Cancer in pregnant women

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The following guidelines are based on results of non-randomised clinical trials (impossible to conduct for ethical reasons) and on clinical experience, and mainly on expert opinions — II–IV category of evidence quality; recommendation level: A–C.

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According to the authors and editors, this report contains the most justified principles of diagnostic and therapeutic procedures prepared considering the scientific value of evidence and category of recommendations. These principles should always be interpreted in the context of an individual clinical situation. The recommendations do not always correspond to the current reimbursement rules in Poland. In case of doubt, the current possibilities of reimbursement of individual procedures should be established.

Definition

The term pregnancy-related cancers refers to malignancies diagnosed during pregnancy or during the year after delivery.

Epidemiology

The occurrence of malignancies in pregnant women is a rare phenomenon, with prevalence ranging between 0.02 and 0.1% of all pregnancies. However, the increasingly late age of women who become pregnant results in a gradual increase in the incidence of cancers in pregnant women. In the United States, a total of 3500 such cases are reported annually, which pertains to 1 per 1000 pregnancies. The prevalence in European statistics also ranges between 2000 and 5000 cancers in pregnant women per year, representing 1 case in 1000–2000 pregnancies. Newer statistics indicate that the incidence of pregnancy-related cancers is in the range of 81–140/100,000 pregnancies.

The most common cancers diagnosed in pregnant women include: breast cancer (36%) and cervical cancer (12%) — these malignancies constitute about half of all diagnosed cancers in pregnant women, as well as lymphomas (11% — mostly Hodgkin's lymphoma) and melanoma (6–8%). Less common pregnancy-related cancers include leukaemias (primarily acute myelogenous leukaemia), thyroid cancer, ovarian cancer, colorectal cancer, and sarcomas. Furthermore, more recently the coexistence of pregnancy and lung cancer also increased [1, 2].

General principles of management

Diagnosis and treatment of cancers during pregnancy are difficult and often significantly delayed, which results from non-characteristic symptoms of cancer overlapping with pregnancy-related signs and symptoms. At the time of confirming the diagnosis of neoplastic disease, decisions regarding further treatment should be made collaboratively by an oncologist, gynaecologist, perinatologist, and neonatologist, considering the optimal treatment of the mother and maintaining proper development of the foetus. This requires adherence to the following rules:

— undertaking the optimal treatment of cancer and saving the mother's life;
— the use of chemotherapy only for chemosensitive and chemotherapy curable cancers;
— striving for maximum foetal protection;
— striving to preserve the mother's reproductive abilities in the future.

Safety of diagnostic procedures

Diagnostic imaging with the use of ionising radiation can be performed during pregnancy if a single foetal dose does not exceed 100 mGy. There is no increased risk of miscarriage and foetal development abnormalities at the dose below 50–100 mGy. Therefore, X-ray examinations (X-ray) of abdominal cavity, computed tomography (CT), and isotopic examinations are contraindicated in pregnant women [1]. The recommendation of an international expert meeting published in 2010, which allows bone scintigraphy in breast cancer patients at high risk of bone metastases, should be interpreted with caution [3]; it seems that during initial diagnosis it is better to perform a magnetic resonance imaging (MRI) scan of axial skeleton without contrast medium (in the opinion of the authors of Breast Cancer in Pregnancy) [4], and only in the case of lack of clarity should bone scintigraphy be considered. If there are unambiguous indications for bone scintigraphy, the patient should be hydrated, and a catheter should be placed into a bladder (smaller pelvic accumulation of isotope) during and several hours after the examination. In justified cases, however, chest X-ray and mammography (MMG) can be performed. CT of the head, cervical spine, limbs, and chest could theoretically be performed during pregnancy because the radiation dose is low (about 8–30 mGy). However, many authors indicate the need to avoid these tests in pregnancy, because of the unknown dose of scattered radiation. Positron emission tomography with CT (PET/CT) is not performed during pregnancy, although this is not ruled out by some authors of recommendations [2, 5, 6].

Currently, there are no contraindications to perform any ultrasound examinations (US) except for those demanding use of contrast. In justified situations, if other imaging examinations are not conclusive, MR scans are also performed, which are considered quite safe (especially in the second and third trimester of pregnancy, providing the of use of gadolinium contrast medium is abandoned). Animal studies have shown that gadolinium crosses the placenta at an increased level in foetal circu-

lation, which could lead to foetal damage. In contrast, in adults gadolinium may cause kidney fibrosis. Foetuses and children under one year of age have a lower chance of kidney damage due to low level of maturity; however, it has been proposed that gadolinium in pregnancy be replaced with safer contrast media or imaging should be performed without contrast (especially for skeletal examinations). If possible, the test time should also be shortened (due to an unfavourable overheating effect on the foetus) [2, 5, 6]. It is also recommended that a 1.5-Tesla MR apparatus be used because a stronger magnetic field can be harmful.

Safety of therapeutic management

Surgical treatment

Conventional and laparoscopic surgeries can be performed at any time during pregnancy. However, it is recommended that they are performed in the second trimester of pregnancy, when the size of the foetus still allows interventions in the abdominal cavity and the risk of miscarriage or premature birth is relatively small compared to another period of pregnancy. Performing surgical procedures with high risk of complications is also discouraged because they may adversely affect the course of pregnancy [2]. It is preferred-if possible-to use local or regional anaesthesia.

An increased risk of foetal damage after operations with peritonitis has been observed.

When performing surgery after the 20th week of pregnancy, pregnant women should be placed in a left-sided inclined forward position to avoid compression of the vena cava. However, in order to reduce the risk of aspiration, especially in the Trendelenburg position during laparoscopy, the head of the pregnant woman should be lifted slightly upwards.

Making therapeutic decisions, especially regarding surgical operations, it should be remembered that in patients with cancer during pregnancy, disturbances of pregnancy, delivery, and foetal development may be associated with hypercoagulability (related to both cancer and pregnancy itself). The most important factors that increase the risk of hypercoagulability include fluid retention, increased circulating blood volume, and haemostasis disorders (in the third trimester the concentration of fibrinogen, VII, VIII, and X-coagulation factors and von Willebrant factor increase, factor XIII and protein S level decrease, and fibrinolytic activity is impaired). Anticoagulation prophylaxis should therefore be used during surgery in pregnant women. Increased thrombotic readiness resolves within a few days after giving birth.

After surgery foetal development should be closely monitored with cardiotocography (CTG) and/or US.

Use of chemotherapy in pregnant women

The degree of teratogenic effects of cytotoxic drugs on the foetus is associated with the period of pregnancy, dose and route of administration, as well as duration of treatment.

According to the principles of transport across biological membranes almost all cytostatic drugs cross the placenta; the amount of drug that reaches the foetus is a derivative of the concentration of free drug delivered to the foetus per unit time. The dose, the route of administration, and the duration of treatment have a major impact on the foetus. The biophysical characteristics of cytostatic agents are also very important — drugs made up of small molecules (< 600 kDa), highly lipid-soluble, and with a lower degree of protein binding cross the placenta more easily and show increased risk of foetal damage. While crossing the placenta by anthracyclines, vinblastine, taxanes, and active metabolites of cyclophosphamide is very limited, carboplatin crosses the barrier in a proportion of about 50%, and cisplatin concentration in the umbilical cord blood is approx. 31–65% of the level in maternal blood [7–9].

Additionally, the pharmacology of chemotherapeutic agents is commonly disturbed in pregnant woman by physiological changes associated with pregnancy. They include the following:

— increased renal excretion of drug (increase in creatinine clearance by approx. 50%);
— impaired liver function;
— malabsorption in gastrointestinal tract;
— disturbed binding of drugs to plasma proteins (decrease in albumin level);
— increased volume of total body fluids.

However, one of the most important risk factors associated with the teratogenic effects of cytotoxic drugs is the period of pregnancy in which they are used. The majority of foetal defects are reported during embryo- and organogenesis (up to the 60th day of pregnancy), which justifies avoidance of chemotherapy in the first trimester of pregnancy. It is recommended that chemotherapy is not used before the 14th week of pregnancy. After administration of cytotoxic drugs to pregnant women — mainly in the first trimester — about 20% of foetal defects and malformations are observed, 40% of neonates have low birth weight, and 33% of children have pancytopaenia. In the second and third trimester of pregnancy the percentage of foetal damage during chemotherapy is significantly lower, accounting for 8% and 6%, respectively [10] (according to other authors, even as low as 1.3%) [11].

In connection with the aforementioned facts, many experts — including experts from the European Society of Clinical Oncology (ESMO) — recommend the following:

— do not use chemotherapy in the first trimester of pregnancy, and in patients who need to start treatment in this period, possibly terminate pregnancy;
— calculate a dose of cytotoxic drugs according to standard rules, but taking into account impaired pharmacokinetics of certain drugs during pregnancy;
— do not use chemotherapy 3 weeks before planned delivery due to the possibility of neutropenia and thrombocytopenia (both in mother and newborn) and for the same reasons also after the 33th week of pregnancy;
— use — if possible — chemotherapy at weekly intervals because it is easier to monitor pregnancy in this way, and the doses of medication are lower, so there is a shorter nadir of neutropenia [1, 10].

Chemotherapy used in pregnant women may cause early (spontaneous abortions, organ damage, premature birth, and low birth weight) and late adverse effects (infertility, delays in physical and mental development, risk of malignancy in children, mutations and teratogenic effects in subsequent generations).

Most teratogenic drugs include antimetabolites and alkylating drugs; their use in the first trimester of pregnancy is associated with foetal damage and the occurrence of congenital malformations in 20% and 14% of cases, respectively. The most harmful antimetabolites are aminopterin, methotrexate, and cytosine arabinoside, and chlorambucil, chlormethine, and cyclophosphamide in the group of alkylating drugs (the risk of damage caused by cyclophosphamide is significantly lower than with other alkylating agents, especially in the second and third trimester, due to lower ability of its active metabolite to cross the placenta) [7]. Intrauterine exposure to methotrexate may cause foetal death or development of congenital malformation syndrome (mandibular hypoplasia, delayed ossification of cranial vault, hypertelorism, broad base of the nose, distortion of the ear and other hearing defects, deformities of limbs, and nervous system defects).

Cyclophosphamide and fluorouracil have been used in many pregnant women (primarily the FAC scheme in breast cancer patients). In 161 cases of administration of these drugs in the second and third trimester of pregnancy, only two cases of foetal defects (1.2%) were observed. Fluorouracil was also administered in the second and third trimester (monotherapy or in combination with oxaliplatin and/or irinotecan) in eight pregnant patients treated for colorectal cancer (CRC), and apart from one case of hypoplasia of the thyroid, no other lesions were observed. However, the use of fluorouracil in the first trimester may cause foetal damage in up to 1/3 of cases. Delays in foetal development and intrauterine foetal death were also observed in isolated cases when fluorouracil was combined with cyclophosphamide and methotrexate. Capecitabine and gemcitabine have been used in pregnant women only in isolated cases (without adverse effects on offspring), which makes it difficult to draw any conclusions [9, 10, 12].

The literature provides information on individual adverse reactions of anthracyclines and plant alkaloids. These drugs are made up of large molecules and are probably less likely to cross the placenta [7, 8]. Therefore, anthracyclines belong to the group of the safest cytotoxic drugs, which have been used successfully for many years in pregnant women. The largest amount of data in the literature concerns the use of doxorubicin. Only single complications have been reported (including cardiovascular). The majority of foetal defects are observed after administration of idarubicin, which is more lipophilic, and after the use of daunorubicin. Doxorubicin and epirubicin appear to be the safest in pregnant women, although three deaths of foetuses and newborns have been described in a group of 13 mothers receiving epirubicin [9, 13]. Other authors [14] found in 20 women with breast cancer treated during pregnancy, that weekly use of epirubicin is effective and safe. There are also reports that epirubicin crosses the placenta more slowly compared to doxorubicin and may therefore be safer.

Platinum derivatives cause delay in foetal development and possible hearing loss. In a group of 60 pregnant women treated with platinum derivatives in the second and third trimester — except for two cases of foetal damage (ventriculomegaly after cisplatin and spontaneous abortion after carboplatin) — other complications were not observed [15]. However, after the use of oxaliplatin in seven pregnant women, one case of thyroid gland hypoplasia was observed. Etoposide may cause pancytopaenia in foetuses and newborns as well as increase the risk of secondary leukaemias.

Numerous reports on the use of toxoids (docetaxel and paclitaxel) during pregnancy indicate no adverse effects on the foetus in the second and third trimester of pregnancy in women treated for breast cancer and ovarian cancer (exceptions were one case of pyloric stenosis and three cases of myelosuppression in children). Since taxoids are substrates for P-glycoprotein, found in placenta in high concentration and metabolised by cytochrome P-450, the concentration of which increases in the third trimester of pregnancy by 50–100%, they can be relatively safely used during pregnancy [7]. If anthracyclines are indicated during pregnancy, doxorubicin (the best-known anthracycline in clinical trials in pregnant women) and epirubicin are proposed. The use of liposomal forms of anthracyclines is more dangerous due to the greater degree of crossing the placental barrier [13, 16].

Among targeted drugs, the largest amount of data in literature concerns the use of rituximab, trastuzumab, and imatinib. In the case of rituximab, no adverse effects on the foetus have been described, but only a transient (normalisation 3–6 months after birth) reduction in the number of B-lymphocytes in neonates without symptoms of infection. In addition, due to its large molecular size,

rituximab should not have a negative effect on the foetus during the period of organogenesis. However, the small number of pregnant women treated with rituximab demands its careful use [17, 18]. The use of trastuzumab in pregnant women has been described in over a dozen reports, and in some cases oligohydramnios developed leading to the death of several newborns due to lung and kidney damage. Oligohydramnios (high levels of HER2 in foetal kidneys, disturbed urine and foetal water production, and subsequent high drug concentration) may be associated with incomplete foetal lung development; therefore, trastuzumab should not be used in pregnant women. However, in the case of unplanned pregnancy during treatment with trastuzumab and after its rapid discontinuation, the pregnancy can be continued because short-term treatment with this drug in the first trimester probably has no adverse effects on the foetus. Contraception is recommended during treatment with trastuzumab and up to six months after its completion [2, 16, 18]. Imatinib is potentially teratogenic, especially when used in the first trimester of pregnancy. In their first report, Pye et al. [19] discussed 180 cases of imatinib use in pregnant women and presented 12 foetal defects (skeletal malformation, encephalocele and meningocele, hypospadias, *etc*.), mainly due to its use during the first trimester. In another report from the US Department of Health and Human Services [12], 19 (12%) spontaneous abortions were observed in a group of 157 patients receiving imatinib. In this group, as many as 151 patients received imatinib in the first trimester because they became pregnant while being treated. However, in the remaining patients treated in the second and third trimester, no foetal damage was observed. Nevertheless, this group of patients was too small to draw final conclusions regarding the use of imatinib in pregnant women. We also know that in women who discontinued imatinib during pregnancy, a good response to re-inclusion of the drug was obtained only in those who at the time of discontinuation were in complete molecular remission of disease.

Regarding use of other targeted therapies in pregnant women, we have too little information to draw specific conclusions.

A previously planned termination of pregnancy in women undergoing chemotherapy should be carried out 3–4 weeks after its use, in order to normalise bone marrow aspirates in the mother and foetus

Breastfeeding while using chemotherapy is contraindicated because the medicines pass into human milk.

The use of radiotherapy in pregnant women

Pregnant women are irradiated in special circumstance; radiotherapy is inadvisable between 8th and 11th week of pregnancy and is difficult to perform due to the position of the foetus and high position of the uterine fundus in the third trimester of pregnancy. The decision on the use of radiotherapy depends on the type and severity of cancer, age of pregnancy, as well as general condition of the mother and the child. There are no guidelines for pregnant patients, and therefore individualisation of treatment is preferred. Rare cases of irradiation in the first or second trimester of pregnancy are usually due to Hodgkin's lymphoma in supraphrenic (cervical or axillary) locations in a situation when the patient cannot be closely observed or if there is disease progression before delivery [20, 21].

Prior to irradiation, measurements are made on phantoms. Before commencing irradiation in pregnant woman dosimetry measurements are made on a permanent anthropomorphic phantom — the upper half of the body, where there is a dissimulated field (e.g. cervical) with water phantom, remodelling conditions in the abdominal cavity. In the water phantom, ionisation chambers are placed at the depth at which the foetus is located in the mother's body, based on ultrasound examination. The size of the foetus is evaluated during irradiation twice a week. Ionisation chambers are most often located at the level of proximal, middle, and distal parts of the foetus. Measurements are made with and without abdominal covers. In the case of irradiation of cervical and axillary areas, thoracic and abdominal covers are made of lead apron, special block shields, and special 3D planning using collimators [20, 22].

During irradiation, *in vivo* dosimetry is used, including measurements within the critical organs of the mother and foetus. HARSHAW 100 or Thomson and Nielsen t.MOSFET TN-RD thermoluminescent detectors are used for this purpose [20].

The dose received by the foetus depends on the following: the irradiation beam, scattered radiation generated in the mother's body, scattered radiation arising in collimators, wedges, filters, and covers, as well as the field size, foetal distance from the lower limit of the irradiation field, and the thickness of covers. Recent studies on the dose measurements that a foetus can receive in different clinical situations depending on the type of cancer and in every trimester of pregnancy, in the case of X6 MV photon irradiation of Hodgkin's lymphoma, nasopharyngeal cancer, breast cancer, and lung cancer, confirmed the relationship with age of pregnancy (size foetus) and foetal distances from the lower edge of the irradiation field [23].

Irradiation treatment is associated with the risk of damage to the foetus and child, which depends on the age of pregnancy, absorbed dose, size of irradiation field, and the distance of the foetus from the lower limit of the irradiation field [24, 25]. Dose-independent effects (so-called stochastic) have also been reported, increasing the risk of leukaemia or sarcoma after 2–10 years of irradiation treatment. The total admissible dose

(threshold) for the foetus is 0.05–0.1 Gy (5–10 cGy), i.e. up to 100 mGy according to ICRP recommendations [24]. Undesirable effects of irradiation comprise mainly the following: spontaneous abortions, organ damage during organogenesis, delay of physical and mental development, and risk of secondary tumours in the child (mainly leukaemia and solid tumours) [26].

Treatment of the most common cancers in pregnant women

Breast cancer

According to the commonly accepted definition, breast cancer coexisting with pregnancy is a cancer that is diagnosed in a pregnant woman and within 12 months of delivery.

The incidence of such a clinical situation is estimated at 1/3000–10,000 pregnancies (depending on the source of data) and is expected to increase, because for many years the age of primiparous women has been systematically increasing and at the same time the prevalence of breast cancer in young women is growing [4, 5, 25, 27]. In one of five women aged 25–29 years currently diagnosed breast cancer will co-exist with pregnancy [28].

Breast cancer during pregnancy histologically corresponds to the subtypes most often diagnosed in young women; therefore, pregnancy itself neither determines the biology of this cancer nor affects its course and dynamics. Usually it is a ductal carcinoma, poorly differentiated (G3), "triple-negative", or with HER2 overexpression (28–58% of cases), and often also with concomitant infiltration of tumour lymphatic vessels [5, 27, 29].

Diagnostics

Despite growing knowledge and access to numerous literature data regarding the coexistence of malignant tumours and pregnancy, the problem of delayed diagnosis is still serious, and each month of delay in the time to start proper therapy increases the risk of involvement of regional lymph nodes by 0.9–1.8% [5, 27].

The majority of diagnostic tests to verify focal lesions in the breast can be safely performed in pregnant woman. Ultrasound examination is characterised by high sensitivity and specificity, enabling differentiation between cystic and solid lesions [5, 6, 27, 28].

Bilateral MMG is recommended for all women with confirmed or highly probable malignant disease. The radiation dose in this case is less than 3 mGy, which corresponds to a nearly seven-week exposure to background radiation. The estimated dose per uterus and foetus does not exceed 0.03 mGy [28].

Clinically, breast cancer during pregnancy is usually a painless, palpable mass, very rarely accompanied by bloody nipple discharge [5, 6, 27, 28].

Pathomorphological diagnosis is based on examination of material obtained using core-needle biopsy (CNB). It is not recommended that a fine-needle biopsy (FNB) (apart from the possible need to verify the involvement of axillary lymph nodes) be conducted due to the very high risk of false negative results. The pathomorphologist must always be informed about the coexistence of pregnancy [5, 6, 27, 28].

If breast skin is red, swollen, and without obvious presence of tumour, and those symptoms persist after using one line of antibiotics, a skin biopsy is necessary [5, 6, 27, 28].

Primary generalisation of tumour spread in pregnant women is uncommon and the decision regarding diagnosis of possible spread should be guided by the principle that the foetus should not be unnecessarily exposed to ionising radiation [5, 27].

Depending on the clinical situation, standard chest X-ray with foetal cover and ultrasound with assessment of abdominal parenchymal organs should be considered, and MR is recommended for assessment of the skeletal system [5, 6, 27, 28].

The sentinel lymph nodes examination procedure can be safely carried out in pregnant woman, but only radioisotope labelling is recommended; blue dye should be avoided because it is a factor potentially responsible for the anaphylactic reaction in pregnant woman and thus significantly jeopardising the normal course of pregnancy. A one-day procedure requiring a lower dose of radiocolloid is preferred [5, 6, 27, 28, 30].

Surgical treatment

From an anaesthesiological point of view, surgery is possible at every stage of pregnancy. The scope of operations is defined by the same indications used outside of pregnancy, but the advancement of pregnancy poses some limitations regarding breast-conserving surgery (BCS) [5, 6, 27, 28, 30].

In patients in the late second and third trimester of pregnancy, conservative treatment may be considered because intimately associated supplementary radiotherapy would be performed after delivery (as a rule, radiotherapy is used after approx. six months of postoperative systemic treatment) [5, 6, 27, 28, 30].

The most challenging is the treatment of patients with early breast cancer in early pregnancy. In this situation, radical mastectomy remains the optimal and most frequently used solution, and possible supplementary irradiation is used after delivery [5, 6, 27, 28, 30].

During surgery, the patient should be placed in a left-sided, inclined position. At the same time, monitoring of uterine contraction and foetal heart activity should be ongoing. Any situations that may give rise to premature delivery should be avoided (e.g. hypoxia, fever, pain, infection, or thrombosis) [4, 27].

Radiotherapy

There are available reports that supplementary radiotherapy of breast cancer in early pregnancy (first trimester and the beginning of second trimester) seems safe for the foetus (provided all necessary covers are used) due to its relatively large distance from the irradiation field. However, these data are based on calculations on anthropomorphic models and extrapolated from observations of pregnant women exposed to nuclear explosions in Hiroshima and Nagasaki, and in Chernobyl [25, 27]. However, the procedure based on postponing irradiation for the period after terminating pregnancy is still considered to be the safest [5, 6, 27, 28, 30].

During consideration of validity and safety of BCS during pregnancy, one should not forget about difficult to predict aesthetic outcomes due to the constantly changing structure of the mammary gland during pregnancy and its preparation for lactation [6].

In practice, the most commonly used surgical treatment is the option, that allows the use of supplementary radiotherapy only after delivery [5, 6, 27, 28].

The possibility of radiotherapy in a generalised disease depends on the location of metastases (CNS, metastases in bones outside the pelvis, and nearby areas) [6, 27, 28].

Chemotherapy

The risk of teratogenicity of drugs used during breast cancer chemotherapy depends on the type of active substance, dose, and time and frequency of its administration, and generally ranges between 10 and 20% in the first trimester of pregnancy and up to 1.3% in the second and third trimester. Chemotherapy can be used in the second and third trimester of pregnancy, and the indications are the same as for breast cancer unrelated to pregnancy [5–7, 27–29].

Studies on the treatment of breast cancer unrelated to pregnancy clearly showed that delaying chemotherapy leads to an increased risk of relapse, so it is recommended that treatment be started during pregnancy (after week 14), and it should be carried out in the manner being the closest to non-pregnant patients [5–7, 27–29].

Intrauterine exposure to methotrexate may cause foetal death or development of congenital malformations — the CMF scheme (cyclophosphamide, methotrexate, fluorouracil) is absolutely contraindicated in pregnant women. Doxorubicin, cyclophosphamide, and taxoids can be safely administered in patients with breast cancer coexisting with pregnancy, preferably within sequential regimens (taxanes before or after anthracycline) [4–7, 25, 27, 29].

Current recommendations exclude treatment with anthracycline or taxanes as monotherapy, because it is suboptimal (similar to non-pregnant patients). The addition of fluorouracil to anthracycline and taxoid-based regimens is not associated with additional benefits and is not recommended for pre- or post-operative treatment [6, 28].

However, in patients with triple-negative breast cancer platinum derivatives may be used. It has not been unambiguously determined which of them is the most effective; carboplatin should be safer when assessing crossing the placenta and toxicity profile, so it should be the drug of choice when this group of cytostatic agents is used in pregnant women [6, 28].

Due to its established greater effectiveness, the use of "dose-dense" (DD — the same dose administered in a shorter rhythm than usual) and "intensified dose-dense" (IDD — higher than standard dose and additionally administered in a shorter rhythm) regimens are more and more widely used in the adjuvant treatment of breast cancer unrelated to pregnancy. DD programs may be a therapeutic option also for pregnant women with breast cancer [contrary to IDD programs, which no longer should be used due to very few available reports on their use during pregnancy and association with high rates of clinically significant anaemia and febrile neutropaenia despite the use of primary prophylaxis with granulocyte colony stimulating factor (G-CSF)] [6, 28].

There are no data available on the use of nab-paclitaxel during pregnancy, and this drug is not recommended [6, 28].

Vinorelbine (both intravenous and oral) is characterised by a low rate of crossing the placenta, so this is the drug recommended in patients with resistance to taxoids and/or anthracyclines or with other contraindications to their use [28].

Hormone therapy

The use of hormone systemic therapy is contraindicated during pregnancy. Although there are reports of safe use of tamoxifen in pregnant women with generalised breast cancer, the risk of congenital foetal damage due to intrauterine exposure to tamoxifen is also very well known (Goldenhar syndrome — hemifacial microsomia [incomplete development of the ear, nose, soft palate, lip, and mandible] and genital malformations) [5, 6, 27–29, 31, 32].

Anti-HER2 treatment

Anti-HER2 drugs are also contraindicated during pregnancy because HER2 receptor participates in the process of foetal kidney development, and blocking it during pregnancy results in impaired amniotic fluid production, which in turn may cause serious risk to the course of pregnancy [5, 6, 27–29, 31, 32].

Delivery

The method of terminating pregnancy in a breast cancer patient is primarily determined by obstetric

indications — only in exceptional situations (*e.g.* very high disease severity or dynamic progression) should oncological indications be decisive indicators that can guide the decision about preterm labour.

Patients who continue systemic treatment after delivery require cessation of lactation [5, 6, 27–29, 31, 32].

Prognosis

There is no evidence that breast cancer in pregnancy is associated with a worse prognosis than in the case of the disease outside of pregnancy. This correlation has not been demonstrated for luminal subtypes of breast cancer, which in the past were wrongly considered to be the most dangerous during pregnancy due to hypotheses regarding the influence of hormonal factors on cancer progression [27, 33, 34].

It is clearly established that termination of the pregnancy does not improve the prognosis [27, 33, 35].

Cervical cancer

Characteristic

Cervical cancer is one of the most common malignancies diagnosed during pregnancy (0.1–12/10,000 pregnancies) [34].

The prognosis in patients with cervical cancer during pregnancy is similar to non-pregnant women. Due to the essence of disease, scientific data is category IV, B (small groups of patients/expert opinions). Planning and conducting treatment should take place in a multispecialty team (perinatologist and neonatologist and specialists in oncology), and the aim should be to ensure proper treatment of the mother and foetal safety [36].

The methods of treatment include conservative treatment and surgery or chemoradiotherapy, and they depend on the patient's desire to term pregnancy, intention to maintain the possibility of becoming pregnant in the future, and the degree of tumour progression, tumour size, and gestational age [34, 36].

Due to frequent gynaecological examinations during pregnancy, the possibility of diagnosing cervical cancer is three times greater in this period. Additionally, as a result of effective screening and vaccination programs implemented in many countries, the incidence of invasive cervical cancer decreases, similarly to the risk of co-existence with pregnancy. At the same time, due to shifting of the procreation period in Western societies, the incidence of this cancer in non-screening groups is increasing [36].

Precancerous conditions HSIL (CIN2+)

In the case of intraepithelial dysplasia type HSIL (high grade intraepithelial lesion) (cervical intraepithelial neoplasia grade 2, CIN2+), "wait-and-observe" is a keystone management strategy. The incidence of progression to invasive form is very low (0–0.4%). The main part of this procedure is to repeat the colposcopy every 12 weeks. It can be the only procedure if, in the opinion of examining healthcare professional with extensive experience, a result indicating a lack of invasion features is convincing. In case of doubt, it is reasonable to perform a targeted biopsy.

Scraping of the cervical canal or ablative methods are not recommended.

Conisation should be performed if there is a discrepancy between cytological and colposcopic examinations with suspicion of invasion.

Definite treatment is postponed until the post-partum period, especially since these changes often may self-resolve (48–70% of cases). There are no oncological indications for termination of pregnancy by caesarean section [37].

Invasive types

Treatment methods significantly differ depending on the patient's desire to term pregnancy or intention to maintain the possibility of becoming pregnant in the future.

Management should be based on the following results:

— gestational age precisely determined by means of an ultrasound scan;
— colposcopic examination carried out by an experienced specialist;
— clinical examination;
— gynaecological examination (if necessary, under general anaesthesia);
— ultrasound examination;
— MR scan, which is a reference method in assessing the size of the lesion and infiltration of surrounding tissues, and detection of lymph node metastases (contrast use should be avoided).

Serum markers are not useful in diagnostics and monitoring of treatment, while CT and PET-CT examinations can only be used in a clinically justified situation (suspicious of disease generalisation).

In the case of a patient with no desire to preserve the current pregnancy and with no further reproduction plans, management is not different from the treatment of non-pregnant patients, except for the necessity of its termination, which depends on the severity of disease (Tab. 1).

In patients who do not want to preserve their current pregnancy, but plan to become pregnant in the future, the ability to maintain this ability is limited to Grade IIA1 with a tumour size of up to 2 cm. In higher stages, uterine conserving treatment is not rational.

In patients with grade IA–IIA1 (tumour size up to 2 cm), the treatment of choice is termination of pregnancy with subsequent radical trachelectomy [36].

Table 1. Treatment methods of patient with lack of will to preserve the current pregnancy and with no further reproduction plans

FIGO grade	Therapeutic option
IA1	Simple hysterectomy with foetus in uterus
IA2 to IIA1	Radical hysterectomy up to the 24th week of pregnancy
IIA2 to IIIB	Chemoradiotherapy (in the first trimester radiotherapy causes a miscarriage. After instrumental emptying of the uterus, no delay in radiotherapy is required. In the second trimester, foetal death occurs after 10–15 radiotherapy fractions)

If the patient is willing to preserve the pregnancy, the treatment depends on gestational age at diagnosis and cancer stage. The maximum time of foetal intrauterine growth should be ensured [38].

Gestational age and cancer stage also determine the possible therapeutic options. If cervical cancer is diagnosed: in the first trimester, treatment should be postponed until the second trimester (in low-stage tumours, the delay of definitive treatment by 6–8 weeks is safe) [39]; in the second trimester of pregnancy, the treatment depends on cancer stage:

— for stage IA1 — conisation; in the case of positive cutting margins (46–50% of cases), a second conisation is recommended; the risk of lymph node involvement is approximately 1.5%; delivery through the natural passages is possible;
— stage IA2–IB1 (tumour size of up to 2 cm) — pelvic lymphadenectomy (laparoscopic), which allows identification of patients with high risk of tumour dissemination:
  • negative result — conisation or simple trachelectomy [radical trachelectomy is associated with a significant risk of miscarriage (33%) with the risk of lesions in parametrium of less than 1%],
  • positive result — NACT (neoadjuvant chemotherapy);
— stage IB1 (tumour size more than 2 cm) — pelvic lymphadenectomy (laparoscopic), which allows identification of patients with high risk of tumour dissemination:
  • negative result — NACT,
  • positive result — in advanced disease (with diagnosed lymph node metastases) it is proposed that pregnancy be terminated and standard management used, as in non-pregnant patients;
— stage IB2 and higher — NACT to stabilise the disease (reducing the size of the tumour is not the primary goal):
  • cisplatin 50–100 mg/m^2 every 21 days,
  • carboplatin AUC 5.0,
  • cisplatin 60 mg/m^2 + paclitaxel 135 mg/m^2 (the number of cycles depends on time required to achieve foetal maturity; if it is only possible to give one CTH cycle until foetus maturity, then this treatment should be foregone),
  • delivery by caesarean section followed by a procedure analogous to the standard one — radical hysterectomy or radio-chemotherapy [40].

In the case of progression during initial chemotherapy, standard treatment should be followed.

In the third trimester there is an indication to perform a caesarean section at the time of foetal maturity followed by standard treatment.

Malignant ovarian neoplasms

Characteristics

The incidence of adnexal lesions is 2–4% [15, 41]. Approximately 6% of lesions undergoing surgery are malignant (epithelial tumours — 49–75%, sex-cord cancers — 9–16%, or germ-cell tumours — 6–40%) [42].

Due to the essence of disease, scientific data is category IV, B (small groups of patients/expert opinions). Planning and conducting treatment should take place in a multispecialty team (perinatologist and neonatologist and specialists in oncology), and the aim should be to ensure proper treatment of the mother and foetal safety.

Ovarian tumours during pregnancy are often less advanced than in non-pregnant women due to frequent gynaecological and ultrasound examinations during this period. In 25% of cases, ovarian cancer during pregnancy manifests as symptoms of acute abdomen due to tumour torsion or rupture [43].

After diagnosis of ovarian tumour in a pregnant woman, a specialist with appropriate experience should perform an ultrasound examination. The diagnostic usefulness of tumour markers is limited due to changes associated with pregnancy.

Determining the diagnosis is possible after laparotomy/laparoscopy; however, the mentioned procedures should be optimally performed between the 13th and 16th week of pregnancy.

Non-epithelial malignant tumours

In most cases, tumours that do not originate from the epithelium are recognised in stage I according to FIGO (80%). Typically, a sufficient procedure includes excision of changed ovary together with fallopian tube and omentum, collection of lavage fluid, and biopsy

from the peritoneal cavity. In the absence of enlarged lymph nodes, lymphadenectomy is not recommended. Manipulation of the uterus should be minimised.

Surgical treatment is sufficient for dysgerminoma and stage I immature teratoma.

If chemotherapy is necessary, regimens with paclitaxel and platinum derivative are recommended, and the other option is a BEP scheme (bleomycin, etoposide, cisplatin). Some experts suggest replacing etoposide with vinblastine in the BEP scheme due to lower risk of toxicity (secondary leukaemia and myelosuppression).

Close monitoring is indicated. The effectiveness of markers is limited. After pregnancy, a surgical procedure should be considered to assess disease staging [43, 44].

Epithelial tumours — tumours with limited malignancy

Tumours with limited malignancy are usually diagnosed in stage I according to FIGO. They occur 1.5 times more often than cancers. The therapy of choice is surgical treatment (unilateral adnexectomy, omentectomy, collection of lavage fluid and biopsy of peritoneal cavity) without lymphadenectomy conducted via laparotomy or laparoscopy. Avoiding tumour rupture is of the highest importance.

In the case of bilateral lesions in ovaries, they can be removed after the 13th week of pregnancy. There are no indications for chemotherapy. Delivery through the natural passages is possible.

Due to high frequency of stage III changes, surgical verification after pregnancy is indicated.

Epithelial malignant tumours

Management depends mainly on cancer stage. In stage IA (G1) surgical treatment is efficient (unilateral adnexectomy, omentectomy, collection of lavage fluid, and biopsy of peritoneal cavity) without lymphadenectomy with staging verification after pregnancy. Avoiding tumour rupture is of the highest importance. In stages IA (G2) to IIA adjuvant chemotherapy should be considered.

In cases of more advanced stages, the choice of treatment depends on the patient's will to maintain pregnancy, expected cancer stage, and gestational age (threshold of gestational age to preserve a pregnancy — 20 weeks; previously optimal cytoreduction combined with hysterectomy and CTH; after 20 weeks — possibility of preserving pregnancy and surgical operation mainly to confirm the diagnosis).

The strategy of treatment of pregnant patients with the diagnosis of advanced ovarian cancers involves carrying out the following:

— primary resection combined with termination of pregnancy via caesarean section and subsequent CTH;
— primary resection with subsequent CTH during pregnancy and complementary surgical treatment during labour or postpartum.

If the patient is willing to preserve pregnancy, suboptimal surgical procedures, which do not prolong survival and additionally expose the foetus, should be avoided.

It has been proposed that adjuvant and advanced disease chemotherapy during pregnancy should consist of cisplatin or carboplatin and paclitaxel (doses and regimens analogous to non-pregnant patients). Foetal biometry is recommended after each cycle of chemotherapy. The childbirth should occur between the 35th and 37th week of pregnancy after at least a three-week interval from the last cycle of chemotherapy. There are no data on the safety of bevacizumab.

Delivery through the natural passages can be considered followed by elective laparotomy, or delivery by caesarean section with simultaneous reduction of tumour mass [43, 45–47].

Lymphomas

Characteristics

Lymphoma is the fourth most frequent malignancy among pregnant women. Hodgkin's lymphoma is most often diagnosed with the incidence ranging from 1/1000 to 1/3000 of pregnancies (0.7–8.1/100,000 births) [48]. Co-existence of non-Hodgkin's lymphomas is less frequent and amounts to 1/5000 pregnancies (7.7/100,000 births in 2011), which is associated with the diagnosis of these types of lymphoma more commonly among women over 40 years of age [49]. The most common types of non-Hodgkin's lymphomas diagnosed during pregnancy include: diffuse large B cell lymphoma (DLBCL), T-cell lymphoma, Burkitt's lymphoma, and immunoblastic lymphoma in high clinical stages.

The aetiology of lymphoma in pregnant women is identical to that generally known. There are no additional causes for lymphoma during pregnancy. A study by Lishner et al. (1992) confirmed that the clinical course of disease, response to treatment, and overall survival are similar to the group of non-pregnant patients [50]. Aviles et al. (1991) did not show unfavourable effects of lymphoma on pregnancy, foetal development, or the course of delivery or confinement. Prognosis of lymphoma patients is similar to that observed in non-pregnant women provided that appropriate diagnostic and therapeutic procedures are used [51].

Conducting necessary examinations in the diagnosis of lymphoma during pregnancy is difficult. It is associated with the necessity to carry out tests assessing the clinical stage of malignancy while imposing teratogenic effects on the foetus (e.g. PET/CT, CT of abdominal cavity with pelvis, radiography of gastrointestinal tract, and others). Ultrasound examination of the abdominal cavity should be used to determine the extent and size (e.g. retroperitoneal localisation) of lymphoma; determination of the clinical stage should be based not only on physical evaluation but should also include laboratory

tests and in special cases bone marrow trepanobiopsy (e.g. in the presence of general symptoms — B and abnormalities in complete blood counts, such as anaemia, thrombocytopaenia, or leukopenia) [51]. It is possible to perform a chest X-ray with a foetal cover, or a safer MR imaging instead of a CT scan. However, foetal US is required at the time of diagnosis as well as commencement and monitoring of treatment. Histopathological diagnosis of lymphoma should be based on examination of excised lymph node, tissue sampled during surgical operation, biopsy, or cytometry.

Treatment

Connors et al. (2008) and Bachanova et al. (2013) [52] confirmed that the decision about treatment of lymphomas during pregnancy should take into account not only medical but also religious, social, psychological, ethical, and cultural beliefs of the patient and the child's father, as well as the position of the physician who is to conduct the medical treatment. Treatment of pregnant women with lymphoma depends on: histological type of lymphoma, clinical presentation (including clinical stage), gestational age, maximum protection of foetus, risk for mother and foetus, and the possibility of maximum benefit for the patient, maintaining her reproductive capacity in the future. Gobbi et al. [53] and Nisce et al. [53] confirmed that there are no differences in overall survival in patients with lymphoma, who have undergone therapeutic abortion, compared to those who have not undergone the procedure. Aviles et al. [53], Pereg et al. [54, 55], and El-Hemaidi et al. [56] presented the algorithm for Hodgkin's lymphoma management depending on the trimester of pregnancy and stage of disease. A recommended indication for irradiation in the first trimester of pregnancy may be stage IA in isolated hyperdiaphragmatic lesions (e.g. cervical or axillary lymph nodes; mandatory abdominal cover). In lower stages in the first trimester of pregnancy, it is possible to consider vinblastine monotherapy, and in advanced disease in the first trimester of pregnancy it is necessary to consider termination of pregnancy. However, at higher stages immediate treatment after therapeutic abortion should be undertaken. In patients with Hodgkin's lymphoma in the second-third trimester of pregnancy, the use of the ABVD regimen is considered, taking into account the myelosuppressive effect of this treatment.

The results of particular systemic treatment regimens (ABVD, MOPP, vinblastine monotherapy, ABV) in small groups of patients were presented by Azim et al. [17]. Since the 1990s, in the Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology in Warsaw 54 pregnant women with Hodgkin's lymphoma were treated with EVA regimen (etoposide, vinblastine, and doxorubicin) with high efficacy.

A treatment algorithm for non-Hodgkin's lymphomas suggested by Perega et al. [54, 55], Avivi et al. [57], and Vandenbriele et al. [58] assumes B-cell lymphomas at stage I with low bulk consideration of irradiation in cases in women in the first trimester of pregnancy with isolated cervical or axillary lesions, but in the case of aggressive clinical course and symptomatic patients in this trimester, immediate treatment after therapeutic abortion is obligatory.

In patients with non-Hodgkin's lymphoma in the second-third trimester of pregnancy, individualised treatment is recommended depending on the clinical stage, microscopic type, and general symptoms. Pereg et al. [55] and Rizack et al. [59] consider chemotherapy with doxorubicin, cyclophosphamide, and vinca alkaloids as well as the possibility of applying irradiation to selected fields above the diaphragm.

In patients with lymphomas with slow course and location above the diaphragm, e.g. follicular lymphoma, the treatment should be deferred until the postpartum period or R-CVP (rituximab with ciclophosphamide, vincristine and prednisone) chemotherapy or rituximab monotherapy should be considered [53].

The results of chemotherapy of non-Hodgkin's lymphoma in pregnant women using CHOP and other regimens with or without anthracycline and CHOP in combination with rituximab [17] do not yet allow recognition of them as an indication recommended in clinical practice. Pending more clinical data, it is necessary to rely on the individualisation of management in these clinical situations [39, 49].

Skin melanoma

Characteristics

Melanoma accounts for about 6–8% of all cancers co-existing with pregnancy and occurs at a frequency of 2.8–5/100,000 pregnancies. Diagnosis should always be determined based on total excision of the lesion. After surgery, the sentinel node assessment procedure may be considered. During pregnancy, there is an increase in pigmentation and changes within naevi, justifying strict dermatological supervision including dermatoscopic evaluation.

The impact of melanoma on the course of pregnancy is not clearly defined. However, melanoma is the most common cancer that leads to metastases to the placenta and foetus. In melanoma patients during pregnancy, the placenta after delivery must be subjected to histological evaluation to detect or rule out metastases. Confirmation of the presence of metastases requires close observation of children towards the development of this cancer because, according to some reports, mortality in this group of children may be as high as 25% [60].

Treatment

Treatment of melanoma involves surgical excision of lesions with margins of 1–2 cm depending on infiltration

thickness. Thickness of melanoma infiltration ≤ 2 mm — 1 cm, and > 2 mm — 2 cm. In pT1b–pT4b stages, excision of the sentinel lymph node can be considered. In stages III and IV the lymph nodes and possible satellite lesions should be excised. Chemotherapy is of no practical use, especially in localised disease. There are reports of small groups of patients for whom interferon alpha or dacarbazine (approximately 20% RR) was used in advanced pregnancy. There were 36 cases of dacarbazine treatment in pregnancy, monotherapy, and polychemotherapy; serious foetal damage was observed with the use of the drug in the first trimester, and in the group of patients treated in the second and third trimester one foetus died and 50% of children were born prematurely. The use of interferon as a supplementary treatment is controversial in the absence of reports on the effects on long-term survival. Currently, targeted drugs are used in non-pregnant women because they are more effective. There are anecdotal case reports of vemurafenib use — when the drug was used in a pregnant woman from the 25th week of pregnancy for five weeks before delivery, the child was born in the 30th week with low birth weight but without serious injury. There are no data in medical literature on the use of pembrolizumab and nivolumab in pregnant women yet, but due to their structure and mechanism of action, there is a high risk of teratogenicity. They can be responsible for miscarriages, dead pregnancies, and other complications. Due to its mechanism of action, ipilimumab should not be used in pregnant women.

Melanoma is the most common cancer that leads to metastases to the placenta and foetus. In a group of 87 patients with various malignancies with foetal and placental metastases, 27 (31%) were melanoma patients. In this group, six foetuses had metastases and five children died within 0–8 months of delivery, while 18 children were born without disease symptoms, although melanoma cells were found in the placenta. Also, in this group it was observed that metastases occurred mainly in boys [61].

Colorectal cancer (CRC)

Colorectal cancer occurs with a frequency of 1/13,000 pregnancies, and the most common during pregnancy is rectal cancer (60–86%). Although it is a cancer that occurs mainly in the elderly (average age about 68 years), 5.4% of colorectal cancers are diagnosed in people under 45 years of age, and it is predicted that by the year 2030 in people aged 20–34 years the morbidity will increase by approx. 100%. So far, about 350 cases of pregnancy complicated by colon cancer have been described. This cancer is very often diagnosed in advanced stage (about 62% grade C and D according to Dukes classification), which results from the attribution of symptoms associated with cancer to pregnancy (e.g. constipation, anaemia, lower abdominal pain, rectal bleeding, nausea, vomiting). Diagnostics of colorectal cancer during pregnancy includes chest X-ray, abdominal and pelvic ultrasound, and endorectal ultrasound, as well as optional MR and colonoscopy or sigmoidoscopy with biopsy. In a study describing 48 sigmoidoscopies and eight colonoscopies performed in pregnant women, no complications were observed. International recommendations also suggest performing a chest CT (relatively low exposure of the foetus to ionising radiation — 0.002–0.2 mGy) [62].

Treatment

In the case of diagnosis before the 20th week of pregnancy and the existing treatment options, a radical tumour excision should be performed with subsequent adjuvant chemotherapy, which should be implemented after the first trimester of pregnancy. If cancer is diagnosed after the 20th week of pregnancy, surgical treatment may be postponed until the foetus has reached maturity, or pregnancy should be terminated earlier and radical measures should be undertaken 1–2 weeks after delivery (principles in accordance with standards for all pregnant patients). Alternatively, radical surgery and maintaining the pregnancy may be proposed, followed by adjuvant chemotherapy after delivery. In rectal cancer, it is proposed that the pregnancy be terminated via caesarean section, because the local tumour may obstruct delivery through the natural passages.

In the case of unresectable lesions (e.g. infiltration of surrounding structures, including uterus or ileus), the management is individualised (e.g. hysterectomy, colostomy, and initial chemotherapy). In advanced disease, termination of pregnancy in the first trimester or the use of palliative chemotherapy in the second-third trimester could be considered.

Fluorouracil-based chemotherapy seems to be the treatment of choice because this drug used in the second and third trimester of pregnancy is safe [12]. In the group of 161 pregnant patients, only two children (1.2%) had serious complications in the form of webbed fingers (syndactyly) and hypertrophy of lower extremity. Extending chemotherapy by adding oxaliplatin or irinotecan could also be considered, but so far there have been few reports of use of these drugs in pregnant women. Oxaliplatin was used only in seven patients, including six after the first trimester, and no adverse symptoms were observed except one child with hypothyroidism. On the other hand, irinotecan was used only in two patients after the first trimester, and in one child impaired intrauterine development was revealed immediately after delivery [8, 10].

The prognosis in patients with colorectal cancer during pregnancy is similar to non-pregnant women and

depends primarily on the clinical stage of the disease. In the INCIP study, in a group of 41 patients, the two-year survival rate was 65% [62].

Gastric cancer

Gastric cancer is extremely rare in pregnant women; it is diagnosed in around 0.1% of all pregnancies. The most common histological type of gastric cancer diagnosed during pregnancy is diffuse-type adenocarcinoma. Similarly to colorectal cancer, symptoms of disease can be confused with those of an ordinary pregnancy, so cancer is often diagnosed very late. Diagnosis in pregnancy is based on gastroscopy with biopsy, and disease stage is established based on ultrasound examination, MR of the abdominal cavity, and chest X-ray. If there are life-threatening symptoms (e.g. bleeding or perforation), surgical operation should be performed regardless of gestational age. If operable gastric cancer is diagnosed before the 24th week of pregnancy, surgical treatment can be used or pregnancy can be terminated and the patient treated as non-pregnant. In the case of diagnosis during later pregnancy surgery may be postponed after delivery. There is very limited evidence regarding the use of chemotherapy in gastric cancer during pregnancy, but available data suggest safe chemotherapy based on paclitaxel and fluorouracil after the first trimester.

Sakamoto et al. [63] presented an unfavourable prognosis in 85 patients with gastric cancer in pregnancy, because one- and two-year survival rates were 18.0% and 15.1%, respectively.

It is not recommended to become pregnant earlier than 3–5 years after completion of treatment for gastric cancer due to the high risk of relapse [62, 63].

Pancreatic cancer

Pancreatic cancer in pregnant women is even less common than gastric cancer. Only a few cases of such patients have been described so far in English language medical literature. The most frequently pancreatic cancer is detected at a very advanced stage, which may result from the fact that symptoms of disease are attributed to those of an ordinary pregnancy as well as from the biology of this cancer. Diagnosis is based on ultrasound examination (preferably transoesophageal) with biopsy and MR imaging. If operable cancer is diagnosed before the 24th week of pregnancy (approx. 20% of cases), surgical treatment can be used in any case. In patients diagnosed during later pregnancy possible options include surgery with preservation of pregnancy, surgery after delivery, or termination of pregnancy and treating the patient as non-pregnant. There is no experience with chemotherapy in pregnant women treated for pancreatic cancer, and standard cytotoxic drugs in this indication (e.g. gemcitabine) have been used in pregnant women only in isolated cases. The prognosis in patients with pancreatic cancer during pregnancy is poor. In one study, 5/10 patients died within four months of delivery. Also, as in gastric cancer, pregnancy is not recommended earlier than five years after treatment for pancreatic cancer due to the high risk of relapse [62].

Lung cancer

Lung cancer is very rare in pregnant women. Only 66 cases of pregnant patients suffering from lung cancer have been described so far in the English language medical literature — in the majority (82%) of cases it was non-small cell lung cancer (NSCLC) (mainly adenocarcinoma) in advanced stage (97% in III and IV stage). Small cell lung cancer occurred in 18% of pregnant patients. The prognosis was very poor. The majority of patients survived from three to nine months, and 12% died within a month after delivery. Only 12 patients, less advanced, survived 12 months or slightly longer.

Treatment

In the presented group of patients, more than half were treated systemically after delivery and only 24% during pregnancy. Platinum-based chemotherapy in combination with vinorelbine, taxoids, gemcitabine, or etoposide was mainly used. In one case erlotinib was used at the beginning of pregnancy (the patient became pregnant during treatment), but the drug was discontinued at week 8 — no negative effect on the foetus was observed. In addition, three patients were treated with erlotinib and gefitinib, and two patients received crizotinib. Targeted treatment resulted in stabilisation of the disease lasting a few months, while the response to chemotherapy was unfavourable. Due to the severity of the disease and the poor general condition of the pregnant women, in many of them preterm birth was initiated. Nevertheless, 82% of children were born healthy. In 14 cases, metastases to the placenta were observed and in an additional three, to the foetus.

It is very difficult to develop guidelines for the management of women with lung cancer in pregnancy due to the rarity of this clinical situation, limited experience, and poor prognosis. The patient should be informed about the prognosis and limited therapeutic options so that she can make an informed decision regarding maintaining her pregnancy. If there is a will to remain pregnant, the patient may be offered platinum-based chemotherapy in combination with vinorelbine or taxanes after the first trimester of pregnancy [64, 65].

Thyroid cancer

Thyroid cancer occurs with a frequency of 14 cases per 100,000 pregnancies, and about 6–10% of thyroid

cancers are diagnosed during pregnancy. Diagnostics should include thyroid ultrasound and thyroid hormone tests, and nodular lesions with diameter 1 cm and above should be histologically verified by means of fine-needle aspiration regardless of gestational age. Confirmed thyroid cancer, especially when the tumour grows rapidly and with unfavourable histological picture, should be treated surgically in the second trimester of pregnancy (subtotal or total excision). In the case of follicular cancer (according to some authors, this diagnosis is an indication for surgery) or small papillary cancer in early stage, surgical treatment may be postponed until after delivery. In such situations the patient should be closely monitored (at least thyroid ultrasound in every trimester), and if the tumour grows by 20% or lymph node metastases or compressive symptoms appear, then it should be removed. In patients treated with levothyroxine, TSH should be maintained at a low but significant level (0.1–1 mU/L) and T4 should be within normal limits. Radioiodine therapy is contraindicated during pregnancy and breastfeeding. Treatment with tyrosine kinase inhibitors is also contraindicated in pregnant women. Prognosis in thyroid cancer during pregnancy is similar to non-pregnant patients [2].

Acute and chronic myeloproliferative diseases (MPDs)

Diagnosis of acute or chronic myeloproliferative disease (MPD) during pregnancy is one of the most dramatic events for a woman and her family and also a challenge for the medical team, who must choose a procedure that will ensure optimal treatment of the mother and at the same time minimise adverse effects in the foetus. Disease clinical presentation is the same as in the general population. Physiological changes occurring during pregnancy may mask some symptoms and contribute to the delay of diagnosis, but in some cases more commonly performed complete blood counts allow faster detection of anomalies and guide further diagnostics.

Acute leukaemias

The incidence of acute leukaemia during pregnancy is estimated at 1/75,000 pregnancies.

Acute myelogenous leukaemia (AML) is predominant, accounting for 2/3 of cases; acute lymphoblastic leukaemia (ALL) occurs in less than 33% of cases. The clinical course of acute leukaemias is analogous to that observed in non-pregnant women, and the prognosis is similar to the overall prognosis. Most diagnoses are made in the third trimester of pregnancy (40%), and the disease is most rare in the first trimester (23%). Diagnostic criteria are the same for pregnant as for non-pregnant women, and identical diagnostic tests are used to assess prognostic factors. Antileukaemic treatment should be initiated immediately after diagnosis. The use of chemotherapy in the first trimester is associated with the risk of miscarriage or major foetal defects. For this reason, abortion should be considered when leukaemia is diagnosed prior to the 12th week of pregnancy. Cytotoxic drugs inhibit the proliferation and migration of trophoblast cells, which may result in abnormal placement of placenta, and secondarily lead to inhibition of intrauterine growth (in extreme cases: foetal death). Administration of cytotoxic drugs in the second and third trimester does not significantly increase the risk of major congenital malformations. Treatment of acute leukaemia in the first trimester (if the patient does not consent to abortion) should consist of medicines with a low teratogenic index. The disease diagnosed in the second or third trimester can be treated in the standard manner (with exclusion of drugs with a high teratogenic index — e.g. methotrexate), with regular assessment of foetal development and monitoring of foetal heart function when using cardiotoxic drugs (anthracycline antibiotics). If disease is diagnosed after the 32nd week of pregnancy, acceleration of delivery should be considered prior to commencing antileukaemic therapy. Delivery should be scheduled about three weeks after the last administration of chemotherapy. This procedure gives time for recovery of maternal bone marrow and elimination of drugs from foetal tissues, which minimises the risk of prolonged myelosuppression in newborns.

A pregnant woman should be under multidisciplinary team care, including an obstetrician, haematologist/oncologist, anaesthetist, and neonatologist. The woman should be fully informed about the diagnosis, treatment methods, and possible complications. In all cases the management should be discussed with the pregnant woman [66, 67].

Chronic myeloproliferative diseases

It seems that pregnancy does not adversely affect the natural course of chronic myeloproliferative diseases, but more often in this group obstetric complications are observed: premature delivery, placental insufficiency conducive to suppression of intrauterine foetal growth, development of preeclampsia, and foetal death as well as thrombotic and haemorrhagic complications.

Chronic myelogenous leukaemia

The incidence of chronic myelogenous leukaemia (CML) during pregnancy is estimated at 1/75,000–100,000 pregnancies. The basic drugs in CML therapy are tyrosine kinase inhibitors, but there is very little data on their effects on pregnancy, the foetus, and lactation.

The rate of congenital anomalies in children of mothers treated during pregnancy with tyrosine kinase inhibitors is estimated at 9.6%; however, in the majority of cases the drug was administered in the first trimester. From the foetal safety perspective — due to the potential teratogenic effect — treatment with an inhibitor should be stopped, but discontinuation of treatment is associated with a very high risk of exacerbation of maternal disease.

A safe drug during pregnancy (especially in the first trimester) is interferon alpha (IFNα). This cytokine is effective in treatment during the chronic phase, and in addition — due to the large molecule (19,300 D) — it does not cross the placenta and does not impose a teratogenic effect.

In any case, the management should be determined individually, balancing the risk against the benefits (e.g. continuation of treatment with tyrosine kinase inhibitor during pregnancy), and it should be discussed with the pregnant woman [68].

Essential thrombocytopaemia

In the majority of patients with essential thrombocytopaemia (ET) during pregnancy, the number of platelets decreases by 20–44% of the pre-pregnancy value. In the course of 2–5% of pregnancies in patients with NS, thrombotic complications are observed, and haemorrhagic complications occur in 4–9% of pregnancies. Patients treated with hydroxyurea or anagrelide should discontinue the drug administration 3–6 months before the planned pregnancy. In the case of continuation of cytoreductive therapy, IFNα is a drug of choice, showing significant efficacy and in most cases being well tolerated by pregnant women [69].

Polycythaemia vera

Pregnancy in a patient with polycythaemia vera is burdened with a high risk of complications: miscarriage (36%), foetal death (8%) and preterm delivery, pregnancy-induced hypertension (PIH), and preeclampsia. Haematocrit should be maintained within the limits of the values characteristic for the appropriate period of pregnancy, which can be achieved by phlebotomy or use of IFNα.

The majority of patients with chronic myeloproliferative diseases during pregnancy require anticoagulant prophylaxis; acetylsalicylic acid (ASA) is recommended at a daily dose of 75 mg, administered until the $34^{th} \pm 2$ weeks of pregnancy followed by a continuation of prophylaxis with low-molecular-weight heparin (LMWH) administered in standard doses.

In pregnant women at high risk of thrombotic complications (concomitant risk factors, like congenital or acquired thrombophilia, history of venous thromboembolism, obesity, varicose veins, twin pregnancy) combined prophylaxis is recommended (ASA with LMWH).

In each case of malignancy in the mother, the placenta and umbilical cord should be examined for the presence of tumour cells. In acute leukaemias, blood control of the newborn (possible umbilical cord blood) for the presence of leukaemia cells is also indicated. The placenta is not an excellent barrier, and pathological cells that have penetrated the foetal circulation should be destroyed by the immune system of the child within six weeks of delivery [70, 71].

Supportive care for cancer treatment in pregnant patients

White blood cell growth factors

White blood cell growth factors cross the placental barrier in the second and third trimester of pregnancy and may theoretically pose a threat to the foetus. Observations of patients undergoing chemotherapy together with growth factors (G-CSF) in comparison with patients treated without granulopoietins showed no significant differences in congenital malformations, gestational age at birth, birth weight, or other complications [71, 72]. However, due to limited experience with the use of white blood cell growth factors in pregnant women, there are no clear recommendations in English language medical literature regarding their use, and the FDA has classified these drugs into group C [72, 73].

Red blood cell growth factors

There are no data on the use of red blood (RBC) growth factors in pregnant women suffering from cancer, but there are reports of erythropoietin use in pregnant women due to renal failure and anemia, without adverse effects on mother and fetus. There is also evidence that these agents do not cross placental barrier. Therefore, it seems that use of erythropoietins in pregnant women is quite safe, but requires further observation, especially in pregnant women with cancer [72].

Antiemetic treatment

Antiemetic treatment should be used in pregnant women undergoing chemotherapy for cancer in a similar way to non-pregnant women, except for new-generation antiemetics, because there is no clinical experience so far. The majority of data in the literature is regarding the use of ondansetron and metoclopramide. In the largest group of over 600,000 pregnant patients in Denmark, ondansetron was administered in all trimesters and no increased risk of miscarriage, premature delivery, intrau-

terine death, low birth weight, or other complications was observed. There are also many positive experiences with the use of metoclopramide in pregnant women. Therefore, in antiemetic treatment in pregnant patients with cancer, ondansetron is recommended in the first-line setting (followed by metoclopramide). Data on the use of other setrons during pregnancy are very limited, which also applies to NK1 inhibitors, although animal experiments did not show adverse side effects. There is one case report published of a pregnant patient treated with NK1 inhibitor during chemotherapy for breast cancer without complications. For the above reasons, the FDA has assigned aprepitant and fosaprepitant (aprepitant *i.v.*) to category B, and the drug being a combination of netupitant and palonosetron to category C [72].

Corticosteroids

In a situation requiring administration of corticosteroids in cancer patients during pregnancy, methylprednisolone or hydrocortisone should be given, both of which are extensively metabolised in the placenta. Contrary to this, betamethasone and dexamethasone to a lesser extent are metabolised in the placenta and cross the placental barrier more easily (in addition, both drugs used in the first trimester of pregnancy may cause malformations — cleft palate, children's cerebral palsy, and others) [72].

Bisphosphonates

Bisphosphonates should not be used in pregnant women because they can cause hypocalcaemia, low birth weight, and foetal osteoclast inhibition, as well as maternal hypocalcaemia, and they persist in the bone system of the mother and foetus for many years [73].

Antibiotics

The risk of bacterial complications increases during chemotherapy. Antibiotics that can be used during pregnancy include penicillin, cephalosporins, carbapenems, and many macrolides (e.g. azithromycin, erythromycin, and spiramycin). The above-mentioned antibiotics are classified by the FDA as category B agents [72].

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