

TACTICS OF MANAGING PREGNANT WOMEN WITH INVASIVE CERVICAL CANCER

Tugizova Dildora Ismoilovna,

Karimova Mavluda Nematovna,

Ulmasova Zilola,

Davronov Bekzod

Summary

In recent years, the incidence of gynecological malignant tumors during pregnancy has increased, mainly due to an increase in the number of pregnant women in old age. The most common gynecological malignant tumors during pregnancy are cervical cancer (71.6%), followed by ovarian malignancies (7.0%). The incidence of cervical cancer in pregnancy itself is not very high, and symptoms can be easily confused with other diseases during pregnancy. During pregnancy, gynecological examination is limited, which means that the likelihood of a misdiagnosis is higher. Treatment for cervical cancer during pregnancy is associated with many factors, such as tumor size, pathological type, gestational age, lymph node involvement, and the patient's desire to maintain the pregnancy. Due to these factors, it is difficult to determine the optimal treatment. This article looks at the progress in research into the diagnosis and treatment of cervical cancer in pregnancy to balance effective tumor management with protecting fetal health, while avoiding treatment delays and premature birth.

Keywords: cervical cancer, diagnosis, pregnancy, pregnancy with cervical cancer, tumor treatment, tumor staging.

Cervical cancer ranks 3rd in the world in terms of prevalence among all cancers in general and 2nd in developing countries among all malignant neoplasms in women (13% - 452,000 cases), while in developed countries it takes only 10th place (76,000 cases) [27,25].

Invasive cervical cancer ranks first among gynecological tumors associated with pregnancy, and is detected, according to various authors, on average from 0.8 to 1.2 cases per 10,000 pregnancies [9.42].

The relevance of the combination of malignant tumors with pregnancy is increasing every year. This is primarily due to the delay in childbirth. In 2014, the average age of Russian women at birth was 28.1 years, as opposed to 24.9 years in 1995. [1]. In this age group (25-29 years old) that cervical cancer occupies a leading position (19.17%)

among all oncological diseases at this age, ahead of lymphoproliferative diseases and breast cancer. At the age of 30-34 years, the proportion of cervical cancer also remains high (23.76%), leaving this tumor in the first place among all oncological diseases in young people [2,3].

One third of all cervical carcinomas are diagnosed in women of reproductive age [26,36]. About 3% of cervical cancer cases are diagnosed during pregnancy (3), which leaves a woman and her family with a difficult choice between giving birth to a new life and terminating the pregnancy. These cases correspond to half of the cancers diagnosed during the gestational period. The estimated incidence of cervical cancer is 1 per 1000-5000 pregnancies [37,31].

According to several foreign studies, in 76% of cases, cervical cancer during pregnancy is diagnosed only at stage 1B [34,37,31,30,32,39,17,12].

The prognosis for early forms of cervical cancer in non-pregnant women and during pregnancy is practically the same. The choice of treatment tactics depends not only on the stage of the disease and the duration of pregnancy, but also on the decision of the patient herself regarding pregnancy and the method of treatment [4].

To date, on the basis of large studies, no recommendations for the management of pregnant women with cervical cancer have been carried out. When diagnosing and treating patients with this category, it is based on research materials with the participation of non-pregnant patients. At the same time, in addition, the tactics of managing pregnant women with cervical cancer is determined by the gestational age, the stage of the tumor process and the patient's desire to preserve the pregnancy. In these cases, treatment should be individual, timely, with minimal risk to the woman and the fetus [8].

When studying the historical literature data until the 80s devoted to cervical cancer associated with pregnancy, we found out that pregnancy negatively affects the course of cervical cancer, and even clinical studies until the 80s indicated a worsening prognosis of the disease in combination with pregnancy [7,5,6]. This was associated with a significant change in hormonal status during pregnancy, which affects the immune state of the maternal organism. Another explanation may be the duration of the symptoms of the disease and its late diagnosis, often at the stages of metastatic lesions. At the same time, the first report was published about a significant delay in treatment before delivery (until the moment of fetal viability) with a gestational age of more than 20 weeks, and for women with a period of up to 20 weeks in case of an unwanted pregnancy, various methods of abortion were recommended. Since then, many studies have reported on the possibility of delaying the treatment of cervical cancer when combined with pregnancy [5,6,7]. When analyzing the literature review, there was a work in which it was reported about 82 patients, mainly stage 1 of the disease, who decided to postpone treatment for 1-32 weeks until the moment of fetal viability.

Although the duration of the delay in treatment was different, the progression of the tumor process was recorded only in 3 patients. Despite the fact that there were no differences in the survival rate of patients from the type of delivery [5,7]., Because of the possible bleeding and dissemination of the tumor, preference was given to the abdominal delivery. Several patients after vaginal delivery developed relapses in the area of episiotomy [6,7]. In many works devoted to the treatment of cervical cancer in pregnant women before 2005, especially in the early stages of the disease, regardless of the gestational age, it was considered preferable to postpone treatment until the birth of the child. In the treatment of cervical cancer stages 1A1 and 1A2, if there was a desire to preserve the pregnancy, the treatment was postponed until the end of pregnancy, and if there was a desire to further preserve fertility, then after childbirth (vaginal or abdominal) after 4-8 weeks, a wide conization of the cervix was performed. In stage IB and II cervical cancer in early pregnancy, it was recommended to perform radical hysterectomy (removal of the uterus with the fetus) with iliac lymphadenectomy. If the gestational age is more than 20 weeks, it was recommended to prolong pregnancy up to 28 weeks, when the chances of fetal viability reach 75% or up to 32 weeks (with more than 90% chances for the fetus). Delivery was carried out by abdominal access followed by a one-stage radical hysterectomy with iliac lymphadenectomy. Radiation therapy was planned in the postoperative period. In the treatment of cervical cancer stage III-IV, the standard was considered the use of combined radiation therapy in combination with chemotherapy. Given the poor prognosis at this stage of cervical cancer, treatment should be started immediately. If the fetus is viable, then a caesarean section was performed and radiation therapy was prescribed 2-3 weeks later. In the I-II trimesters of pregnancy, external irradiation was prescribed without preliminary termination of pregnancy. The recommendations proposed by the authors had a number of disadvantages, especially in terms of the treatment of cervical cancer in the early stages, where expectant tactics were used until the end of pregnancy, regardless of the gestational age and in terms of postponing treatment with a gestational age after 20 weeks by 10-12 weeks. The postponement of treatment in these life situations, preferably should not exceed 4-8 weeks, since each delayed month in the treatment of both pregnant women and non-pregnant women can worsen the prognosis of the disease.

Over the past 10 years, a new ESGO clinical recommendation has been applied on the management of pregnant women with cervical cancer. In Russia, there is a conviction among doctors about the need to terminate pregnancy at any time, not only with confirmed cervical cancer, but even with suspicion of it. Especially when cancer is detected in the 1st trimester, the situation becomes even more complicated [15,16]. In the case of prolongation of pregnancy due to a long waiting period, the invasion of the process is not excluded, up to the progression of cancer.

Five factors influence the determination of the tactics of treating patients with cervical cancer during pregnancy:

1. Stage (FIGO, TNM), tumor size
2. Histological tumor subtype
3. Duration of pregnancy at the time of diagnosis
4. Involvement in the process of regional lymph nodes
5. The patient's wishes regarding the continuation of the pregnancy.

The tactics of treating patients with cervical cancer is mainly determined by the stage of the disease, gestational age, and involvement in the process of regional lymph nodes. The main methods of treatment are surgical and drug (chemotherapy) [14,19,10]. If signs suspicious of a microinvasive process are detected, atypical conization of the cervix with a height the cone is not more than 1.5 cm. Conization of the cervix can be performed at any gestational age, but not less than 4 weeks in advance before the expected birth. At stage IA1 (invasion up to 3 mm and horizontal length up to 7 mm without vascular invasion) conization is the optimal and safe method of treatment.

If you suspect pelvic lymphatic involvement nodes, pelvic lymphadenectomy is indicated (PLAE) or sentinel lymph node biopsy [15].

Management of patients up to 22 weeks gestation with IA2 and IB1 stage and tumor up to 2 cm. At the first stage, atypical conization of the cervix with lymphadenectomy. If lymph node metastases are confirmed, termination of pregnancy should be considered. In the absence of damage to the lymph nodes, prolongation of pregnancy is possible with standard therapy after childbirth (with IA2 stage) or neoadjuvant chemotherapy (NACT) (with IB1 stage) with delayed standard treatment after childbirth [16]. Patient follow-up for more than 22 weeks with IA2 and IB1 stage with a tumor up to 2 cm. At this gestational age for staging the process, atypical conization of the cervix is performed. Pelvic lymphadenectomy is not performed due to technical limitations related to the size of the uterus. Upon confirmation of IA2 postpartum stage, standard treatment is carried out, at stage IB1, neoadjuvant polychemotherapy is started [16]. Management of pregnant women up to 22 weeks with stage IB1 and tumor up to 2–4 cm. To clarify the extent of the process, PTAE is performed. Upon confirmation of engagement lymph nodes recommended termination of pregnancy followed by standard treatment. When intact lymph nodes after 12 weeks start NAHT [16]. Pregnant women in gestation up to 22 weeks with confirmed cervical cancer IB2 and IIA stages, termination of pregnancy is recommended, regardless of the involvement of the lymph nodes [16]. After 22 weeks conduct several courses of NAHT. The last course must be completed no later than 3 weeks. before giving birth.

Neoadjuvant Chemotherapy

In case of prolongation of pregnancy in patients with locally advanced cervical cancer, NACT can stabilize the tumor process [19]. Payment the therapeutic dose and the choice of the drug are identical to those outside of pregnancy. However, it must be borne in mind that physiological changes associated with pregnancy (hemodilution, hypoproteinemia, acceleration of the glomerular filtration rate, the appearance of the third space -amniotic cavity), affect the pharmacokinetic properties of chemotherapy drugs.

Chemotherapy according to international protocols not performed in the first trimester of pregnancy due to the high risk of embryotoxic and teratogenic effects. During pregnancy, in patients with cervical cancer, chemotherapy can be performed starting from the second trimester:

Stage IB1, absence of lymph node metastases and tumor size <2 cm; with stage IB1 and tumor size 2-4 cm, in the absence of metastases in the lymphatic nodes or if it is impossible to carry out lymphadenectomy, as well as in IB2-IIB stages - until the period of reaching maturity of the fetus [43, 11]. In the overwhelming majority of cases, NACT allows you to stabilize the tumor process and prolong the pregnancy until the period of reaching the fetus of vitality and maturity. Most often the therapy regimen includes cisplatin (50-100 mg / m²) alone or in combination with paclitaxel (175 mg / m²). Courses are held every 3 weeks. [24]. Less often a combination of cisplatin (75 mg / m²) with ifosfamide 2 g / m² is used in cycles every 2 weeks. [11.35].

Tactics of delivery of pregnant women with cervical cancer.

The last course of polychemotherapy should be completed within 3 weeks before the expected due date. It's connected with the risk of giving birth to a child with suppressed bone marrow and a high probability of developing infectious complications [35,29]. Currently recommended prolong pregnancy at least until full-term (37 weeks), in the absence of such an opportunity - at least up to 34 weeks. [35,29,40]. After conization of the cervix, performed at IA1– IA2 stages, theoretically possible vaginal delivery [16]. In the case of widespread cervical cancer, the method of delivery is a corporal cesarean section followed by Wertheim's operation. The choice of delivery method depends on the stage of the disease, taking into account the patient's desire to maintain fertility [21, 8, 11, 20, 23, 41].

Conclusion

The "gold standard" of cervical cancer treatment in pregnant women still not developed. It should be recognized that the above the ESGO clinical guidelines, unfortunately, cannot answer all questions. So, for example, from our point of view, an important prognostic factor is the biological characteristics of the neoplasm, which are not taken into account in the recommendations. It is also not clear what the tactics

are treatment at advanced stages of the process and are not whether the recommended vaginal delivery is risky at stage IA2 of the disease, etc.

Nevertheless, it is advisable to follow the suggested variant of tactical approaches, taking into account the recommendations of the International Consensus Meeting on "gynecological cancers", based on the world experience. Clinical manifestations of pregnancy complicated by cervical cancer are atypical, easy to confuse with pregnancy diseases, easily concealed by pregnancy status, and difficult to diagnose. Pregnant women often neglect prenatal screening, making it difficult to detect tumors. Hence, a traditional three-step screening for cervical cancer during pregnancy is needed. When choosing a treatment plan, we must consider factors of both the fetus and the mother. In conditional hospitals, you can create a multidisciplinary counseling team (MDT). By combining patients' clinical stages, lymph node status, histological tumor types, weeks of gestation, imaging data, patient and family readiness for pregnancy, we can weigh the advantages and disadvantages and formulate an individualized treatment plan. It is the best choice for pregnancies complicated by cervical cancer. There is currently no single standard of care.

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