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CANCER DURING PREGNANCY AND POSSIBLE TREATMENT OPTIONS - LITERATURE REVIEW

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ABSTRACT

Cancers during pregnancy are a relatively rare phenomenon, but the risk of developing them increases with a woman's age. As more women choose to become pregnant at an older age, the incidence of cases may rise in the future. This article discusses the diagnosis and treatment of the most common cancers in pregnant women: breast cancer, cervical cancer, ovarian cancer, thyroid cancer, colorectal cancer, lung cancer, lymphomas, and melanoma. The aim of this work is to present optimal methods for the treatment and diagnosis of cancers during pregnancy, as the approach for pregnant patients is limited in options.

Methods: We analyzed scientific papers on the safety of diagnostics and treatment of breast cancer, cervical cancer, ovarian cancer, thyroid cancer, colorectal cancer, lung cancer, lymphomas, and melanoma. We used PubMed, Google Scholar, and specialized literature to search for information.

Conclusions: Due to the limited options for treatment and diagnosis in pregnant women, each case of illness should be considered individually, with an assessment of potential risks and benefits for both the mother and the child. Increased oncological vigilance should be maintained in pregnant women since some pregnancy symptoms often overlap with the initial symptoms of cancer.

Keywords: medicine, cancer, pregnancy, radiotherapy, chemotherapy

INTRODUCTION

The coexistence of a cancer process with pregnancy is rare, but the increasingly later age at which pregnancy occurs is one of the reasons for the gradual increase in the incidence of cancer in pregnant women. The state of immunological tolerance that occurs physiologically during pregnancy may facilitate the spread of cancer due to the production of the so-called fetal immunosuppressive factor. In vitro studies have shown that estrogens, glucocorticosteroids, hCG and AFP have an inhibitory effect on the natural response of lymphocytes. This weakens the body's immune response to the onset of cancer. Additionally, symptoms of cancer may be interpreted by patients as a sign of the body's adaptation to a new condition, such as pregnancy. During the physiological course of pregnancy, the concentration of some tumor markers increases, including CA-125, AFP, beta-hCG, which also makes it difficult to recognize pathological changes. [11,8,28]

Cancers occurring during pregnancy can be divided into benign and malignant. Cancer treatment in pregnant women, depending on the clinical case, is divided into surgery, chemotherapy and radiotherapy. In our work, we want to focus on the diagnosis and treatment of malignant tumors.

Table No. 1 Examples of benign and malignant tumors occurring in pregnant women.

BENIGN TUMORS	MALIGNANT TUMORS
Fibromyoma	*Breast Cancer*
Mature Ovarian Teratoma	*Cervical Cancer*
Ovarian Cystadenoma	*Ovarian Cancer*
Corpus Luteum Cyst	*Lymphoma*
Endometrial Cyst	*Melanoma*
	Thyroid Cancer
	Colon Cancer
	Lung Cancer

METHODS

We thoroughly analyzed articles available on PubMed, Google Scholar, and specialized literature.The aim of our work was to present the phenomenon of cancer occurring during pregnancy, as well as the possibilities of their diagnosis and treatment. This work will bring the topic closer to doctors and make them aware of the scale of the problem as well as the elements they must pay attention to in their clinical practice.

RESULTS AND DISCUSSION

DIAGNOSTIC PROCEDURES IN PREGNANCY AND THEIR SAFETY

The examinations involving ionizing radiation are possible to conduct on pregnant women, provided that the single dose does not exceed 100mGy to the fetus.Below this dose, there are no negative effects such as miscarriage or fetal developmental disorders. Therefore, X-ray, CT, and isotope examinations are contraindicated during pregnancy.[45] The use of abdominal shielding during pregnancy is not recommended, as most of the dose reaching the uterus and fetus comes from internal scatter [2]. In justified situations, a chest X-ray and mammography can be performed. CT of the head, cervical spine, limbs, and chest provides 8-30 mGy, so theoretically it can be performed in pregnant women. However, these examinations are not routinely recommended due to the lack of known data on scattered radiation dose.[42]

18F-FDG PET-CT has a significant impact on the treatment of cancers related to pregnancy and does not seem to cause adverse effects on the fetus, suggesting that the examination is feasible during pregnancy as the benefits to the mother outweigh the risk to the fetus.[19] Another radioisotope, iodine-131 (131I), penetrates the placenta and remains in the fetus for several days (i.e., the half-life is 8 days), potentially damaging the fetal thyroid, especially after 10-12 weeks of pregnancy [50].

Currently, there are no contraindications for ultrasound examinations. So far, there is no evidence of harm to the fetus from an MRI examination performed at a field intensity of 1.5 T or 3 T.[30] Magnetic resonance imaging is safe for pregnant women, especially in the 2nd and 3rd trimesters. It is performed in justified cases without the use of contrast-gadolinium. Studies in animals have shown that gadolinium passes through the placenta, and therefore its level may increase in the fetus, potentially leading to its damage. [16]

SAFETY OF TREATMENT

SURGICAL TREATMENT

Most solid tumors require surgical treatment. Both the procedure and anesthesia adversely affect the fetus. The use of anesthetics in the first trimester of pregnancy increases the risk of miscarriage. Therefore, it is recommended to perform surgery in the 2nd trimester, when the size of the fetus allows for abdominal interventions. [38,15] During the operation, it is recommended to reduce pressure on the inferior vena cava by placing the patient on the left side from the 20th week of pregnancy. Tocolytics should not be administered during surgery unless uterine contractions are observed.

Laparoscopic procedures result in fewer adverse events for the fetus and mother compared to laparotomy and should be chosen for oncologically safe procedures, performed by an experienced surgeon, with limited operation time (90–120 min) and low intra-abdominal pressure (10–13 mmHg). Pelvic lymphadenectomy can be performed up to 22 weeks of pregnancy, both by laparotomy and laparoscopy. In later stages of pregnancy, the size of the uterus prevents a complete pelvic lymph node dissection and should be avoided. [3,43]

In the case of surgery performed after the 24th week of pregnancy, the patient should be informed about the possibility of performing a cesarean section in case of a threat to the child's life [3].

CHEMOTHERAPY

Chemotherapy administered during the embryonic phase of conception is dangerous and can lead to a miscarriage. In the case of cancer diagnosis in the 2nd or 3rd trimester of pregnancy or when there is a possibility to delay the start of chemotherapy beyond the 14th week, the risk of serious problems for the fetus is low, and there is no need to terminate the pregnancy. [27] During the first trimester, intense fetal organogenesis occurs, and chemotherapy can induce a teratogenic effect, especially in organs such as the heart, limbs, palate, kidney tubule, eyes, and ears. [66] Thus, administering cytotoxic drugs in the first trimester is associated with the risk of malformations, embryo death, and spontaneous miscarriage. The risk of malformations is 7-17% with single-agent treatment, and it increases to 25% with combination therapy. [24]. Furthermore, the use of chemotherapy in the second or third trimester of pregnancy has little effect on the long-term outcomes of the child, as shown in several studies, favoring its use in controlling cancer in pregnant women. [12,13].

Many drugs used in the treatment of malignant tumors have a low molecular weight and are lipid-soluble, which promotes passive diffusion through the placenta. [26] The absorption of drugs during pregnancy is also influenced by changes in gastric secretion and motility, an increase in progesterone concentration, and hemodynamic changes occurring during pregnancy. The drug concentrations in the fetus are always lower compared to those in the mother's body, but they vary between drugs. Marginal penetration to the fetus occurs with paclitaxel - 0%-1%, whereas with carboplatin, it is relatively high - 60%.

The most teratogenic drugs include antimetabolites and alkylating agents, the use of which in the 1st trimester of pregnancy is associated with fetal damage in 20% of cases and congenital malformations in 14% of cases. The most harmful antimetabolites are aminopterin and methotrexate, as well as cytarabine arabinoside. Among the alkylating agents, the highest risk pertains to chlorambucil, chlormethine, and cyclophosphamide. [65,3]

Methotrexate administered in the first trimester of pregnancy can lead to fetal demise or a congenital malformation syndrome [14]

The safest for pregnant women appear to be doxorubicin and epirubicin. It was found in 20 breast cancer patients treated during pregnancy that weekly administration of epirubicin is effective and safe. Epirubicin may be safer than doxorubicin because it shows slower transfer through the placenta. [45]

RADIOTHERAPY

Guidelines for irradiating pregnant women are not established, so the decision and course of action for each patient must be individualized. Radiotherapy is undertaken in special cases. It is not recommended to irradiate from 8-11 weeks of pregnancy due to the embryonic and organogenesis process, and in the 3rd trimester of pregnancy due to the position of the fetus and the high position of the uterus. In the case of Hodgkin's lymphoma in the supradiaphragmatic location, radiotherapy is rarely performed in the 1st or 3rd trimester of pregnancy when there is disease progression during pregnancy or there is no possibility of observing disease progression.[36,51]

The radiation doses used in cancer treatment are much higher than the doses used in diagnostics - they range from 4000–7000 cGy (40–70 Gy). The amount of damaging dose that the embryo or fetus will receive depends on the therapeutic device used, the target dose, the size of the radiation field, the distance from the field edges to the fetus, the technique used, and the type of radiation. The dose can be reduced by reducing the fields and increasing the distance between the field edges and the fetus. Increasing this distance to over 30 cm reduces exposure by 4–20 cGy compared to non-pregnant patients. [60,5]

The safe and permissible dose for the fetus is 10–15 cGy. Therefore, irradiation of the abdominal area in pregnant women is absolutely prohibited. However, treatment of cancers of the head and neck, breast, lungs, brain, and bones (except the pelvis) is permissible, especially when monitoring the doses received by the fetus and when using lead shielding.

The risk of developmental defects decreases with increasing gestational age. Deferring cancer treatment until delivery is justified in very few cases[47,60]

In children exposed to a dose of 10 mGy in fetal life, there is one death from cancer in 1700 individuals aged 0 to 15 years [29]

Adverse effects of radiation in the first trimester of pregnancy include: miscarriages and disorders of organogenesis. After the completion of organogenesis, the most sensitive to damage are the reproductive system, bone marrow, and the central nervous system. Fetal exposure to radiation in the second and third trimesters of pregnancy may result in delayed intellectual development, epilepsy, and secondary tumors in children (mainly leukemias and solid tumors) [57,58]

CANCERS OCCURRING DURING PREGNANCY

BREAST CANCER

Breast cancer (BC) is the most commonly diagnosed cancer during pregnancy. In pregnant women, it is defined as cancer diagnosed during pregnancy or within 1 year after delivery. Nearly 1 in 3,000 pregnancies are complicated by BC, and approximately 10% of BC patients under the age of 40 develop the disease during pregnancy.[6] Because breasts change with pregnancy, these changes pose certain challenges for diagnosis, monitoring, and treatment breast cancer.[54] The diagnosis is made much later in pregnant women than in non-pregnant women. This is important from the point of view of prognosis, because delaying diagnosis by each month increases the risk of metastases to regional lymph nodes by 0.9-1.8%. [11]

The mammary gland is a dynamic organ that undergoes significant changes during the menstrual cycle, development, pregnancy, lactation and involution. Normal mammary gland development and homeostasis is a stem cell-driven process, and key signaling pathways have been identified that control these processes. Evidence shows that the same genes that control the physiological development and function of organs are often dysfunctional in cancer.[25]

The diagnostic procedure in pregnant women is very similar to that in non-pregnant women. The essential stages and diagnostic requirements in a pregnant woman are based on a clinical examination, imaging tests and histological assessment. The basis is palpation, and each change in the breast must be verified by ultrasound examination. [11] The most common symptom of breast cancer in pregnant women is the appearance of a painless lump detected by the patient or gynecologist during a periodic check-up. Digital mammography is also an imaging test necessary for diagnosis. The radiation that reaches the fetus is 0.004 Gy (0.4 mrad), it should be noted that only a dose above 0.05 Gy (5 rad) is toxic to the fetus. [11]

Chest X-ray examination using fetal shields is allowed and safe for pregnant women and should be performed if necessary. MRI examination, either of the breasts or other areas of the body, is not routinely recommended. There is no mandatory contraindication to this test, even in the first trimester of pregnancy, although it should be performed only when the MRI result will have a decisive impact on the therapeutic procedure. CT, PET, bone scintigraphy and computed tomography are contraindicated due to adverse effects observed in the fetus. To assess bone involvement by the tumor, non-contrast MRI is recommended. [11,32]

The final step in the diagnosis of breast cancer during pregnancy is histopathological examination. It is recommended to perform a core needle biopsy of suspicious lesions under ultrasound guidance. The test result provides information on the histological type of the tumor, assessment of the expression of estrogen and progesterone receptors and the expression of human epidermal growth factor receptor 2 (HER2) and Ki67. [31,32,54,11] Breast cancer diagnosed during pregnancy is usually a ductal carcinoma, poorly differentiated (G3) with overexpression of the HER2 receptor. Coexistence of tumor lymphatic vessel invasion is often observed.[11]

Treatment

The choice of breast cancer treatment method in pregnant women depends on the gestational age and the stage of advancement of the cancer. Surgical treatment is safe at any stage of pregnancy. [31]

If a patient has pain resulting from metastatic disease, it may be necessary to seek help from a palliative care specialist or an anesthesiologist experienced in running a pain clinic. The recommended drug for pregnant women according to the analgesic ladder is paracetamol. If it is necessary to use stronger drugs, morphine preparations can be used.[4]

1st Trimester of Pregnancy

After diagnosis of invasive breast cancer in the first trimester of pregnancy, surgical treatment is recommended. Mastectomy with lymphadenectomy should be performed if lymph node metastases are found, or mastectomy with SLNB if the lymph nodes are clinically unchanged.[1] It is completely safe to administer a colloid with the Tc-99m isotope to perform lymphoscintigraphy before SLNB.[32] During SLNB, the administration of a dye, e.g. methylene blue, is contraindicated due to the risk of causing anaphylactic

shock. [31]

Chemotherapy, radiotherapy, hormone therapy and targeted therapy in the first trimester of pregnancy are contraindicated. [11]

2nd and 3rd Trimester of Pregnancy

In the second and third trimester of pregnancy, all surgical procedures that are performed on non-pregnant women can be performed. Conserving treatment may be used when the expected start of radiotherapy is after the due date.

Indications for chemotherapy are based on the analysis of predictive factors and the stage of cancer advancement. The risk of teratogenicity of drugs used in the treatment of breast cancer depends on the type of active substance, dose and frequency of administration and is approximately 1.3%. The CMF regimen (cyclophosphamide, methotrexate, fluorouracil) is absolutely contraindicated.[11] The mechanism of methotrexate teratogenicity is best known. The use of this drug may cause fetal death or the development of a set of congenital defects, such as mandibular hypoplasia, delayed ossification of the skull base, limb deformities and defects of the nervous system.[59] The degree of transplacental penetration of cytostatics indicates the possibility of safe use of anthracillins and taxoids.

Platinum derivatives may be used in the treatment of patients diagnosed with triple-negative breast cancer (TNBC). Carboplatin should be the cytostatic of choice if a decision is made to use this group of drugs in a pregnant woman.[35] Chemotherapy in pregnant women may cause transient myelosuppression in newborns, which disappears naturally 2-3 weeks after delivery. For this reason, chemotherapy should not be used in women over 34 weeks of pregnancy or a decision should be made to give birth within 3 weeks of the last administration of chemotherapy drugs.[35]

Monotherapy is not recommended for the treatment of breast cancer in pregnant women. The use of radiotherapy, hormone therapy and anti-HER2 therapy is contraindicated. [11]

The treatment for breast cancer after giving birth is the same as for non-pregnant women. Due to the use of therapy, lactation should be stopped.[11]

One of the most important aspects of breast cancer treatment in pregnant women is ensuring fetal safety. Therefore, doctors try to choose the safest treatment methods for mother and baby, minimizing the risk of harmful effects on pregnancy. It is important for pregnant women to regularly examine their breasts and report any disturbing symptoms to their doctor. Early detection of breast cancer increases the chances of effective treatment and improved prognosis for the patient and her child.

CERVICAL CANCER

Cervical cancer (CC) is one of the main malignant tumors occurring in women during pregnancy. The percentage incidence of cervical cancer among all gynecological cancers is as high as 71.6%, followed by ovarian cancer, which accounts for 7%. The occurrence of CC during pregnancy is not very common, and the symptoms can be easily confused with completely separate gynecological diseases. [44] Diagnosis of this cancer occurs with an incidence of 0.8-1.5/10,000 pregnancies. Cervical cancer is preceded by cervical intraepithelial neoplasia (CIN). In pregnant women, CIN occurs with a frequency of 3.4 - 10%. CIN in pregnancy most often occurs in the form of LSIL, i.e. low-grade intrasquamous lesions, which include CIN1 and lesions caused by HPV infection. High-grade HSIL changes include CIN2 and CIN3. These occur quite rarely in pregnant women, approximately 0.1-1.8%.[7] Due to the natural course of CIN, the only indication for treatment is suspected cervical cancer.[1]

CIN diagnosis is based on a cytological test, which is safe for the mother and fetus. They should be performed during the first gynecological visit of a pregnant woman, regardless of the date of the last cytological examination. [55]Abnormal test results are an indication for colposcopy. When abnormalities are detected, a sample should be taken for histopathological examination. [1]

Collecting tissue material from the cervix in pregnant women is safe regardless of the gestational age, but curettage of the cervical canal is absolutely contraindicated due to the risk of pregnancy loss.[23]

Cervical intraepithelial neoplasia during pregnancy is most often asymptomatic or it is accompanied by non-specific symptoms such as vaginal discharge, itching or contact spotting, which leads to a high risk of developing cervical cancer. [11]

Invasive cervical cancer is one of the most common oncological causes of death among women in the world. Symptoms such as vaginal bleeding or vaginal discharge are often interpreted by the patient as specific pregnancy-related disorders. The diagnosis is based on speculum examination and cytological examination of smears from the disc and cervical canal. [11] The scope of treatment depends on the pregnant woman's plans for carrying the pregnancy to term, the advancement of the disease process, the desire to maintain fertility and the gestational age.

Uterine-sparing treatment involves termination of pregnancy and radical trachelectomy.

If the patient wants to maintain the current pregnancy, the treatment depends on the advancement of the cancer process and the age of pregnancy. Treatment of cervical cancer should begin in the second trimester of pregnancy. At this gestational age, the choice of therapy is made according to the FIGO classification.

In stage IA1, the treatment of choice is cervical conization. It is a diagnostic and therapeutic procedure to remove abnormal tissue.[1,11]

When the stage of the cancer is between IA2-IB1, we perform pelvic lymphadenectomy. Depending on the result, we use conization when the lymph nodes are not involved or neoadjuvant chemotherapy when the lymph nodes are involved.

Once the fetus reaches respiratory maturity in the third trimester, the pregnancy should be terminated by cesarean section.[11]

If cervical cancer is diagnosed in a pregnant woman, treatment is complex and must be carefully considered to ensure the safety of mother and baby. Treatment of cervical cancer during pregnancy requires cooperation between specialists in gynecological oncology and obstetrics. As with breast cancer, regular screening and awareness of the symptoms of cervical cancer are key to early detection and treatment of the disease. Pregnant women should report any disturbing symptoms to their doctor and follow recommendations regarding preventive examinations.

OVARIAN CANCER

Ovarian cancer is one of the most frequently diagnosed cancers in pregnant women. The incidence of concomitant adnexal tumors during pregnancy is estimated at 0.15–5.7%, while ovarian cancer causes complications in 1 in 15,000 to 1 in 32,000 pregnancies and is the second most frequently diagnosed gynecological cancer during pregnancy. [56,20]

The therapeutic process is complicated due to its location near the developing fetus and the risk of chemotherapy-related toxicity. The largest percentage are epithelial tumors (49–75%), while sex cord tumors occur in 9–16% and germ cell tumors in 6–40%. [56,39]

Due to frequent diagnostic tests (both ultrasound and full gynecological examination) of pregnant women, ovarian cancer diagnosed for the first time during this period is often at a less advanced stage than in non-pregnant women. Symptoms of acute abdomen caused by rupture or twisting of the ovary affected by cancer are the first symptoms of the disease among 1/4 of patients. The diagnostic and therapeutic process should begin with an ultrasound examination, and the diagnosis should be confirmed after laparotomy/laparoscopy, optimally between the 13th and 16th week of pregnancy. [56] It is recommended that if access is difficult and it is not possible to reliably assess the sinus of Douglas and the pelvic peritoneum, reoperation should be performed after delivery. Patients considering pregnancy should undergo cystectomy or adnexectomy, followed by platinum-based chemotherapy and cytoreductive surgery to the extent possible after delivery. There is no evidence of a worsening prognosis in pregnant women diagnosed with ovarian cancer [39]. Due to changes occurring during pregnancy and the possibility of obtaining false results, diagnosis using tumor markers is not recommended. [56,39]

In a retrospective analysis of 83 pregnant women conducted by Szczepańska M., Rajewski M., Skrzypczak J., it was found that only 27.5% of patients reported pain. The most common histopathological diagnosis was mature teratoma (37.9%) followed by serous cyst (34.5%). 86% of the operated pregnant women gave birth to healthy children on time, and no complications during pregnancy were observed. In 85% of patients without surgical intervention during pregnancy, regression of changes was observed within 6 weeks of delivery.

This confirms the high diagnostic value of ultrasound performed routinely during follow-up visits in pregnant women, as it reduces the frequency of surgical interventions among patients diagnosed with ovarian cancer. According to research results, it seems that the rate of premature births is higher among pregnant women who decided to undergo surgery. [62]

The treatment method for pregnant patients is determined based on the initial diagnosis, FIGO stage and gestational age. [56]

The optimal treatment of non-epithelial ovarian cancers, such as dysgerminoma or teratoma, is usually to remove the affected ovary together with the fallopian tube and omentum, and to collect lavages and perform a biopsy from the peritoneal cavity. It is recommended to limit interference with the uterus whenever possible. If chemotherapy is necessary, regimens consisting of paclitaxel and a platinum derivative are recommended, while BEP (bleomycin, etoposide, cisplatin) is used as second-line therapy. [56]

In the case of borderline epithelial tumors, the treatment of choice is to perform unilateral adnexectomy, omentectomy, collection of washings and peritoneal cavity biopsy) without lymphadenectomy by laparotomy or laparoscopy. It is very important to maintain the continuity of the removed tumor and not cause it to burst. In case of simultaneous involvement of both ovaries, surgical intervention may be considered after the 13th week of pregnancy. There are no indications for chemotherapy. [56]

When diagnosing epithelial malignant tumors, the treatment depends on the stage of advancement. In stage IA (G1), surgical intervention (a procedure such as in borderline tumors) without lymphadenectomy is sufficient. It is important to ensure that the continuity of the tumor is uninterrupted during surgery. In stages IA (G2) to IIA, adjuvant chemotherapy should be considered in a regimen consisting of cisplatin or carboplatin and paclitaxel. Doses and regimens are selected in a similar manner to non-pregnant patients. Fetal biometry is recommended after each chemotherapy cycle, and delivery should occur between 35 and 37 weeks of pregnancy after a break of at least 3 weeks since the last cycle. In the case of more advanced changes, the choice of therapeutic procedure depends on the patient's will to maintain the pregnancy and gestational age. If the patient decides and wants to preserve the pregnancy, it is recommended to avoid suboptimal surgical interventions because they do not improve the prognosis and increase the risk of fetal loss. [56]

Moreover, regardless of the diagnosis, surgery is recommended after pregnancy to revise and assess the advancement of the disease. [56]

It was noted that laparoscopy, compared to laparotomy, is associated with a shorter hospital stay, shorter operation time and fewer side effects in the fetus. Moreover, premature contractions occur more frequently in pregnant women undergoing laparotomy for ovarian tumors than in patients undergoing laparoscopic surgery. However, it should be remembered that laparoscopy may cause uterine perforation, hypercapnia and reduced blood flow due to increased intra-abdominal pressure and carbon dioxide consumption. [20]

The entire diagnostic and therapeutic process in pregnant patients diagnosed with an ovarian tumor should take place in a multidisciplinary team, which should include specialists in gynecological oncology, perinatology and neonatology, and psychological care should also be provided. The goal should be optimal anticancer treatment for the mother and ensuring the safety of her unborn child. [56,20]

LYMPHOMA

The diagnosis of lymphoma in pregnant patients is rare. It is a therapeutic challenge that requires the use of an optimal treatment method for the mother, taking into account the minimal risk to the developing fetus. A multidisciplinary team consisting of an obstetrician-gynecologist, an anesthesiologist, a hematologist, a neonatologist and a psychologist should be involved in the diagnostic and therapeutic process. The choice of the optimal treatment regimen depends on the trimester of pregnancy at the time of diagnosis, the histological type of cancer, the stage of disease advancement and the presence of life-threatening symptoms. [48,49]

Hodgkin's lymphoma is diagnosed in 1:3,000, while non-Hodgkin's lymphomas (diffuse large B-cell lymphoma, T-cell lymphoma, Burkitt's lymphoma and clinically advanced immunoblastic lymphoma) are diagnosed in 1:5,000 pregnancies. The pathogenesis, clinical picture, response to therapy and overall survival after optimal treatment of lymphoma in pregnant women do not differ from those in non-pregnant women.

The frequency of diagnosis of lymphomas during pregnancy depends on the frequency of occurrence

lymphomas in young women and their fertility rate. Given that the incidence rate of Hodgkin's lymphoma among young women has increased over the past decade, it is possible that diagnosis of lymphoma during pregnancy will become more common. However, the late age of the pregnant woman influences the increase in the frequency of non-Hodgkin's lymphoma diagnoses. [56,49]

The diagnostic test used to assess the size of lymphoma is ultrasound. To determine the stage of progression, a physical examination is used (particular attention should be paid to the presence of B symptoms), laboratory tests, and sometimes also a bone marrow trepanobiopsy. Other tests useful in non-pregnant patients, such as PET/CT, CT or X-ray, are not applicable here due to their teratogenic effect on the fetus. If necessary, an MRI scan may be performed. The diagnosis of the type of lymphoma is based on histopathological examination of the collected lymph node. It is important to regularly monitor the condition of the fetus using ultrasound. [56]

According to the latest reports, the optimal therapeutic strategy is to postpone treatment until the first trimester of pregnancy, and in some patients even until the postpartum period. Unfortunately, there is still no detailed data on the impact of new drugs used in the treatment of lymphoma in pregnant women and their toxicity to the fetus. [48]

MELANOMA

It accounts for approximately 6% of all cancers occurring during pregnancy. It is believed that pregnancy leads to a state of immunosuppression, which favors the development of cancer. [22]A characteristic feature of pregnant women is that their skin lesions become more pigmented. This makes it more necessary to examine these lesions using a dermatoscope and, in case of diagnostic doubts, perform an excisional biopsy and histopathological examination of the lesion. Each new nevus should also be subject to detailed diagnostics. That is why it is so important to educate pregnant women and make them aware of it. [34] This is the only way to establish a reliable diagnosis of melanoma. [56] Minor excisional procedures are considered safe during pregnancy. [52] Melanoma is the most common cancer that metastasizes to the placenta and fetus, therefore, if a pregnant woman suffered from melanoma, after delivery the placenta must undergo a thorough pathological evaluation for the presence of metastases of this cancer. If such metastases are detected, the newborn is closely monitored for the development of this cancer. This is due to the serious consequences of its occurrence in a newborn; some scientific reports estimate that the mortality rate among these children may be up to 25%. [56,53]

Treatment of melanoma is based on its surgical excision with a margin of healthy tissue, which depends on the size of the infiltration. During the procedure, a sentinel node biopsy is performed and, if metastases are present, the lymph nodes are removed. Procedures requiring anesthesia, such as wide excision of the lesion or removal of lymph nodes, should be performed in the second trimester. They should be avoided in the first trimester to avoid pregnancy loss. [52] Delaying surgery could potentially impact the patient's prognosis and should be discussed in detail with the patient.When diagnosing cancer, it is often necessary to perform various imaging tests that allow us to assess the stage of the cancer and possible metastases. During pregnancy, it is very important to select diagnostic methods so that they are not harmful to the fetus. [17] Ultrasound and magnetic resonance imaging are recommended. [52]

It was once believed that pregnancy had a negative impact on the course of melanoma. However, current research shows no differences in the prognosis of women with or without melanoma in the early stage of the cancer. However, in more advanced situations, pregnant women are at greater risk of recurrence. [52]

Advanced melanoma may predispose to premature birth, low birth weight, higher rates of pregnancies ending in cesarean section, and miscarriage. [52]

THYROID CANCER

Thyroid cancer occurs in 14 out of 100,000 people pregnancies. We examine the thyroid gland using ultrasound, but we assess its function using thyroid hormones.

Ultrasound lesions larger than 1 cm or lesions of oncological concern (e.g. uneven shape, abundant vascular pattern, calcifications) should be subjected to fine needle biopsy regardless of the period of pregnancy. [56]

It is believed that high levels of beta hcG, which stimulates the thyroid gland to produce hormones, may be responsible for the occurrence of cancer during pregnancy. [37]

If we diagnose a cancer that grows rapidly during pregnancy, we should perform total or subtotal thyroid resection in the second trimester.

If it is an early stage cancer or small papillary cancer, surgery can be postponed until after childbirth. However, the patient should be closely monitored and ultrasound should be performed at least once a trimester. If the tumor enlarges by 20% or lymph node metastases occur, the patient should be operated on. [56]

After surgery, treatment with levothyroxine should be initiated because thyroid hormone deficiency during pregnancy may be very harmful to the child's development. [37]

Treatment with iodine isotope and tyrosine kinase inhibitors is contraindicated during pregnancy. [61]

COLORECTAL CANCER

Colorectal cancer is the most common gastrointestinal tumor during pregnancy. The risk of this tumor is estimated at 0.028 per 1000 births.[18] 85% of the tumors are located in the lower third of the colon, mainly in the rectum. Pregnancy masks the symptoms of colorectal cancer, making diagnosis challenging. Various factors affect the different course of the disease during pregnancy, including increased blood flow and lymphatic drainage in the pelvic organs, altered immunomodulation, and elevated levels of steroid hormones.

Characteristics that distinguish the course of colorectal cancer during pregnancy include a longer duration of symptoms before diagnosis, more frequent localization in the rectum (86% of cases), more common metastasis to the ovaries, and a higher percentage of the mucinous histological form of cancer.[9]

In pregnant women, a frequent correlation between the occurrence of cancer and genetic syndromes can be observed, such as Lynch syndrome, familial adenomatous polyposis syndrome, Peutz-Jeghers syndrome, and juvenile polyposis syndrome.[63]

Diagnosing colorectal cancer during pregnancy is often delayed because the symptoms accompanying this type of tumor usually overlap with those of a normal pregnancy. Rectal bleeding, a symptom that occurs with colorectal cancer, is attributed to hemorrhoids during pregnancy. Other symptoms that may accompany colorectal cancer, such as nausea, vomiting, abdominal pain, abdominal bloating, constipation, back pain, anemia, and changes in bowel habits, are considered normal symptoms of pregnancy. Consequently, diagnosing this tumor can be significantly delayed, worsening the prognosis for pregnant patients. [41,21]

Diagnosing and determining the stage of colon cancer in pregnant women is not easy. Diagnosis of colorectal cancer during pregnancy includes chest X-ray or CT scan (not recommended in early pregnancy), abdominal and pelvic ultrasound, and endorectal ultrasound. The sensitivity of ultrasound is estimated at 75%. An MRI examination and colonoscopy or sigmoidoscopy with biopsy sampling can also be performed. [56,67]

In most pregnant patients, colorectal cancer is diagnosed after the 20th week of pregnancy, and the prognosis is unfavorable (stage C and D according to the Dukes classification).

Treatment includes surgical intervention, radiotherapy and chemotherapy. If the diagnosis is made before the 20th week of pregnancy, the optimal treatment is radical excision of the lesion with neoadjuvant chemotherapy initiated after the first trimester of pregnancy. If diagnosed after 20 weeks of pregnancy, treatment should be postponed until the postpartum period. Radical therapy can then be started 1-2 weeks after the end of pregnancy. If the disease is very advanced at an early stage of pregnancy, consideration should be given to discontinuing it or starting palliative treatment - chemotherapy based on fluonrouracil in the second and third trimester. It should be remembered that in the case of rectal cancer, delivery should be performed by cesarean section because the local growth of the tumor mass may make physiological delivery difficult.

The prognosis in pregnant patients is similar to that of non-pregnant with the same stage of disease progression. [56,67]

LUNG CANCER

Lung cancer is diagnosed in pregnant women with a frequency of 57:100,000 pregnancy.[11] 82% of patients had non-small cell cancer, mainly adenocarcinoma, at a significant stage, i.e. 97% of cases had clinical stage III and IV. [48]Lung cancer in pregnancy is most often diagnosed in the second trimester, and the average age is 38 years. 60% of cases were women who smoked tobacco products.[67] Most patients survived 3-9 months, and 12% of women died within one month after delivery.[56]

A pregnant woman with suspicious symptoms, such as chronic cough and recurrent pneumonia that does not respond to antibiotic therapy, should be tested for lung cancer. In each case, a chest X-ray should be taken. This test is considered safe for the fetus due to the low radiation dose. [11] In case of a suspicious result, it is necessary to deepen the diagnostics with a magnetic resonance imaging (MRI) examination to assess the degree of tumor spread. In 18% of cases, metastases to the placenta are detected, and in 5% to the fetus. For this reason, a histopathological examination of the placenta should be performed and diagnostics should be extended in the child after delivery. [10]

Treatment

Therapeutic treatment depends on the gestational age and the stage of the cancer. In most cases, treatment is carried out after delivery.[11]

Chemotherapy based on platinum compounds is used in combination with vinorelbine, taxanes, gemcitabine or etoposide.[40]

Labor is usually induced before term, usually around 35 weeks of gestation.[11]

It is very difficult to develop guidelines for the management of lung cancer in pregnant women due to the rarity of such clinical cases, limited experience and poor prognosis. The patient should be informed about the limited therapeutic options so that she can make an informed decision about whether to continue the pregnancy. If she wishes to carry the pregnancy to term, platinum-based chemotherapy combined with vinorelbine or taxoids may be offered after the first trimester of pregnancy.[10,40]

CONCLUSIONS

Cancer in pregnant women is a complex issue that requires a multidisciplinary approach in terms of diagnosis and treatment. Taking into account the developing fetus, many diagnostic and therapeutic

methods cannot be used due to their teratogenic impact. Particular attention should be paid to disturbing symptoms reported by the pregnant woman during follow-up visits. Each case should be considered individually, and diagnostic tests and therapeutic procedures should be adapted to the type of cancer, stage of pregnancy and general condition of the patient.

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