PCT regimens in the clinical groups did not differ (Fig. 29). The number of courses ranged from 1 to 9 (Fig. 30), with 58 patients (87.88%) administered 1-5 cycles in the main group, 28 patients (77.78%) in the comparison group, and the remaining patients were administered 6 or more courses of PCT (chi square = 1.72, ND).

Figure 29. The frequency of different polychemotherapy regimens in the study groups

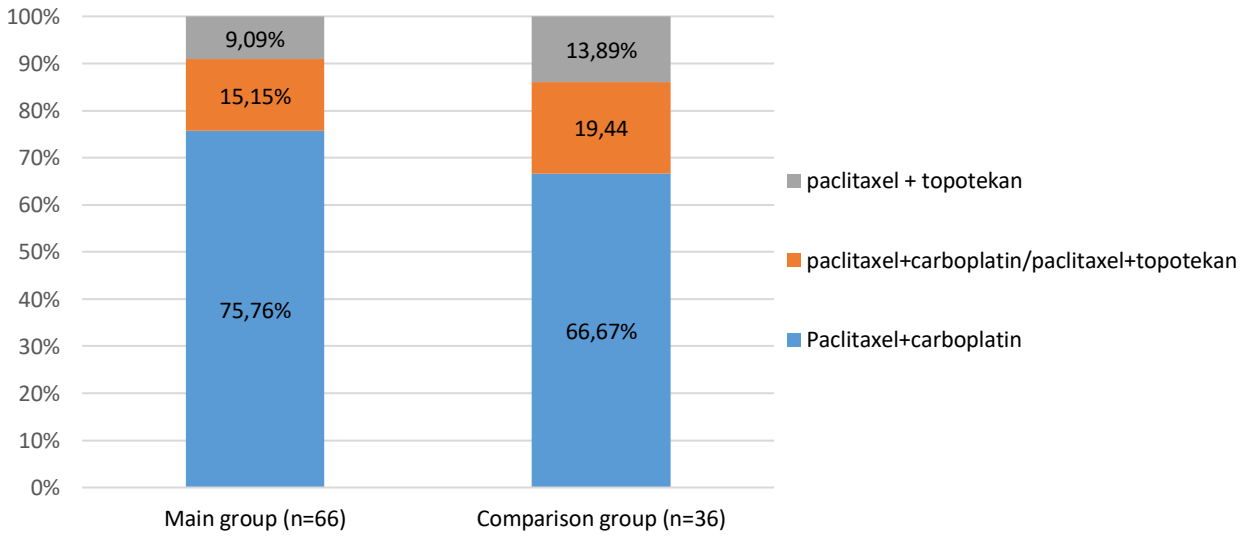
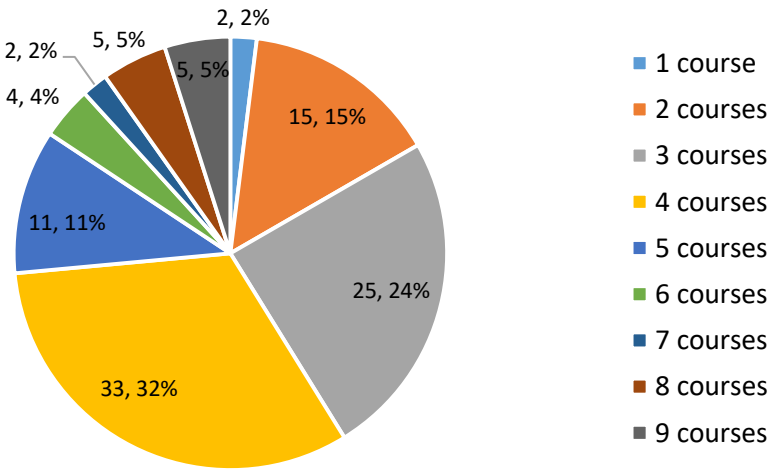
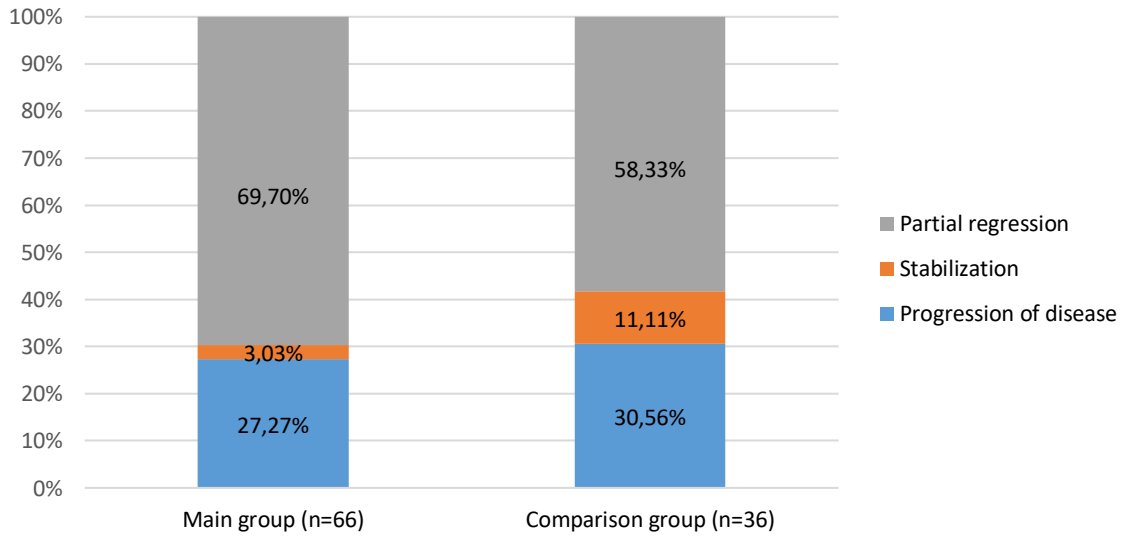


Figure 30. Number of polychemotherapy courses for women



By the end of PCT, the majority of patients in both groups showed partial regression of cervical cancer (Fig. 31), 6 patients (5.88%) showed stabilization, and 29 patients (28.43%) showed tumor progression. In the main group, PCT was performed starting from the 2nd trimester of pregnancy, in the comparison group - from the moment of verification of the diagnosis of cervical cancer. The dynamics of cervical cancer was assessed based on the results of serial MRI.

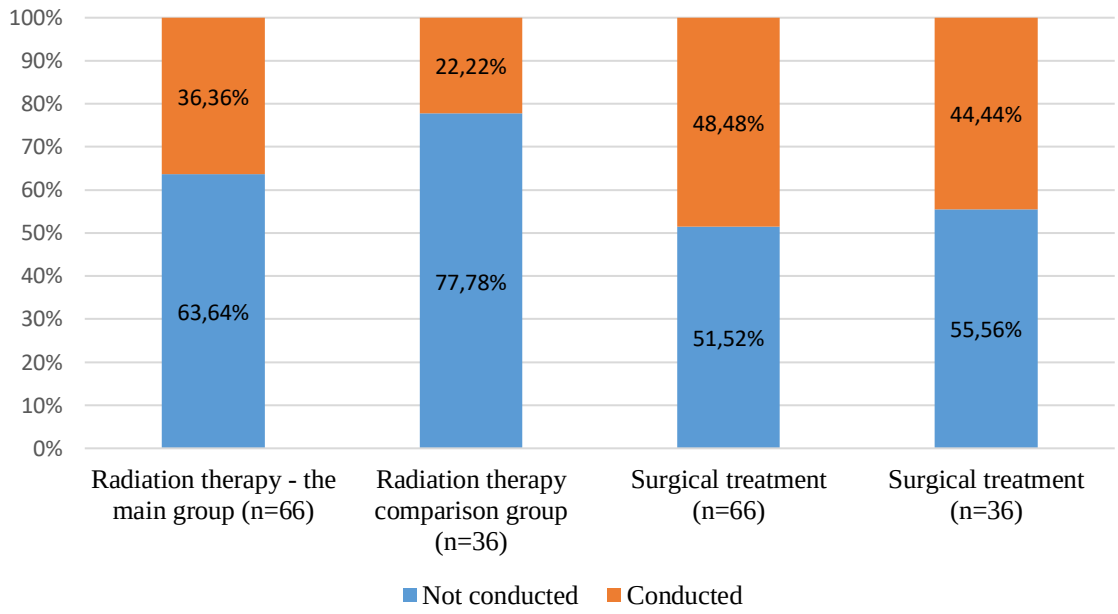
Figure 31. Dynamics of cervical cancer under the influence of polychemotherapy in the study groups



In addition to chemotherapy, 40 women in the main group (60.61%) and 20 patients in the comparison group (55.56%, chi square=0.27, ND) underwent other

anti-cancer treatments: 32 women (31.37%) underwent radiation therapy (in the main group after the resolution of pregnancy), 46 (45.10%) underwent surgical treatment, including 39 (38.24%) radical treatment (Fig. 32).

Figure 32. The use of radiation therapy and surgical treatment for cervical cancer in women of childbearing age, depending on the clinical groups



A study of the frequency of complications of chemotherapy (Table 9) revealed a higher frequency of cardiovascular complications in pregnant women compared to non-pregnant women (chi square = 7.12, $p < 0.01$) and more pronounced renal complications (chi square = 9.64, $p < 0.05$), which is probably due to background nephropathy in pregnant women.

Table 9

Type of complications	Degrees	Main group (n=66)	Comparison group (n=36)	Chi square
Hematological	1/2	64/2	36/0	2.99, nd
Gastrointestinal	0/1/2	16/26/24	8/13/15	0.28, nd
Renal	0/1/2/3/4	60/4/0/0/2	28/4/4/0/0	9.64, p<0.05

Cardiovascular	0/1	24/42	23/13	7.12, p<0.01

The study of the dynamics of the general health score (Table 10) showed that before the start of chemotherapy, pregnant women suffering from cervical cancer often demonstrate a higher score compared to non-pregnant women (chi square = 5.78, $p < 0.05$). After the course of chemotherapy, in both groups the number of patients with a higher score on the Karnofsky scale increased significantly (for the main group, chi square = 23.23, $p < 0.001$, for the comparison group, chi square = 31.75, $p < 0.001$), and in the comparison group it reached 100%, which is explained by the toxic effects of the drugs used.

Table 10

Dynamics of the general condition scores according to the Karnofsky scale and WHO EGOS during the first course of chemotherapy (frequency of occurrence of the assessment 1 point/2 points)

Time points	Main group (n=66)	Group comparisons (n=36)	Chi square
Before the course of chemotherapy	24/42	22/14	5.78, p<0.05
After the course of chemotherapy	2/64	0/36	2.11, nd
Chi square	23.23, p<0.001	31.75, p<0.001	

It is interesting that the subjective assessment of the dynamics of the patients' condition by the end of the chemotherapy treatment was positive in most patients (67 people - 65.69%), and only 28 women (27.45%) reported a deterioration in their condition. The remaining women included in the study assessed their condition as unchanged (7 people - 6.86%). In particular, in the main

group, 42 women noted an improvement in their condition, 20 - a deterioration, and 4 - unchanged; in the comparison group - 25, 8 and 3 women, respectively (chi square = 0.85, ND).

Thus, the branch of the study devoted to PCT showed that the use of PCT, including paclitaxel and carboplatin or topotecan, in pregnant patients with cervical cancer is associated with tumor dynamics and general health comparable to non-pregnant women according to subjective and objective assessment. However, the toxic effect of PCT is more pronounced in the group of pregnant women in terms of cardiovascular and renal complications.

The endpoints for assessing the effects of chemotherapy in this study were overall and cancer mortality, time of tumor recurrence, time of distant metastasis, survival, and relapse-free survival. In addition, pregnancy outcomes were assessed in the main group: intrauterine fetal death, premature termination of pregnancy, stillbirth, and fetal birth weight.

In the main group, 8 women had relapses of cervical cancer: 2 women after 3 months, 4 women within 9-12 months - 1 year, and 2 women within 1-2 years. The rest (58 women) did not have any tumor relapses during 3 years of observation. In the comparison group, 1 woman had a relapse within 3-6 months, 6 women - 6-9 months, and the remaining 29 women had no relapses during 3 years. In general, cervical cancer relapses were detected with comparable frequency in both study groups: 8 women in the main group (12.12%) and 7 patients in the comparison group (19.44%, chi square = 0.96, ND).

At inclusion in the study, distant metastases were detected in 2 patients in the main group and 1 patient in the comparison group (chi square = 0.41, nd). After treatment, no new cases of metastasis to distant regions were noted during 3 years of observation.

Analysis of 3-year survival in the groups demonstrated comparable survival rates, which were 84.94% in the main group and 84.85% in the comparison group (calculated using the Kaplan-Meier method, Table 11). All deaths in the present study were cancer-related and related to cervical cancer. There were no dropouts

from the study except for cancer-related deaths, and therefore intergroup survival comparisons were performed using chi-square conjugation tables.

Table 11

Dynamics of 3-year survival of women of childbearing age with cervical cancer depending on belonging to a clinical group

Time point	Main group (n=66)			Group comparisons (n=36)			Chi square, p<0.05
	died	Survival rate	Survive bridge	died	Share survivors	Survive bridge	
1 year	2	96.97%	96.97%	0	100%	100%	
2 years	2	96.88%	93.94%	2	94.44%	94.44%	2,129, 0,149
3 years	6	90.32%	84.85%	4	83.33%	83.33%	0.729, 0.394

Relapse-free survival was also assessed using the above methods. The 3-year relapse-free survival rates were comparable in the main group and the comparison group and were 84.85% and 80.55%, respectively (chi square=0.94, nd).

Table 12

Dynamics of 3-year relapse-free survival of women of childbearing age with cervical cancer depending on belonging to a clinical group

Time naya dot	Main group (n=66)			Comparison group (n=36)			Chi square
	Died li	Survival rate	Survive bridge	died	Survival rate	Survive bridge	
1 year	6	90.91%	90.91%	2	94.44%	94.44%	0.67, nd
2 years	0	100%	90.91%	1	97.06%	91.66%	2.12, nd
3 years	4	93.33%	84.85%	4	87.88%	80.55%	0.94, nd

In cases of detection of damage to the uterine body, parametrial tissue, walls of surrounding organs (ureter, bladder), pregnancy termination and surgical treatment were performed (6 women). In the group of pregnant women with cervical cancer, pregnancy outcomes were assessed, including pathological outcomes and fetal weight at birth (Table 12, Fig. 33). Live births and viable children were observed in 57 women (86.36%), which indicates the safety of the applied chemotherapy regimens during the 2nd-3rd trimesters of pregnancy.

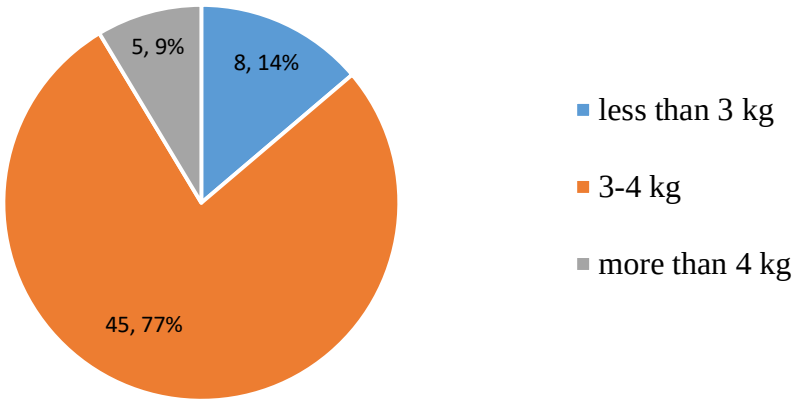
Table 13

Pregnancy outcomes in women with cervical cancer who received PCM in the 2nd and 3rd trimesters of pregnancy (n=66)

Indicator	Absolute quantity	Relative share in the group
Termination of pregnancy due to the need for surgical treatment	4	6.06%
Intrauterine fetal death	2	3.03%
Premature birth	2	3.03%
Premature birth, non-viable fetus	1	1.52%
Preterm birth, viable fetus	2	3.03%
Delivery on time, viable fetus	55	83.33%

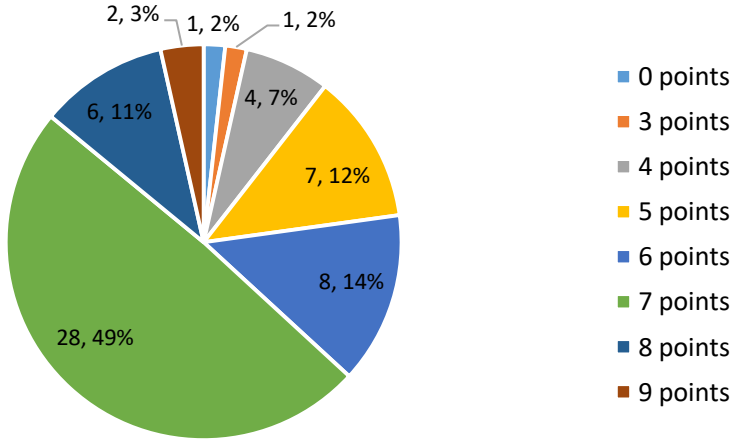
Most pregnancies ended in birth, including 83.33% with term births. Most of the babies born were viable with a birth weight category of 3-4 kg (77%).

Figure 33. Fetal weight at birth (liveable and unable fetuses) in women receiving polychemotherapy for cervical cancer in the 2nd and 3rd trimesters of pregnancy



Assessment according to the Apgar scale (Fig. 34) showed that the condition of 63.16% of newborns was moderate (mild asphyxia, 6-7 points), 19.30% was severe (moderate asphyxia, 4-5 points), 14.04% was satisfactory (normal, 8-10 points) and 1.75% were extremely severe (severe asphyxia) and stillborn.

Figure 34. Distribution of newborns born to mothers who received polychemotherapy for cervical cancer during pregnancy according to the Apgar scale



Thus, the present study showed that the use of PCT in women of childbearing age with cervical cancer is an effective method of antitumor treatment, both in pregnant and non-pregnant women, associated with more than

83% 3-year survival and more than 80% 3-year relapse-free survival, comparable both in the group of pregnant and non-pregnant women. The applied PCT regimens are safe for the fetus, ensuring the birth of viable children in 86.36% of cases, the condition of most of whom is assessed as satisfactory and moderate.

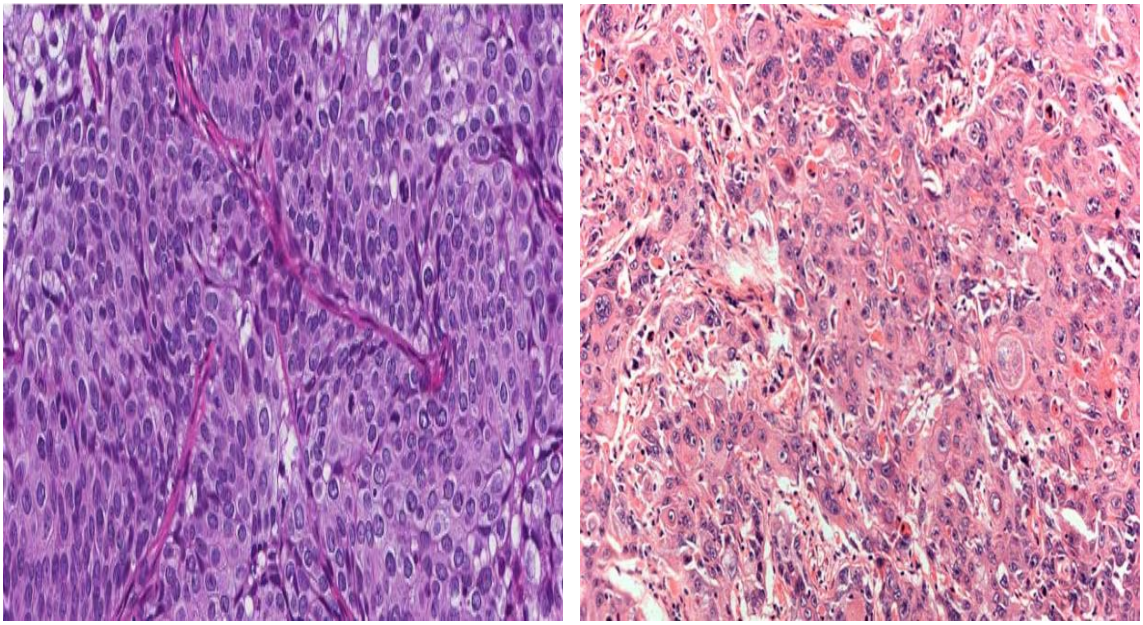


Figure 35. Histological picture of cervical cancer

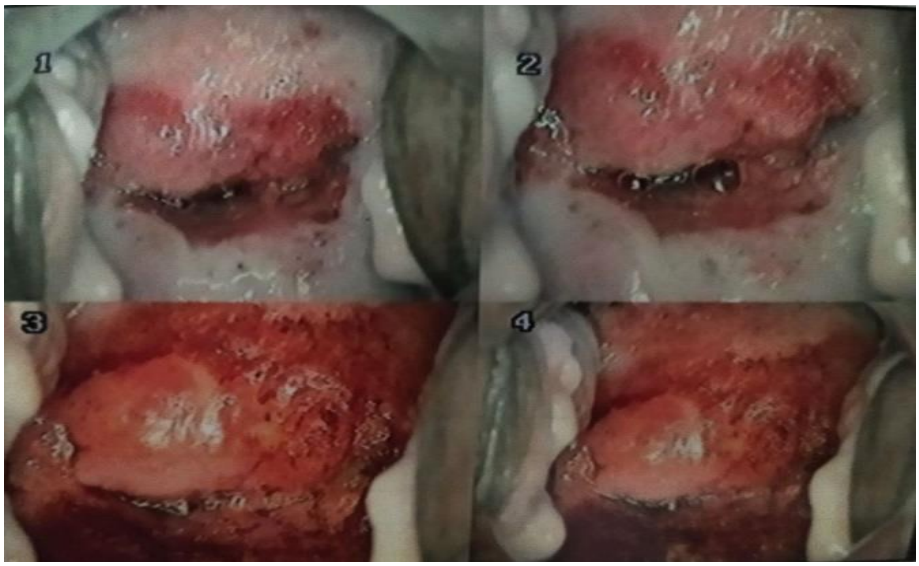


Figure 36. Colposcopic examination during pregnancy

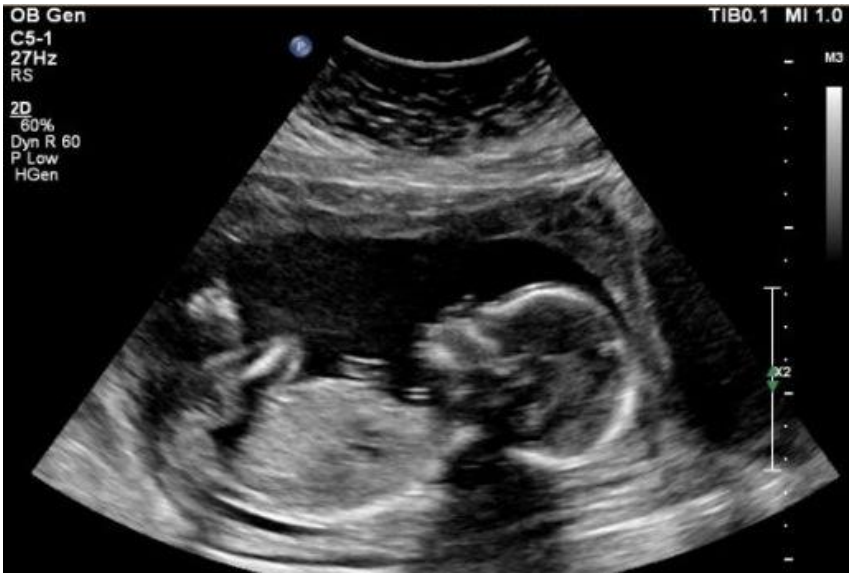


Figure 37. Ultrasound examination of a pregnant woman with cervical cancer

CHAPTER IV

ALGORITHM FOR CARE OF PREGNANT WOMEN WITH DIAGNOSED CERVICAL CANCER

Based on the results of the study, an algorithm for managing pregnant women in terms of diagnosis and treatment of cervical cancer was developed.

The algorithm is based on alertness in the aspect of the possibility of cervical cancer in pregnant women. For this purpose, the algorithm assumes 1) filling out a questionnaire, including complaints that may indicate the presence of cervical pathology (Table 14) and 2) conducting an examination of pregnant women during the first visit in mirrors and filling out a form that allows identifying possible signs of cervical cancer (Table 15). A positive answer to at least 1 point of the first questionnaire and a mark on the presence of at least one pathological sign of the second form requires the mandatory use of colposcopy to verify the condition.

Filling out these forms algorithmizes the process and allows you to detect signs of cervical cancer in the shortest possible time and with maximum reliability.

Table 14

Subjective signs that potentially indicate the presence of cervical cancer in pregnant women (accompanying text: Please mark the signs that you experience)

No.	Question	Not really
1	Bleeding from the genitals	
2	Pathological discharge	
3	Lower back pain	
4	Pain in the lower abdomen	
5	Pain in the legs	
6	Menstrual cycle disorders	
7	General weakness	
8	Decreased appetite	
9	Pain in the right hypochondrium	
10	Constipation	
11	Dyspnea	

Table 15

Signs indicating the presence of cervical cancer in pregnant women (the form is filled out by the doctor during the gynecological examination of pregnant women during the initial visit. Accompanying text: Please mark the signs found during the examination)

No.	Sign	Yes
1 Inspection:		
1a	Deformed	
1v	Eroded	
1s	Eroded and deformed	
2 Consistency:		
2a	Rocky	
2v	Dense	
2s	Tight elastic	
3 Mobility:		

3a	Sedentary	
3v	Movable	
3s	Stiff	
4 Pain:		
4a	Painless	
4v	Painful	
5 Parameters:		
5a	Infiltrated to the bone	
5v	Not infiltrated to the bone	
5s	Rigid	
5d	Free	
6 Vaults:		
6a	Fit	
6v	Rigid	
6s	Free	
7 Discharges:		
7a	Watery	
7v	Watery-bloody	
7s	Bloody	
7d	Bloody	
7th	Whites	

Colposcopy should include sampling for cytological and histological examination. In case of cervical cancer diagnosis, the next step should include visualization methods - transvaginal ultrasound and MRI of the pelvis, as well as ultrasound of the parenchymatous organs and MRI of the whole body to verify the diagnosis and stage the disease.

After verification of cervical cancer, the therapeutic branch of the algorithm involves conducting polychemotherapy according to the scheme: 1) Paclitaxel 175

mg/m2 on the 1st day + carboplatin 300-400 mg/m2 intravenously by drip for 15-60 minutes on the 1st-3rd days with an interval of 21 days and 2) Paclitaxel 175 mg/m2 on the 1st day + topotecan 0.75 mg/m2 on the 1st-3rd days with an interval of 21 days. The beginning of polychemotherapy is postponed until the 2nd trimester of pregnancy. Radiation therapy and surgical treatment are postponed until the resolution of pregnancy, except in cases of invasion of the body of the uterus, parametrium and walls of adjacent hollow organs, when termination of pregnancy and urgent surgery with the most complete excision of the tumor, surrounding tissue and regional lymph nodes are required.

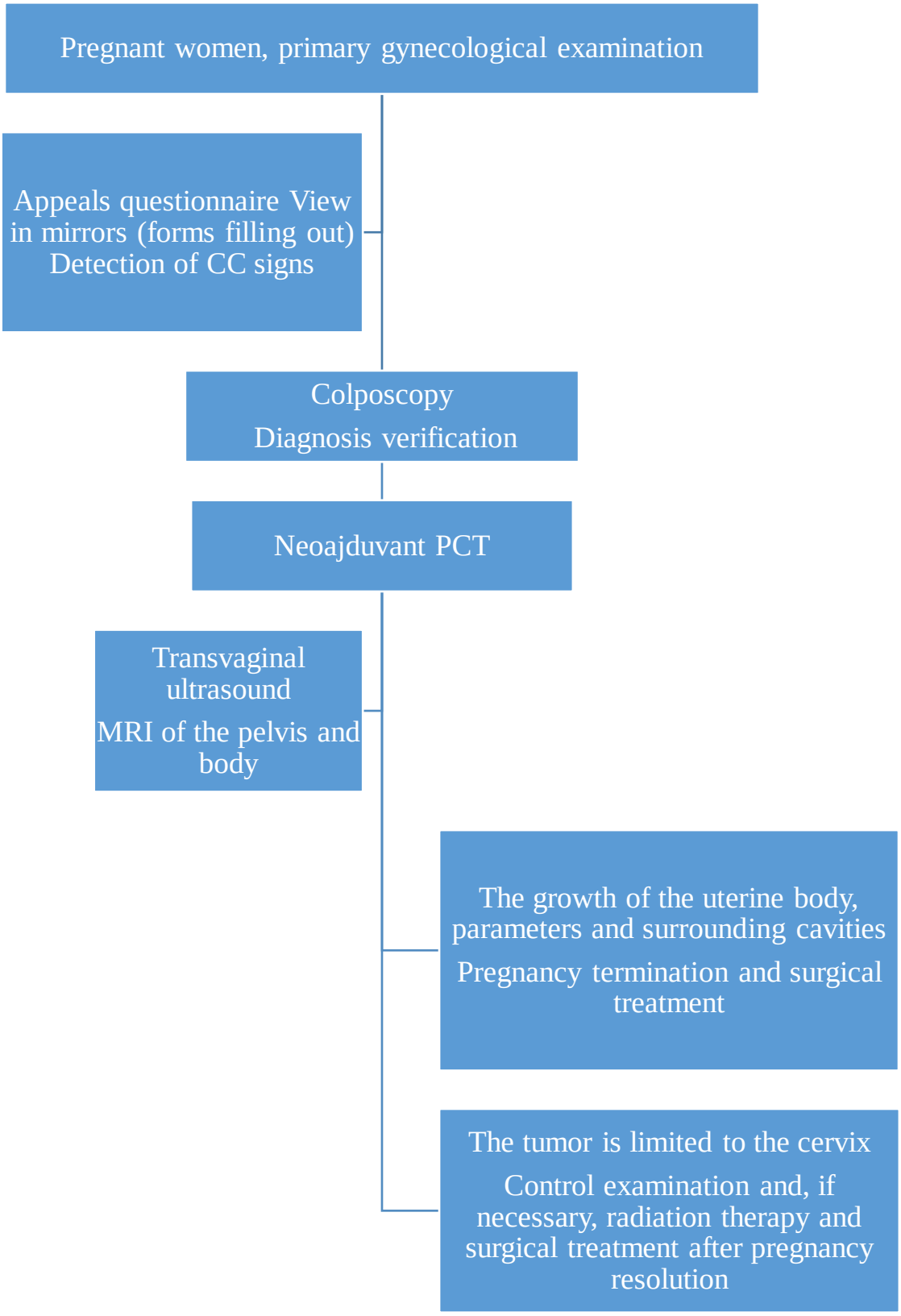


Figure 38. Algorithm for managing pregnant women for timely detection of cervical cancer and determining tactics

The use of the developed algorithm allows for the most efficient and rapid diagnosis of cervical cancer in pregnant women and early initiation of chemotherapy treatment to prevent tumor progression and regression.

CONCLUSION

Recently, the incidence of gynecological malignancies in pregnant women has increased, which is mainly due to the increasing age of pregnant women. The most common malignant tumor of the gynecological organs detected in pregnant women is cervical cancer (71.6%), followed by ovarian cancer (7.0%) [13,17,19]. The incidence of cervical cancer during pregnancy in absolute values is not very high, in addition, tumor symptoms can be mistaken for physiological changes during pregnancy or other pathologies. During pregnancy, gynecological examination is usually limited, so the frequency of erroneous diagnoses is high. Treatment of cervical cancer during pregnancy is determined by many factors, such as tumor size, histological subtype, gestational age, involvement of regional lymph nodes, distant metastasis, and the woman's desire to continue the pregnancy. With so many variables, it is impossible to determine the optimal single management plan for all women, which should ensure effective anti-cancer treatment and safety for the fetus [51]. Cervical cancer is diagnosed in 0.8-1.5 women per 10 thousand births [53,67] or 4 cases of pregnancy per 100 thousand patients with cervical cancer [46,55,73,102].

The present study included 66 pregnant women diagnosed with cervical cancer and 36 non-pregnant women with cervical cancer as a comparison group. The study assessed the informativeness of various examination methods, including subjective data, gynecological examination and instrumental techniques. In 84.85% of pregnant women included in the study, cervical cancer was diagnosed for the first time during the current pregnancy. The tumor is most often diagnosed at stage 2b (55.88%) and T2N0M0 (52.94%).

Clinical manifestations of cervical cancer in pregnant women depend on the clinical stage and size of the tumor. Pregnant women with an early stage of the

tumor may not present any symptoms. However, a thorough examination can reveal vaginal discharge of a purulent, serous or bloody nature, periodic vaginal hemorrhages. In later stages of the tumor, women may complain of pain, chronic anemia, severe vaginal bleeding [41,73,98]. However, these same symptoms can be mistaken for manifestations of pregnancy. The slightest suspicion requires cervical exfoliative cytology.

In the present study, clinical manifestations were revealed in all patients included in the study, both among pregnant patients and in the comparison group, during the survey. All women had pathological discharge from the genital tract, the second most common complaint (99.02% of patients) was pain in the lower abdomen and lumbar region. Contact bloody discharge was noted in 58% of patients, more often among pregnant women compared to the comparison group, which can be explained by physiological changes in the cervix during pregnancy - looseness of the epithelium, increased blood flow, which are superimposed on oncological pathology.

The anamnesis of 98% of patients was burdened by cervical pathology, which could contribute to the development of cervical cancer, and in the group of pregnant women with cervical cancer, precancerous pathology was significantly more common (69.70%, $p<0.05$), including dysplasia of the cervical epithelium. The study also revealed the fact of late appeal of women with cervical cancer - thus, 31.68% sought help more than a year after the appearance of the first signs of the disease, which indicates insufficient medical education, as well as the inadequacy of primary screening programs.

Gynecological examination of all patients revealed signs of cervical cancer: all women showed visually determined changes during examination - deformation and erosion of the cervix, out of 7 signs, at least 2 signs were found in all patients, and all seven were found in 29.41% of patients.

Screening for cervical cancer in pregnant women includes 3 stages – cervical cytology, colposcopy, cervical biopsy.

Cervical cytology is a method of primary rapid diagnostics of cervical cancer, safe for the mother and fetus, as well as for pregnancy. The diagnostic efficiency of cervical cytology in pregnant women does not differ from the information content in non-pregnant women [10,11,15]. Although some researchers note that physiological changes in the cervical epithelium during pregnancy - glandular hyperplasia, displacement of the junction of squamous and columnar epithelium, active proliferation of basal cells, irregular cell morphology, enlargement of nuclei can be mistaken for signs of cervical cancer [75], which requires examination by a pathologist familiar with the physiology of cervical changes during pregnancy [8,19,39].

Colposcopic examination of pregnant women is also associated with some difficulties due to hormonal changes during pregnancy. Therefore, it is recommended to repeat the examination of the 1st-2nd trimester of pregnancy after 20 weeks. Indications for colposcopy are: vaginal bleeding or contact bleeding in the absence of obstetric causes; cervical anomalies detected during gynecological examination; cervical lesions suspicious for invasive cervical cancer; cervical cytology ASC-US, LSIL, ASC-H, HSIL, AGC [100].

In the present study, colposcopy was performed in all patients. During colposcopy, 91.18% of women were diagnosed with carcinoma, in the remaining patients, leukoplakia and dysplasia of the cervical epithelium were previously detected by colposcopic examination, but biopsy confirmed malignant pathology in all patients included in the study.

Cervical biopsy is performed to verify the diagnosis and determine the histological type of the tumor and can be performed during colposcopy and under visual control. Cervical biopsy does not increase the risk of pregnancy complications and the frequency of premature births and spontaneous abortions. Curettage of the cervical canal during pregnancy increases the risk of early termination of pregnancy and cervical bleeding [78,92], which makes this procedure contraindicated in pregnant women. Given the "looseness" of the cervix in pregnant women, the recommended biopsy thickness should not exceed 1 cm.

Histologically, squamous cell nonkeratinizing cancer was detected in most patients (88%), less often - endometrioid invasive (10%) and epidermoid carcinoma (2%). Moderately differentiated cancer was detected in 64% of patients, highly differentiated - in 14%, poorly differentiated - in 22%.

Visualization methods are used to stage the tumor and identify local spread and regional and distant metastasis. Considering the safety for the body of the pregnant woman and the fetus, ultrasound is safe for pregnant women with cervical cancer. Including transvaginal and MRI [28,35]. In the present study, ultrasound, in addition to a detailed description of the tumor, allowed us to detect invasion into the wall of the uterus, the lower third of the ureter, compression of the bladder and rectum. Local complications were detected in 9.80% of patients. The frequency of detection of local complications did not differ in the group of pregnant women with cervical cancer and in the comparison group.

MRI, which was performed on all women included in the study, made it possible to detect local complications of the tumor - growth into the wall of the uterus (6.86%), ureter (3.92%), bladder (2.94%), rectum (0.98%), surrounding tissue (4.90%), regional lymph nodes (7.84%) with a comparable frequency in the main group of patients and the comparison group, as well as distant metastases in 3.92% of patients.

Treatment of cervical cancer in pregnant women is a complex tactical problem, since the plan for managing such patients should include the most effective measures in terms of time and volume, while significant attention should be paid to safety for the mother and fetus and minimization of the risk of pregnancy complications and its premature termination. Of the three methods of anti-cancer treatment, radiation therapy is contraindicated due to the danger of ionizing radiation of the pelvic area for the fetus. Radiation therapy is possible only after the pregnancy is resolved. In the present study, 31.37% of women underwent radiation therapy.

The use of surgical treatment is limited by the following factors. Size, stage and extent of the tumor: CC infiltrating the surrounding tissues is an indication for

radical hysterectomy as soon as possible, while the presence of pregnancy is not taken into account. There were 6 such patients in the present study (9.09% of women in the main group). In the case of minimally invasive CC, surgical treatment aimed at preserving pregnancy is possible (laser conization with a depth of no more than 1 cm) [75]. However, this approach was not implemented in the present study. In total, surgical treatment was performed in 45.10% of patients included in the study, including 38.24% of patients who underwent radical surgery - hysterectomy with bilateral lymphadenectomy.

The most commonly used anti-cancer treatment option in pregnant women is polychemotherapy. The recommended choice is paclitaxel, carboplatin, topotecan [1,4]. In the present study, all patients underwent polychemotherapy (2-9 courses). Polychemotherapy is used no earlier than the 2nd trimester to minimize the teratogenic effect, and no later than 4 weeks before the expected date of delivery to provide a time window for the restoration of hematopoietic function. As a result of polychemotherapy, 65.69% of patients showed partial tumor regression, assessed by serial MRI data.

The use of PCT is associated with toxic effects. In the present study, hematological complications (in 100% of patients), gastrointestinal (76.47%), renal (13.73%) and cardiovascular (53.92%) were recorded. At the same time, the frequency of nephrological and cardiovascular complications of PCT was higher in pregnant women compared to non-pregnant women, which is probably noted by cardiovascular changes characteristic of pregnancy and, possibly, gestational nephropathy. The toxic effects of PCT contributed to an increase in the number of women with a high score on the Karnofsky scale: in 43.14%, the score on the Karnofsky scale increased relative to the baseline. At the same time, the subjective assessment of their condition in 65.69% of women included in the study was assessed as having changed for the better, which is probably due to an improvement in their psychoemotional status.

The endpoints considered in patients with oncological pathology are survival and relapse-free survival. The indicators in the present study among pregnant

women with cervical cancer were 84.94% and 84.85%, respectively, and did not differ from the indicators recorded in the comparison group. Live and viable children were born to 86.36% of women included in the study, including at term - in 83.33% of patients, including with a weight of 3-4 kg - in 77% of cases and with an Apgar score of at least 6 points - 77.19% of infants.

Other researchers have also shown the high efficacy and safety of PCT in women with cervical cancer diagnosed during pregnancy for both mother and fetus [5,97].

Based on the data obtained in this study, an algorithm for managing pregnant women with signs of cervical oncological pathology was developed, including diagnostic and therapeutic branches. The use of the proposed algorithm will help reduce cancer mortality, termination of pregnancy and oncologically associated obstetric pathology, which allows us to recommend the widespread implementation of the developed algorithm in health care practice.

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ABBREVIATIONS

GLOBOCAN – a global cancer registry

GIT – gastrointestinal tract

MRI – magnetic resonance therapy

PAP test – gynecological smear with examination by the Papanicolaou method

PCT – polychemotherapy

CC – cervical cancer

US – ultrasound examination

CNS – central nervous system

CM – cervix

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