

Cancers in pregnancy: a multidisciplinary dilemma

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Abstract

Malignancies during pregnancy present a multifaceted challenge, with an incidence of approximately 81–140 cases per 100,000 pregnancies, constituting a statistically rare phenomenon. The number of incidences is constantly growing due to the delay of women's reproductive decisions. Predominant malignancies include breast cancer, cervical cancer, melanoma, and hematological cancers like Hodgkin's disease. Physiological gestational changes can lead to delayed diagnosis by masking the cancer's symptoms. Accurate diagnosis and staging, coupled with considerations of gestational age and assessment of fetal and placental structural development, are pivotal in shaping therapeutic decisions. Chemotherapy, surgery and in some cases radiotherapy are considered possible options depending on gestational age, both maternal and fetal conditions, and the type of cancer. This review provides a concise overview of common cancers in pregnancy, emphasizing their diagnosis and optimal treatment options. The comprehensive approach takes into account both maternal and fetal well-being, recognizing the intricate balance necessary for effective management within the unique context of pregnancy.

Key words: cancers in pregnancy, breast cancer.

Introduction

Malignancy associated with pregnancy is defined as cancer diagnosed during pregnancy or 1 year after labor [1]. Cancers associated with pregnancy are a statistically rare phenomenon, estimating 81–140 in 100,000 pregnancies [1]. The number of incidences is constantly growing due to the delay of women's reproductive decisions [2]. However age as a risk factor stands for only 14% of increased cases [3]. Detailed statistics about incidents vary depending on the geographical region. The most frequently diagnosed malignancies in pregnancy include breast cancer, cervical cancer, melanoma and hematological cancers e.g. Hodgkin's disease. It represents a dilemma and challenge for the physicians in the fields of gynecology and obstetrics, oncology, perinatology and neonatology to provide optimal therapy for the mother and the fetal well-being [4]. Physiological alterations in pregnant woman's organism can make the diagnostic process more demanding. In pregnancy, laboratory testing of tumor markers has less sensitivity and specificity due to mentioned changes [3]. Moreover, choosing imaging methods is always necessary to take into consideration both maternal benefit and fetus risk. Chemotherapy, surgery and in some cases radiotherapy are considered possible

options depending on gestational age, both maternal and fetal conditions, and the type of cancer [5]. Whenever it is possible doctors should adhere to standards of non-pregnant women's treatment and avoid delay of onset of the therapy [6]. However, given the safety of the fetus, some methods need to be adjusted [5].

In this paper we review the most common gynecological pregnancy-associated cancers, taking into account breast cancer as the first cancer worldwide, their diagnostic, treatment options, and prognosis for both mother and fetus. It is crucial to mention that other gynecological cancers such as: endometrial, vulvar, vaginal, and fallopian tube cancers are very rare conditions during pregnancy.

Breast cancer

Breast cancer (BC) is known to be the most common malignancy in women worldwide. It also stands to be the most frequently diagnosed cancer in pregnancy [7]. Controversial definitions of pregnancy-associated breast cancer (PABC) include gestation and the postpartum period. The period to classify malignancy as a special type of PABC ranges from 0.5 to 5 years which leads to different statistical outcomes [7, 8]. Pregnancy is well-known as a long-term protective factor against BC, however, the gestation period temporarily increases the risk of developing breast cancer [7]. The risk of developing PABC is also higher in a group of women older than 35 in their first pregnancy [8]. Other risk factors include family history and BRCA mutation.

Diagnostic process

Diagnostic challenges of PABC are mostly related to physiological changes in breast glandular tissue during pregnancy [3].

Different studies show that the delay of the diagnosis of BC during pregnancy ranges from 1 to 13 months [8]. According to guidelines, every mass found in a breast which persists for more than 2 weeks should be investigated [6].

After the physical examination, the first line of the diagnosis of the breast lesion is ultrasonography (USG) with sensitivity reported to be approx. 100%. Mammography applies to the diagnostic process of extended disease, however, the sensitivity rate is lower than USG (78%). Fetal radiation exposure is minimal (range: 0.00–0.01 mGy) [9]. While the risk of fetal malformation is proved to exist above 100 mGy of radiation exposure.

To determine the histological type of tumor, nuclear grade and receptors presence, the examination of the core needle represents a reference standard as in BC diagnosis in general. It is im-

portant to mention that pathologists should be informed about the pregnancy status of the patient given the risk of false-positive results.

Studies report the unsure usefulness of the Magnetic Resonance Imaging (MRI) diagnosing PABC due to the lack of possibility to distinguish hypervascularization induced by cancer and the glandular hyperplasia of the gestational and breastfeeding period. Furthermore, gadolinium, which is used as an MRI contrast agent is observed in studies of rats as potentially teratogenic and crosses the placenta [9]. However MRI can be a useful diagnostic method for metastatic disease [6].

Treatment

The main goal of PABC treatment remains the same as for nonpregnant women: local control and prevention of distant metastasis. Studies show that pregnant patients should receive adequate oncological therapy without delay and pregnancy should be maintained as long as possible [6].

Chemotherapy

Studies report that there is no absolute contraindication to chemotherapy during pregnancy. The stage and biology of PABC should be considered to using systemic treatment. In metastatic disease chemotherapy will be a method of choice [6].

The high risk of fetal malformation and losing a pregnancy in the first trimester make chemotherapy contraindicated in that period, although, the second and third trimesters, starting at 12 weeks of gestation are claimed to be safe [10]. The preferred group of chemotherapy treatment's stands for anthracycline-based regimens. Moreover, studies by Mir *et al.* also show a favorable prognosis of using taxanes for PABC. High risk of fetal malformations and the third space effect make methotrexate an unrecommended treatment option [10].

It is important to mention that during the treatment period, strict fetus and mother monitoring should be provided as various potential side effects may occur during therapy including the risk of premature delivery, intrauterine growth restriction, and hypertensive disorders of pregnancy. Additionally, after 34 weeks of gestation, chemotherapy should not be administered due to the risk of spontaneous delivery during the hematologic nadir period [6].

Targeted and endocrine therapy

There are limited data and research on targeted therapy for pregnant women with BC due to widely known potential teratogenic effects [11]. While pregnant endocrine treatment (e.g., tamox-

ifen) should not be considered a treatment option due to the high risk of congenital malformations and the risk of spontaneous abortion. Hormonal treatment should be postponed after birth [12]. The same contraindications throughout pregnancy apply to medications for patients with human epidermal growth factor receptor 2 (HER2) positive BC: trastuzumab and pertuzumab due to the association with oligohydramnios or anhydramnios, but also malformations of fetus kidneys and lung function [13]. Moreover, the majority of targeted therapies are dedicated to specific tumor features which also apply to physiological fetus development [11].

Surgical treatment

Surgery is considered a treatment option in every stage of pregnancy [6]. Also anesthetic drugs in adequate concentration are proven to be safe for the fetus. Preferably surgery should be postponed after delivery, however, decisions on surgery timing vary on factors such as gestational age, tumor stage, and characteristics as well as patient expectations [6, 14].

The choice of PABC surgery should follow the same guidelines as for non-pregnant patients [6]. The breast-conserving therapy remains to be a method of choice, with a safe outcome to proceed with prosthetic implants if needed [6].

In the first trimester, modified radical mastectomy with axillary staging is the method of choice due to need of radiotherapy postponement. Breast-conserving surgery is safe to be performed in the second and third trimesters [3].

Radiotherapy

Radiotherapy as a treatment option should be considered only for special cases [14]. The potential fetal risk is estimated by factors such as distance from the radiation target, volumes and radiation, therapy parameters, including size and site of the target volume combined with technical parameters. Radiotherapy as a treatment indication for patients with BC is used for palliative cure in metastatic disease but also in post-surgery treatment [6]. Recently a one-week therapy regimen with 5 fractions of 26 Gy is a recommended option. The collaboration between physicians and the radioprotection team plays a crucial role to calculate individual doses for every patient [14].

Outcome: the women and children

Every patient with PABC is considered as a high-risk obstetric patient. Detailed pregnancy check-up is recommended to be performed every 3 weeks [14]. If no other contraindications exist, vaginal birth is a method of choice for delivery

for PABC patients, since chemotherapy can be restarted immediately after delivery, in comparison to the cesarean section, where 1-week interval for chemotherapy onset is needed [14]. Importantly, the termination of pregnancy has not been shown to improve maternal outcomes [6].

Cervical cancer

Cervical cancer (CC) is the eighth most common malignancy women suffer from. In recent years, more women, especially in developed countries, have decided to get pregnant at a later age, which results in CC being diagnosed during pregnancy more frequently. CC is currently the second most frequently diagnosed malignancy, and the most common gynecological malignancy during pregnancy – around 4 instances per 100,000 pregnancies [11, 15, 16].

Diagnostic process

Over 70% of cases of CC in pregnant women are diagnosed at early stages (IA1-IB3), thanks to cytologic screening tests, and the treatment can be administered after the parturition [15, 17, 18]. At the same time Sonoda *et al.* show that pregnancy may delay the diagnosis of CC, because symptoms, like bleeding, are considered pregnancy-related. That leads to cancer reaching a more advanced stage when diagnosed. Moreover, diagnostic methods – pap smear and colposcopic examination – seem to be less accurate during pregnancy as a result of hyperplasia of the glandular cells, edematous vaginal wall, stromal edema and increased vascularization that occur in that period [15, 19]. When alarming symptoms are found during the examination, a biopsy is recommended. In more suspicious cases, a flat large loop excision of the transformation zone (LLETZ) should be performed (preferably between the 12th and 20th week of gestation as the least number of complications is reported in that time) [15].

Imaging tests like USG and MRI are used in defining the stage of CC. Those tests are recommended during pregnancy, because they are safe for the fetus as MRI can be carried out without contrast in the staging process of CC [15, 20].

Before the 22nd week of gestation staging of pelvic lymphadenectomy can be performed. After that time, the volume of the uterus is too big and access to the pelvic walls and nodes is often restricted. It can be done by laparoscopy preferably between the 14th and 16th week of gestation or laparotomy performed after the 16th week [11, 15].

Treatment

Treatment of CC for pregnant women depends on the stage of disease, histopathological subtype

and also a week of gestation and the patient's desire to preserve the pregnancy and reproductive ability [21]. In the most common histopathological subtypes (squamous cell carcinoma, adenocarcinoma, and glandular-squamous carcinoma) the prognosis is comparable, so the treatment approach can be similar. If another subtype is diagnosed (for example small cell carcinoma) the prognosis may be worse, and termination of the pregnancy should be considered, to introduce proper treatment [20].

Early stage CC

In the case of women with early-stage CC, the progression of the disease is rare and proper treatment may be delayed, for the fetus to mature without additional risks [22]. However, some surgical procedures, like large cone biopsy, simple trachelectomy, or radical trachelectomy can be performed in pregnant women. It is recommended to operate after the first trimester. In the case of radical trachelectomy, surgeries with vaginal access seem to have fewer complications than those with abdominal entry [15].

Locally advanced CC

Locally advanced CC needs to be treated immediately, except for a short delay in the third trimester for fetal lungs to mature [22, 23]. Common treatment of locally advanced CC is chemoradiotherapy, but during pregnancy, radiotherapy of the pelvic region is not recommended as it may cause adverse reactions such as spontaneous abortion or congenital malformations [22, 24]. Because of that, the patients who want to preserve the pregnancy, should be treated with neoadjuvant chemotherapy as soon as possible, followed by radiotherapy after childbirth [24]. Usually platinum-based chemotherapy is administered, however, this treatment administered in the second or third trimester can also cause adverse reactions, like low birthweight, intrauterine growth retardation or prematurity [21, 22].

Metastatic CC

Diagnosis of metastatic CC during pregnancy is rare, and the prognosis is poor. Termination of the pregnancy should be considered, especially if diagnosed at early weeks of gestation, to introduce standard treatment – platinum-based chemotherapy with bevacizumab. If the patient decides to keep the pregnancy, only systemic chemotherapy should be administered as bevacizumab is contraindicated [22].

A few cases have been reported of CC metastasis to the placenta. As this is such a rare situation, there are not much data on the subject. However

it could be the cause of spontaneous abortion, so it is worth keeping that in mind during the diagnostic process [18].

Delivery

Choosing the form of delivery depends on the presence of the tumor. If the surgery has been performed and the tumor has been removed, vaginal delivery (VD) is possible except for radical trachelectomy which is a contraindication to VD. If conservative treatment has been chosen and the tumor is present, a cesarean section is suggested as there is a high risk of excessive bleeding from the tumor. During the cesarean section, trachelectomy or hysterectomy may be performed, if it is recommended in patients' oncological condition [16].

Research also indicates that there are further possible complications of VD for patients with CC. There is a possibility of metastatic spread of cancer to the vagina or its transmission to the newborn by vaginal fluids [19].

Outcome: the women

A study from 2012 on a group of 132 pregnant women diagnosed with CC shows that due to CC being usually diagnosed at the early stage and surgery and chemotherapy being increasingly used during pregnancy, the prognosis for pregnant and non-pregnant patients with CC is similar [25].

Ovarian cancer

Ovarian cancer during pregnancy is rare. In consideration of pregnant women the percentage of ovarian tumors is approximately 2.4% to 5.7%, being the second most common gynecologic cancer diagnosed during pregnancy. Among this percentage, around 5% of the cases are diagnosed as malignant tumors [26, 27]. OC is the fifth most common malignancy affecting pregnant women, following breast cancer, thyroid cancer, cervical cancer, and Hodgkin lymphoma [28]. The most frequent histological types of OC among pregnant women are borderline (48.1%), germ cell tumors (24.6%), epithelial tumors (21.6%), and sex cord-stromal tumors (0.5%) [29]. There were no clinical studies on a large number of pregnant women treated for ovarian tumors and all procedural attempts and medical treatment background is limited.

Diagnostic process

Ovarian cancer presents with symptoms late. Different types of OC have various ranges of presentations, tumorigenesis, and gene expression profiles. Studies show that ultrasound sessions during pregnancy lead to early diagnosis of as-

ymptomatic ovarian masses and there is a larger range of treatment options [27, 29]. USG is a first-choice test as it is cheap and the most readily available. It can show many findings, including tumor size, speed of growth, increased vascularity presence of free abdominal-pelvic fluid and presence of solid areas or multiloculate masses. Moreover, color Doppler imaging can be used to show tumor vascularization. Imaging tests help to confirm the diagnosis and differentiate benign masses from malignancy. If the ovarian mass is too big to access or there is an increased risk of malignancy, MRI is recommended [27]. MRI does not use ionizing radiation so it is not harmful to the embryo or fetus. MRI can show deep soft tissue structures, evaluation of big masses, retroperitoneal space and nodal metastases [29].

Tumor markers are less valuable due to the physiological changes during gestation [26, 29]. It is noted that levels of human chorionic gonadotropin (hCG) and cancer antigen 125 (CA 125) are increased during pregnancy, particularly in the first trimester. However, higher levels of lactate dehydrogenase (LDH), inhibin B, human epididymis protein 4 (HE4), carcinoembryonic antigen (CEA), cancer antigen 19-9 (CA 19-9), anti-Müllerian hormone (AMH) and α -fetoprotein (AFP) might be useful in the diagnosis of ovarian cancer because their levels are expected not to be increased during pregnancy [27].

Treatment

The therapeutic process for pregnant women with ovarian masses is difficult as many complications might occur causing danger both to the mother and the developing fetus. Due to a lack of randomized trials and clinical studies, there are no definitive guidelines regarding the therapeutic process of ovarian cancer in gestation. The diagnostics and management need to be individualized due to the tumor histopathology, its growth, the general condition of the mother and fetus and the duration of pregnancy. A decision should be made individually considering all potential risks and benefits of therapy and the mother's desires regarding pregnancy preservation [27, 29].

Surgery and chemotherapy

The current management of OC includes surgical treatment and chemotherapy [27]. When there is a low risk of suspicion of malignancy, pregnant women should be qualified for the procedure in the planned course. In case of the possibility of malignancy, according to clinical imaging findings, there is no reason to delay the surgery until the second trimester. If it is possible, the procedure should be done during the safest period of ges-

tation – the second trimester [29]. What is more, by the second trimester most of the identified adnexal masses in gestation resolve spontaneously [30]. Studies show that elective surgical therapy of patients with OC results in lower rates of adverse effects including miscarriage, in comparison to emergency surgical interventions. If the ovarian mass was found in the third trimester and there is a low risk of suspicion of malignancy, the surgery can be postponed until postpartum [29]. Laparoscopic or open surgery should be safe if the surgeon is experienced. If a patient desires to preserve the pregnancy, a cystectomy or an adnexectomy followed by platinum-based treatment is recommended. In that case, cytoreductive surgery should be performed after delivery as it is too dangerous to be done during gestation [11, 29]. Chemotherapy (CT) of pregnant women is associated with several complications that are not observed in non-pregnant patients, including spontaneous abortion or hypotrophy. Congenital malformations are noticed to be at the highest risk between 4th and 10th week of pregnancy, so the administration of CT during the first trimester should be avoided and suggested from the second trimester when fetal organogenesis is complete [27, 31]. After 35 weeks of pregnancy, CT is also not recommended as the last three weeks of gestation are needed for the recovery of both fetus and mother before the delivery [27]. Patients can be treated with a combination of carboplatin and taxanes [32].

Other therapies

Radiotherapy in most cases is contraindicated during gestation. Targeted therapy, which is recommended for OC patients, in non-pregnant women is limited due to no evidence-based medicine about it. It is recommended to postpone targeted therapy after delivery [27].

Outcome: the women

The most common complications with an ovarian mass during pregnancy are ovarian torsion and/or rupture, abortion, preterm delivery, and low birth weight. Also, the bigger the size of the mass, the higher the risk of complications [33]. It is proven that pregnant women with cancer are at high risk of suffering from coagulation abnormalities. Coagulation might be also induced by CT used in ovarian cancer management. Thrombotic bleeding can harm the mother and fetus to an extreme degree [26].

OC is mostly associated with poor prognosis in non-pregnant women. The high mortality rate is mainly caused by very late signs and symptoms of cancer and late diagnosis [11, 26]. However, due to the frequency of ultrasounds in gestation,

around 90% of pregnant patients with OC are diagnosed with stage I disease [29]. Due to a lack of trials and clinical studies, there are no precise data about the number of relapses and deaths of patients with ovarian cancers.

Outcome: the children

It was proven that pregnant women with surgical treatment have better obstetric outcomes than patients with chemotherapy or surgery with chemotherapy. Studies showed fewer cases of admission to neonatal intensive care units, growth restriction, preterm premature rupture of the membranes, or preterm contractions or low birth weight [34].

Other gynecological cancers

Endometrial cancer

Endometrial cancer diagnosed during pregnancy is an extremely rare condition. In most cases, it is diagnosed postpartum, manifested by uterine bleeding or while searching for the cause of miscarriage. Standard treatment regimens like surgery or radiotherapy are contraindicated if the patient wants to preserve the pregnancy. In this case patient's informed consent is needed to follow the observational approach [20, 35]. Gynecological cancers such as endometrial, vulvar, vaginal and fallopian tube cancers are very rare conditions during pregnancy.

Summary

Malignancies during pregnancy represent a multidisciplinary dilemma. Diagnosis can be delayed due to gestational changes masking cancer's symptoms. Accurate diagnosis and staging combined with gestational age and assessment of the structural development of the fetus and placenta affect decisions about the therapeutic process. Patient management in an organized multidisciplinary center is crucial for a successful outcome for the mother and the fetus. Appropriate and honest communication with the patient is crucial to maintain the patient's confidence and support. Another important factor in choosing the right method of treatment is the patient's willingness to maintain the pregnancy and preserve reproductive ability [3, 23, 29].

It is believed that due to regular check-ups in pregnancy consisting of gynecological examination, ultrasound sessions, and physical examination of the breast, malignancies can be detected in the early stage [36].

Conflict of interest

The authors declare no conflict of interest.

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