INTERNATIONAL JOURNAL OF
INTEGRATIVE AND
MODERN MEDICINE

Optimization of Early Diagnosis Methods and Management Tactics For Pregnant Women with Cervical Cancer

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Abstract: The relevance of the work presented is a look at an important topic that combines two important areas of women's health - cervical cancer and pregnancy. The scientific and social significance of studying the development features of this pathology is associated with the steady increase in the incidence of cervical cancer and the low percentage of complete cures for patients with this disease. Currently, the problem is being comprehensively studied, but the issue of early diagnosis of this pathology and the establishment of possible causes of the disease remains insufficiently studied .

Key words: cervical cancer, pregnancy, colposcopy, histocytology, neoadjuvant polychemotherapy.

Relevance. Cervical cancer is one of the most common malignant neoplasms among pregnant women and occurs with a frequency of 1/1000–2000 pregnancies [4,5]. According to World Health Organization / International Agency for Researchon Cancer Cervical cancer is the eighth most common malignancy and is particularly common in developing regions, with an estimated 569,847 new cases in 2018 and 311,365 deaths. According to International Network on Cancer , Infertility and Pregnancy , the first place in the incidence of malignant neoplasms among pregnant women is breast cancer (39%) in pregnant women, followed by cervical cancer (13%), lymphoma (10%), ovarian cancer (7%) and leukemia (6%) [5]. The spread of the human papillomavirus (HPV) has caused an increase in precancerous and cancerous lesions of the cervix, especially in younger women of childbearing age, causing an increase in cervical cancer during pregnancy (4 per 100,000 births) [1]. In Russia, the standardized incidence rate of cervical cancer in 2016 was 13.70 per 100 thousand female population [2]. In South Korea, by 2016, cervical cancer accounted for 2.2% of all diagnosed malignancies and 2.6% of cancer deaths among women, with 3,013 new cases and 755 deaths identified [6]. The rate per 100,000 population was 11.7 new cases and 7.5 deaths [6,7]. In Uzbekistan in 2019, cervical cancer was detected in 9 women per 100,000 population. Cervical cancer was most often detected in stage II - 31%, in stage III - 20.9%, in stage I - 10.7%, in stage IV - 4.2%. Tashkent was in first place in terms of detection - 9.8 per 100,000 population, in Samarkand 9.2 per 100,000 population were detected. Of these, in stage I - 11.3%, in stage II - 48.9%, in stage III - 36.9%, in stage IV - 2.8% of cases [3].

Purpose of the study.

To study the features of the course of cervical cancer (CC) in pregnant women, to improve methods of early diagnosis and management tactics.

Materials and methods. The study included 102 women of reproductive age with diagnosed CC. The main group consisted of 66 women who applied during pregnancy, the comparison group - 36 women in whom CC was detected not during pregnancy.

The study included women whose CC was identified in primary health care institutions, and who were referred to regional oncology institutions to verify the diagnosis and develop further tactics. All

women were examined during a clinical gynecological examination in speculum; the diagnosis was verified during a histocytological examination of the tissue of the formation; the prevalence and localization features were used using MRI of the pelvis and transvaginal ultrasound.

After examination and verification of the diagnosis, patients were stratified by stage and according to the TNM system , and further tactics were developed - expectant with planning oncological therapy after resolution of pregnancy, or active, including surgical treatment, polychemotherapy (PCT) and radiation therapy.

Results. The results of the study were – disease outcome – recovery, relapse, metastasis, death; complications of tumor/therapy - bleeding, premature birth, intrauterine fetal death. The majority of women included in the present study lived in rural areas (60%).

The vast majority of women complained of bleeding from the genital organs and pathological discharge (100%), pain in the segments associated with damage to the genital organs - the 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, shortness of breath occurred in less than 7% of patients and cannot clearly indicate cervical pathology, since they are nonspecific.

In the majority of patients, discharge from the genital tract was of a contact-bloody nature (58%) (chi square = 12.92, $p < 0.01$).

All women were assessed for the degree of cervical epithelial dysplasia using the CIN system . Only 30% of patients included in the study had a history of cervical epithelial dysplasia, which may indicate insufficient primary cancer screening.

According to the location of the primary tumor, the majority of women (71 people - 69.61%) had a cervical type, less often - a vaginal type (21 people, 20.59%). However, the distribution of women according to the primary involvement of the cervix or vagina showed that pregnant women are more likely to have cervical involvement (81.82%), while in non-pregnant women the incidence of cervical involvement is slightly more than half of the cases (58.33%) and the frequency of primary vaginal lesions increases (41.67%, chi square = 6.49, $p < 0.05$).

According to the form of tumor growth, most women recorded exophytic growth (57 women - 55.88%), the rest - ulcerative (21.57%) and endophytic (20.59%). Staging of cervical cancer showed that most often the tumor was diagnosed at stage 2b (57 women - 55.88%), comparable in the study groups (chi square = 1.55, n.d.), while tumors were more common in the group of pregnant women than in the comparison group , diagnosed at stage 2b (chi square=4.03, $p <0.05$) and less often - 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 scores are comparable (chi square = 13.19, $p < 0.05$).

TNM system , the most common tumors were with characteristics T2 (71 patients - 69.61%), N 0 (77 patients - 75.49%), M0 (99 patients - 97.06%). In total, there were 54 women (52.94%) with CC characteristics 34/20 T 2 N 0 M 0: 34 in the main group and 20 in the comparison group (chi square = 0.20, n.d.). In 3 women with M1 characteristics, distant metastases were found in the lungs (1 case) and in the lungs and liver (2 cases).

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

Gynecological examination of the cervix in the speculum in all patients allowed us to detect cervical pathology, comparable in both clinical groups of the study.

A mandatory examination is transvaginal ultrasound. 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, in addition, in 2 patients, tumor growth into the uterine cavity was detected, in 2 patients - into

the wall of the lower third of the ureter with the development of ureterohydronephrosis , in 2 patients there was compression from outside by the tumor of the bladder and rectum. In the comparison group, one patient was diagnosed with a polyp of the cervical canal, in the remaining patients - a cervical tumor, complicated in 1 patient by growth 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 (between-group difference in the frequency of tumor growth into the uterus, neighboring organs and compression of neighboring organs according to transvaginal ultrasound - chi square = 2.44, n.d.). Transvaginal ultrasound allows not only to diagnose a tumor, but also to determine its size. An 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 measuring 6 cm or more are more common in non-pregnant patients.

as an additional imaging method to clarify the localization and extent of CC, as well as the involvement of surrounding organs and tissues and the presence of distant metastases. The study was carried out on all patients included in the study. Based on MRI results, patients were identified with metastatic lesions of the lungs and liver, damage to distant lymph nodes, involvement of the pelvic lymph nodes, spread of cervical cancer to the body of the uterus, surrounding tissues, the wall of the ureter, bladder, rectum, while the frequency of complicated course of cervical cancer did not differ in both study groups. The study is safe for both the pregnant woman and the fetus, does not have a teratogenic effect and can be used as a diagnostic and verification method during pregnancy. All women included in the study, after verification of cervical cancer and staging of the disease, underwent neoadjuvant polychemotherapy (for 2 patients of the main group - regional, for the rest of the women included in the study - systemic). The following treatment regimens were used: 1) Paclitaxel 175 mg/m2 on day 1 + carboplatin 300 - 400 mg/m2 intravenous drip for 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.

The frequency of use of various PCM regimens did not differ between clinical groups. The number of courses ranged from 1 to 9, while in the main group 58 patients (87.88%) received 1-5 cycles, in the comparison group - 28 patients (77.78%), the remaining patients received 6 or more courses of PCT (chi square=1.72, nd).

By the end of chemotherapy, the majority of patients in both groups showed partial regression of cervical cancer (Fig. 10), 6 patients (5.88%) had stabilization, and 29 patients (28.43%) had tumor progression. In the main group, PCT was carried out starting from the 2nd trimester of pregnancy, in the comparison group - from the moment the diagnosis of cervical cancer was verified. The dynamics of cervical cancer were assessed based on the results of serial MRI.

A study of the frequency of complications of PCT 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 pregnancy.

A study of the dynamics of the overall health score 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 a course of PCT in both groups, the number of patients with a higher score on the Karnofsky scale significantly increased (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 group comparison reached 100%, which is explained by the toxic effects of the drugs used.

It is interesting that the subjective assessment of the dynamics of the patients' condition by the end of PCT treatment in the majority of patients was positive (67 people - 65.69%), and only 28 women

(27.45%) reported a deterioration in their condition. The remaining women included in the study assess their condition as unchanged (7 people – 6.86%). In particular, in the main group, 42 women noted improvement in their condition, worsening – 20, unchanged – 4; in the comparison group – 25, 8 and 3 women, respectively (chi square = 0.85, n.d.). The end points to evaluate the effects of PCT in this study were overall and oncological mortality, time of tumor relapse, time of appearance of distant metastases, survival and relapse-free survival. In addition, pregnancy outcomes were assessed in the main group: intrauterine fetal death, premature termination of pregnancy, stillbirth , fetal weight at birth.

In the main group, 8 women had relapses of cervical cancer: in 2 people after 3 months, in 4 - within 9-12 months - 1 year, in 2 - within 1-2 years. In the rest (58 women), no tumor recurrences were recorded during 3 years of observation. In the comparison group, 1 woman had a relapse within 3-6 months, 6 women had a relapse within 6-9 months, and the remaining 29 women had no relapses within 3 years.

When included in the study, distant metastases were found in 2 patients in the main group and 1 patient in the comparison group (chi square = 0.41, n.d.). After treatment, no new cases of metastasis to distant regions were observed 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). All deaths in the present study were cancer-related and cervical cancer-related.

Relapse-free survival was also assessed using the above methods. The 3-year disease-free survival rates were comparable in the main group and the comparison group and amounted to 84.85% and 80.55%, respectively (chi square = 0.94, n.d.). In cases of detection of damage to the body of the uterus, parametrial tissue, and the walls of surrounding organs (ureter, bladder), termination of pregnancy and surgical treatment were performed (6 people). In the group of pregnant women with CC, pregnancy outcomes were assessed, including pathological outcomes and fetal weight at birth. The birth of live and viable children was observed in 57 women (86.36%), which indicates the safety of the PCT regimens used during the 2-3 trimesters of pregnancy.

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

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

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

The algorithm is based on alertness regarding the possibility of cervical cancer in pregnant women. For this purpose, the algorithm involves 1) filling out a questionnaire, including complaints that may indicate the presence of cervical pathology and 2) conducting an examination of the pregnant woman at the first visit in the mirror and filling out a form that allows identifying possible signs of cervical cancer. A positive answer to at least 1 point of the first questionnaire and a note about 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 CC in the shortest possible time and with maximum reliability.

Colposcopy should include collection of material for cytological and histological examination. In the case of cervical cancer diagnosis, the next step should include imaging methods - transvaginal ultrasound and MRI of the pelvis, as well as ultrasound of parenchymal 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 PCT according to the scheme: 1) Paclitaxel 175 mg/m2 on the 1st day + carboplatin 300 - 400 mg/m2 intravenous drip for 15 - 60 minutes on the 1st - 3rd days with an interval on day 21 and 2) Paclitaxel 175 mg/m2 on day 1 + topotecan 0.75 mg/m2 on days 1–3 with an interval of 21 days.

The start of PCT is delayed until the 2nd trimester of pregnancy. Radiation therapy and surgical treatment are postponed until pregnancy is resolved, except in cases of germination of the uterine body, 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 is required.

The use of the developed algorithm makes it possible to most effectively and quickly diagnose cervical cancer in pregnant women and begin PCT treatment early to prevent tumor progression and regression.

1. CC in pregnant women is associated with a greater number of pregnancies and abortions in history, compared with women of a comparable age in whom CC did not develop during pregnancy. cervical cancer in pregnant women was associated with contact-bloody discharge in 80.30% of cases versus 63.89% in non-pregnant women ($p < 0.01$), as well as with a higher frequency of pre-carcinogenic background pathology of cervical cancer (69.70% versus 41.67% in non-pregnant women, $p < 0.01$) and cervical epithelial dysplasia CINII (21.21%, $p < 0.05$).
2. In pregnant patients, cervical cancer is more often characterized by a primary cervical localization compared to non-pregnant patients (81.82% versus 58.33%, chi square = 6.49, $p < 0.05$). The growth pattern is often exophytic (51.52%), palpation characteristics are dense (81.82%), immobile (96.97%), stage 2b (51.52%) and T 2 N 0 M 0 (51. 52%), histological structure – squamous cell non-keratinizing cancer (81.82%) moderately differentiated (61.62%).
3. For non-pregnant women, cervical cancer is diagnosed more often within 1 month after the first symptoms of the disease appear, and for pregnant women - more often at a later date ($p < 0.01$).
4. Colposcopy in pregnant women allows in all cases to detect cervical cancer and collect material for histological and cytological examination. Transvaginal ultrasound and MRI of the pelvis are informative and safe imaging diagnostic methods for staging cervical cancer in pregnant women.
5. PCT containing 1) Paclitaxel 175 mg/m2 on the 1st day + carboplatin 300 - 400 mg/m2 intravenous drip for 15 - 60 minutes 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 in the amount of 1-9 courses in pregnant women suffering from cervical cancer allows achieving partial tumor regression in 69.70% and subjective improvement in health status (63.64%). The 3-year survival rate of pregnant women with CC using PCT is 84.85% and does not differ from the rate in non-pregnant women of childbearing age with the same pathology.
6. 6.06% of pregnant women with CC due to damage to neighboring organs require termination of pregnancy and surgical treatment with the maximum possible excision of the tumor. Intrauterine fetal death and the birth of a non-viable child are observed in 7.58%. 86.36% of pregnancies of women with cervical cancer against the background of chemotherapy using paclitaxel , carboplatin and topotecan end in the birth of viable children, the majority of whom (77.20%) have an Apgar score of 6 points or higher.

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