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Management of Pregnant Women with Cervical Cancer

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SUMMARY

Pregnancy complicated by cervical cancer is determined in the case of primary diagnosis of cervical cancer during pregnancy or after 6-12 months after childbirth. The number of pregnancies complicated by cervical cancer is small. In 1-3% of women with cervical cancer, oncology was first diagnosed during pregnancy. Of these, about half were pregnant during the diagnosis of the disease, the rest - 6-12 months after childbirth.

It is not known whether pregnancy increases the risk of onset or progression of cervical cancer. However, elevated estrogen levels and human chorionic gonadotropin are thought to activate the pro-carcinogenic effect of human papillomavirus (HPV) infection. Other researchers believe that increased blood flow and lymphatic circulation in the early phase of pregnancy with a simultaneous decrease in specific immunity and cervical dilatation may contribute to the development of cervical cancer.

RELEVANCE

Cervical cancer (CC) is the third most common oncological pathology in pregnant women (4 cases per 100,000 pregnancies [1]. Various data indicate that the 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 about the reliability of these statistics [2].

The management of oncological diseases during pregnancy includes one of the key points of maintaining pregnancy and minimizing the teratogenic effect while maintaining anti-oncological efficacy not 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 a rapidly progressive or complicated course of the disease. Induction of preterm labor should be avoided whenever possible in order to initiate anticancer treatment, due to adverse effects on the fetus [3].

In order to determine the effectiveness of gestational cancer therapy, large national and international registries have been created [4]. 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 [4]. The change in obstetric management is associated with an increase in knowledge about the natural course of cancer during pregnancy, as well as a trend towards a decrease in 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 frequency of premature caesarean sections and an increase in the frequency of induction of labor in order to initiate full-fledged anti-cancer therapy [5]. Neonatal outcomes in terms of cognitive and cardiovascular status in the first 6 years in children who were under the influence of chemotherapeutic drugs during the prenatal period did not differ from children in

the control (general) population [3,6]. However, if it is necessary to use polychemotherapy, it must be taken into account that the use in the gestational period can affect the growth of the fetus, and earlier use can cause the development of congenital malformations [4].

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

PURPOSE OF THE RESEARCH.

To study the features of the course of cervical cancer (CC) in pregnant women and develop a management algorithm.

MATERIALS AND METHODS. The study included 102 women of reproductive age diagnosed with cervical cancer (CC). The main group consisted of 66 women who applied during pregnancy, the comparison group - 36 women in whom cervical cancer was detected not during pregnancy.

The study included women in whom cervical cancer was detected in primary health care facilities, and who were sent to the regional oncological dispensaries for verification of the diagnosis and development of further tactics. All women included in the study were examined during a clinical gynecological examination in the mirrors, the diagnosis was verified during a histocytological study of the tumor tissue, the prevalence and localization features were performed using MRI of the small pelvis and transvaginal ultrasound.

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

RESULTS. The results of the study were - the outcome of the disease - recovery, relapse, metastasis, death; tumor / therapy complications - bleeding, premature birth, intrauterine fetal death.

The endpoints for evaluating the effects of polychemotherapy (PCT) in the present study were total and oncological mortality, time of onset of tumor relapses, time of onset of distant metastases, survival, and disease-free survival. In addition, pregnancy outcomes were assessed in the main group: intrauterine fetal death, premature termination of pregnancy, stillbirth, and fetal weight at birth.

In the main group, 8 women were found to have CC relapses: 2 people after 3 months, 4 people - within 9-12 months - 1 year, 2 - within 1-2 years. In the rest (58 women), no tumor recurrences were recorded during 3 years of follow-up. In the comparison group, 1 woman had a relapse within 3-6 months, 6 - 6-9 months, the remaining 29 women had no relapses within 3 years. In general, CC relapses were found with a comparable frequency in both study groups: in 8 women in the main group (12.12%) and in 7 patients in the comparison group (19.44%, chi square = 0.96, n.d.).

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 follow-up.

An analysis of 3-year survival in groups showed comparable values of survival rates, which amounted to 84.94% in the main group and 84.85% in the comparison group (calculated by the Kaplan-Meier method, Table 3.9). All deaths in the present study were oncological and

associated with cervical cancer. There were no dropouts from the study, except for oncological death, and therefore an intergroup comparison of survival was carried out using chi-square conjugation tables.

Table 3.9 Dynamics of 3-year survival of women of childbearing age with cervical cancer, depending on belonging to the clinical group

Time point	Main group (n=66)			Comparison group (n=36)			Hee square
	died	Percentage of survivors	Survival	died	Percentage of survivors	survival	
1 year	2	96.97%	96.97%	0	100%	100%	2.12, nd
2 years	2	96.88%	93.94%	2	94.44%	94.44%	0.47, nd
3 years	6	90.32%	84.85%	4	83.33%	83.33%	0.17, nd

Relapse-free survival was also assessed by the above methods. The 3-year relapse-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.).

Table 3.10 Dynamics of 3-year recurrence-free survival of women of childbearing age with cervical cancer, depending on belonging to the clinical group

Time point	Main group (n=66)			Comparison group (n=36)			Hee square
	died	Percentage of survivors	Survival	died	Percentage of survivors	survival	
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

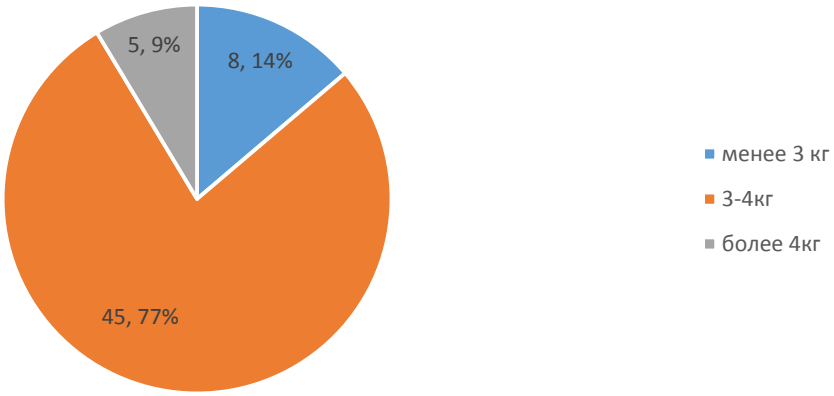
In cases of detection of damage to the body of the uterus, parametric fiber, the walls of surrounding organs (ureter, bladder), abortion and surgical treatment were performed (6 people). In the group of pregnant women with cervical cancer, pregnancy outcomes were assessed, including pathological outcomes and fetal weight at birth (Table 3.11, Fig. 3.23). The birth of live and viable children was observed in 57 women (86.36%), which indicates the safety of the applied PCT regimens during the 2-3 trimesters of pregnancy.

Table 3.11 Pregnancy outcomes in women with cervical cancer who received PCM in the 2nd and 3rd trimesters of pregnancy (n = 66)

index	Absolute Quantity	Relative share in the group
Termination of pregnancy due to the need for surgical treatment	6	9.09%
Intrauterine fetal death	2	3.03%
preterm birth	3	4.55%
Premature birth, non-viable fetus	1	1.52%
Preterm birth, viable fetus	2	3.03%
Term delivery, viable fetus	55	83.33%

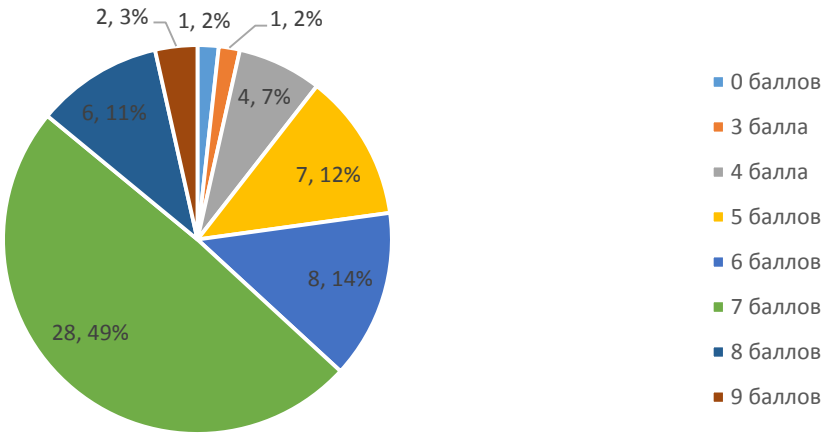
Most of the pregnancies ended in childbirth, including 83.33% - term delivery. Most of the children born were viable with a birth weight category of 3-4 kg (77%).

Figure 3.23. Fetal weight at birth (viable and non-viable fetuses) in women treated with PCT for cervical cancer in the 2nd and 3rd trimesters of pregnancy



The Apgar score (Fig. 3.24) showed that the condition of 63.16% of newborns was of moderate severity (mild asphyxia, 6-7 points), 19.30% was severe (moderate asphyxia, 4-5 points), 14.04 % - satisfactory (normal, 8-10 points) and 1.75% - extremely severe (severe asphyxia) and stillborn.

Figure 3.24. Distribution of newborns born to mothers treated during pregnancy with PCT for cervical cancer, according to the Apgar score (n= 57)



Thus, the present study showed that the use of PCT in women of childbearing age with cervical cancer is an effective method of anti-cancer treatment in both pregnant and non-pregnant women, being associated with more than 83% 3-year survival and more than 80% 3 -x-year relapse-free survival, comparable, both in the group of pregnant women and in the group of non-pregnant women. The applied PCT regimens are safe for the fetus, providing the birth of viable children in 86.36% of cases, the condition of most of which is assessed as satisfactory and of moderate severity.

CONCLUSION

Based on the results of the study, an algorithm was developed for the management of pregnant women in the aspect of diagnosis and treatment of cervical cancer (Fig. 4.1).

The algorithm is based on alertness in terms of the possibility of cervical cancer in pregnant women. To this end, the algorithm involves 1) filling out a questionnaire that includes complaints that may indicate the presence of cervical pathology (Table 1) and 2) conducting an examination of the pregnant woman at the first visit in the mirrors and filling out a form that allows you to identify possible signs of cervical cancer (Table 2) . A positive answer to at least 1 item 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.

Colposcopy should include the 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 small pelvis, as well as ultrasound of parenchymal organs and MRI of the whole body to verify the diagnosis and stage the disease.

After cervical cancer verification, the therapeutic branch of the algorithm implies PCT according to the scheme: 1) Paclitaxel 175 mg/m2 on day 1 + fluorouracil 500 mg/m2 on days 1-3 with an interval of 21 days (PF) or 2) Paclitaxel 175 mg/m2 on day 1 + topotecan 0.75 mg/m2 on days 1–3 at 21-day intervals (PT). The start of PCT is delayed until the 2nd trimester of pregnancy. Radiation therapy and surgical treatment are postponed until the pregnancy is resolved, except for cases of germination of the uterine body, parametrium and walls of adjacent hollow organs, when abortion is required and urgent surgery with the most complete excision of the tumor, surrounding tissue and regional lymph nodes.

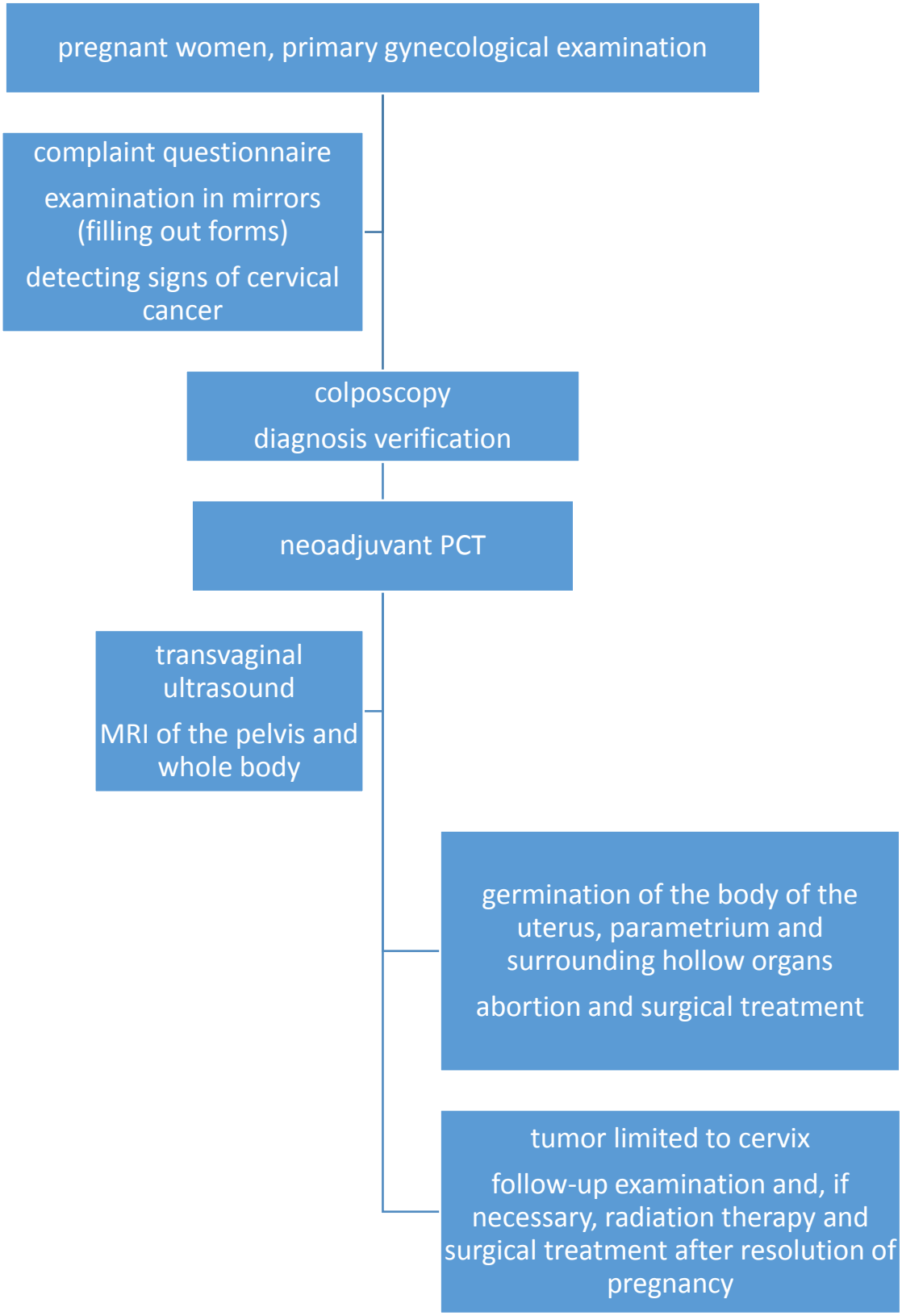


Figure 1. Pregnancy management algorithm for timely detection of cervical cancer and determination of tactics

The application of the developed algorithm makes it possible to most effectively and quickly diagnose cervical cancer in pregnant women and start early chemotherapy to prevent progression and regression of the tumor.

CONCLUSIONS

1. CC in pregnant women is associated with a higher number of pregnancies and abortions in anamnesis, compared with women of comparable age in whom CC did not develop during pregnancy. CC in pregnant women was associated with contact bleeding in 80.30% of cases versus 63.89% in non-pregnant women (p <0.01), as well as with a higher incidence of pre-carcinogenic background CC pathology (69.70% versus 41.67% in non-pregnant women, p <0.01) and cervical epithelial dysplasia CIN II (21.21%, p <0.05).
2. In non-pregnant women, CC is diagnosed more often within 1 month after the onset of the first symptoms of the disease, and in pregnant women, more often at a later date (p <0.01).
3. In pregnant patients, CC is more often characterized by a primary cervical localization compared with non-pregnant patients (81.82% vs. 58.33%, chi square = 6.49, p <0.05). The nature of growth is often exophytic (51.52%), palpation characteristic is dense (81.82%), immobile (96.97%), stage - 2c (51.52%) and T 2 N 0 M 0 (51, 52%), histological structure - squamous nonkeratinizing cancer (81.82%), moderately differentiated (61.62%).
4. Colposcopy in pregnant women allows in all cases to detect cervical cancer, to 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 consisting of 1) Paclitaxel 175 mg/m2 on day 1 + fluorouracil 500 mg/m2 on days 1-3 with an interval of 21 days (PF) and 2) Paclitaxel 175 mg/m2 on day 1 day + topotecan 0.75 mg/m2 on the 1st - 3rd days with an interval of 21 days (PT) in the amount of 1-9 courses in pregnant women suffering from cervical cancer allows 69.70% to achieve partial regression of the tumor and subjective improvement health status (63.64%). The 3-year survival rate of pregnant women with cervical cancer against the background of the use of PCM is 84.85% and does not differ from that in non-pregnant women of childbearing age with the same pathology.
6. 9.09% of pregnant women with cervical cancer require termination of pregnancy and surgical treatment with the maximum possible excision of the tumor due to damage to neighboring organs. Intrauterine fetal death and the birth of a non-viable child are noted in 4.55%. 86.36% of pregnancies of women with cervical cancer against the background of PCM using pacldítaxel, fluorouracil and topotecan end in the birth of viable children, most of which (77.20%) have an Apgar score of 6 points or higher

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