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Review

Pregnancy associated cancer: General principles

Ioannis Rellias[1], Alexandra Tsigginou[1], Flora Zagouri[2], Spyridon Marinopoulos[1], Aris Giannos[1], Kalliopi Pappa[1], Constantine Dimitrakakis[1]

[1] 1st Department of Obstetrics and Gynecology, National & Kapodistrian University of Athens, Alexandra Hospital, Athens, Greece

[2] Department of Therapeutics, National & Kapodistrian University of Athens, Alexandra Hospital, Athens, Greece

Correspondence

Rellias I. 1st Department of Obstetrics and Gynecology, National & Kapodistrian University of Athens, Alexandra Hospital, Athens, 80 Vasilissis Sofias ave., PC 11528, Athens, Greece, Tel: +306947724381

E-mail: giannisrellias@gmail.com

Abstract

Pregnancy associated cancer is defined as the cancer diagnosed during pregnancy or within 1 year postpartum. Since women seem to be delaying childbearing to later ages than in previous generations, the incidence of cancer during pregnancy is constantly increasing. Treatment of cancer during pregnancy is a difficult clinical condition as both mother and fetus may be affected. This article summarizes the general principles in managing pregnant patient with cancer and notes some discrete problems in the management of specific cancers such as breast, cervical, ovarian cancer and melanoma. Of note, guidelines for the proper management of pregnant patient with cancer diagnosis are based on insufficient data from retrospective studies and case series. Hence, the management of these women should be individualized and performed in specialized centers with great experience and all cases should have multidisciplinary approach from multiple specialists such as medical oncologists, obstetricians, surgeons, radiologists and paediatricians.

Key words: cancer; pregnancy; malignancy

Introduction

Pregnancy associated cancer is defined as the cancer diagnosed during pregnancy or within 1 year postpartum[1]. Since women seem to be delaying childbearing to later ages than in previous generations, the incidence of cancer during pregnancy is constantly increasing[2]. Treatment of cancer during pregnancy is a difficult clinical condition as both mother and fetus may be affected. Data for the proper management of pregnant women with cancer are insufficient and guidelines are based on retrospective studies or case series[1,3]. Therefore, this clinical situation should have a multidisciplinary approach from multiple specialists (medical oncologists, obstetricians, surgeons, radiologists and paediatricians).

Epidemiology

Malignancies have an incidence of approximately 1:1,000 pregnancies. Breast cancer, melanoma, cervical cancer, lymphoma and acute leukaemia are the most commonly diagnosed malignancies during pregnancy[4,5]. Breast cancer accounts for one case per 3,000-10,000 live births[6] and most of these are diagnosed post partum. The incidence of melanoma is

about 0.14-2.8 of 1,000 pregnancies[5-7] that of cervical cancer is 0.8-1.5 of 10,000 births[8] and that of acute leukaemia and lymphomas are 1:75,000-1:100,000 and 1:1,000-1:6,000 pregnancies, respectively[9].

Management of pregnant woman with cancer

Management of the pregnant woman with cancer must be individualized, and always keep in mind that both mother and fetus may be affected. Considerations include the type and stage of cancer and the desire for pregnancy continuation with the inherent risks associated with modifying or delaying treatment. The general golden rule is that treatment should not differ between pregnant and not pregnant woman, if this is feasible. But it is important to consider the consequences from the chemotherapeutic drugs on the fetus as well as the long-term complications after in utero exposure to anticancer therapy. Pregnancy complicated with cancer should always be considered as high risk and there must be ultrasonographic monitoring of the fetus with biometry and Doppler of the umbilical artery. The goal should always be a full-term pregnancy and the last chemotherapy dose should be administered 3 weeks before the planned date of delivery, in order to avoid haematological toxicity in both the mother and the baby[3, 10, 11]. The mode of delivery should be based on obstetrical indications, except for cases with gynecological cancer. Placentas from pregnancies in women with cancer should be sent for histological evaluation. The most common type of tumor that metastasize to the placenta and the fetus is melanoma[12].

Staging evaluations during pregnancy

The staging system during pregnancy is always the same as for non-pregnant patients with cancer (i.e. TNM system for breast cancer, and FIGO staging for cervical and ovarian cancer)[1, 10]. Recommended initial staging should include the following: complete history and physical examination, comprehensive metabolic panel and complete blood count. It is important to note that pregnant patients may have anemia due to the increase in circulating plasma volume. They may have increases in serum alkaline phosphatase level that can be doubled or tripled due to the pregnancy itself. Tumour markers are not reliable, they have no diagnostic value and consequently they should not be performed during pregnancy[13]. The staging evaluations may also include chest X-ray and mammogram with abdominal shielding in an effort to limit the exposure to ionizing radiation; echocardiogram prior to the use of an anthracycline based chemotherapy; ultrasound of the abdomen; and a screening noncontrast MRI of the thoracic and lumbar spine to exclude bone metastases. If there is high suspicion of metastases after ultrasound examination, an abdominal non-gadolinium-enhanced MRI may be considered. Gadolinium is considered a pregnancy category C drug, (animal studies have shown diverse fetal effects), hence, use of it during pregnancy is contraindicated, especially in the first trimester[14,15]. Moreover, CT scans, bone scans and positron emission tomography (PET) scans are not recommended for routine use.

Surgery during pregnancy

Surgery can be safely performed in all trimester of pregnancy. However, there is a slightly elevated risk of miscarriage during the first trimester[1, 10]. A recent review of surgery in the pregnant patient recommends that the preferred timing for surgical intervention is 16-20 weeks of gestation[16]. Of note, in major pelvic surgery there is increased morbidity and higher rates of complications, and in these cases should always be involved a multidisciplinary team to optimize outcomes for both the mother and the fetus. Nonetheless, surgery should never be delayed during pregnancy[1,16].

Chemotherapy during pregnancy

Systemic chemotherapy can be given safely during the second and third trimester of pregnancy[17,18]. The first trimester is the period of fetal organogenesis and there is higher risk of miscarriage and congenital malformations. Published reports demonstrate that first trimester chemotherapy exposure is associated with a 10%-20% risk of fetal malformations, while 2nd an 3rd trimester exposure is significantly safer with a fetal malformation risk of 1,3%[19]. In cas-

Gestational age	Fetal effects
From conception to 10 days	Abortion
2-12 weeks	Malformations and intrauterine growth restriction (IUGR)
13-16 weeks	Mental retardation and IUGR
17-26 weeks	Malignancies, sterility, genetic defects

es that chemotherapy administration is mandatory in the first trimester pregnancy termination should be considered[1]. According to available data, it is safe to give chemotherapy during the 2nd and 3rd trimester; however there is a relatively higher risk of premature rupture of membranes, intrauterine growth restriction and premature labour[17-19]. There is limited knowledge regarding pharmacokinetics of chemotherapeutic agents due to the physiologic changes of pregnancy, so the recommended dosage of drugs should not vary from those used outside pregnancy[20].

Radiation therapy during pregnancy

Radiation therapy should be administered only after delivery of the fetus. Radiation exposure during pregnancy may result in fetal death, congenital malformations, mental retardation, intrauterine growth restriction, and carcinogenesis[21, 22]. In general effects such as congenital malformations and mental retardation probably only arise above a threshold dose of 0.1-0.2 Gy[22]. In the following table there is a summary of radiation effects on the fetus in relation to gestational age.

Supportive care during pregnancy

Chemotherapy induced nausea and vomiting can be safely treated with metoclopramide and as second choice ondansetron during pregnancy[23,24]. Granulocyte colony-stimulating factor (G-CSF) is considered as pregnancy category C drug and it should be used only if it is indicated. It crosses the placenta and according to the limited data this agent does not seem to have any detrimental effect to the fetus[25,26]. Our knowledge on the effects of human erythropoietin in pregnant women with cancer is based on data from pregnant women with renal failure. It seems that human erythropoietin does not cross the placenta and consequently it is safe to use it during pregnancy[27,28]. Concerning antibiotics, penicillins, cephalosporins, carbapenems, and some macrolides (erythromycin, azithromycin and spiramycin) are considered as pregnancy category C drugs and may be used during pregnancy[29].

Special considerations by specific site cancer

Breast cancer

Breast surgery can be performed in all trimesters of pregnancy. Modified radical mastectomy is the standard of care in the first trimester due to concerns regarding radiation therapy. Breast-conserving surgery is an option in the second and third trimester by postponing radiotherapy after delivery[1,30]. The safety and efficacy of the sentinel lymph node biopsy (SLNB) is currently not well established. Fetal radiation exposure is low and this concern should not preclude the use of SLNB during pregnancy[31]. However blue dye mapping is not recommended due to concerns of unknown effects for the fetus as well as risk of anaphylaxis for the patient[32, 33]. Sensitivity of SLN mapping may be decreased without using blue dye. The concern of SLNB during pregnancy is not associated with the procedure itself but with the accuracy of the diagnostic information obtained as a result of the procedure.

The indications of chemotherapy administration in pregnant women with breast cancer are identical with those in non-pregnant women with breast cancer. Anthracycline-based regimens (AC, EC, FAC or FEC) are the first choice of treatment, as the majority of safety data are available with the use of anthracyclines[1, 30]. Regarding taxanes (paclitaxel and docetax-

el), there is a systemic review on 50 pregnant patients with breast cancer who received taxanes after the first trimester. The authors concluded that 77% of the neonates were completed healthy at delivery and at 16 months of follow-up 90% of the infants were reported to be completed healthy[34]. Consistent with these results are the data from the American-based and European-based registries[35, 36]. According to these data and to the European Society for Medical Oncology (ESMO) guidelines, taxanes may be used in selected cases during pregnancy (i.e., selected cases of triple-negative or HER2-positive breast cancer) or in cases where anthracyclines are contraindicated[1].

According to current clinical practice guidelines trastuzumab is contraindicated during pregnancy[1,3]. There have been reports of anhydramnios and fetal deaths with its use[37-40]. Zagouri et al. have reported a meta-analysis of trastuzumab administration during pregnancy[41]. The authors concluded that trastuzumab administration seems to be relatively safe during the first trimester, whereas there is a high incidence of oligohydramnios and/or anhydramnios when the monoclonal antibody is used beyond the first trimester. Of note all children exposed to trastuzumab exclusively during the first trimester were completely healthy[41]. According to HERA trial when occurring a pregnancy during trastuzumab administration, this pregnancy can be preserved and trastuzumab should be discontinued[42]. Regarding lapatinib there is only one report of a patient who conceived while on lapatinib[43]. Despite of approximately 11 weeks of in utero exposure, the pregnancy was uncomplicated with delivery of a healthy baby. Nevertheless, the agent should not be recommended during pregnancy because of insufficient safety data. Data on exposure to pertuzumab have not been reported so far so is contraindicated during pregnancy.

Endocrine therapy, if indicated, should be initiated after delivery. It is contraindicated during pregnancy due to the high risk of birth defects, up to 20% of exposures[44,45]. Moreover, for patients becoming accidentally pregnant while on tamoxifen use, termination of pregnancy should be advised due to the high risk of congenital malformations[1,30,45].

Lymphomas

When early stage Hodgkin's lymphoma is diagnosed in the first trimester it is recommended close monitoring and initiation of chemotherapy in the second trimester. On the other hand when there is advanced Hodgkin's lymphoma in the first trimester, pregnancy termination should be considered[1,9,46]. The recommended regimen after the first trimester consist of adriamycin, bleomycin, vinblastine and dacarbazine (ABVD). Non-Hodgkin's lymphoma (NHL) is aggressive and immediate treatment is mandatory; hence, for patients diagnosed in the first trimester of gestation pregnancy termination should be considered, whereas for patients diagnosed in the second and third trimester, CHOP is the standard chemotherapy regimen, without significant increased fetal morbidity[1,9,46]. Regarding Rituximab it can beadministered safely during the second and third trimester of pregnancy without significant increase of fetal adverse effects; however, a relatively increased risk of neonatal infection and transient B cell depletion has been documented[47]. Moreover, patients that conceive during rituximab administration can preserve their pregnancy, provided that treatment with the antibody is hold[1,9].

Cervical cancer

Treatment of cervical cancer in pregnant women is individualized and depends on the clinical stage, fetal age, and individual desire to continue pregnancy. In women with stage IA1 diagnosed by cone biopsy, continuation of pregnancy and vaginal delivery are considered safe. Re-evaluation of the disease should be done 6 weeks postpartum. Cervical cancer stage IA2, IB or IIA demands radical surgery. During the first half of pregnancy, immediate treatment is advised by most, but this depends on the decision whether to continue pregnancy. For pregnant patients with early-stage cervical cancer who want to preserve the pregnancy, therapy may be delayed until after delivery; of note, close monitoring in these cases is of great importance. With diagnosis during the latter half of pregnancy, most agree that pregnancy can safely be continued not only until fetal viability is reached, but also until fetal lung maturity is attained. Another op-

tion is to perform laparoscopic lymphadenectomy and to delay treatment if metastases are excluded. Notably, radical surgery can be performed concurrently with the caesarean section[1,8]. Women with advanced cervical cancer diagnosed prior to fetal viability are offered primary chemoradiation. Spontaneous abortion of the fetus tends to follow whole pelvis radiation therapy. If cancer is diagnosed after fetal viability is reached and a delay until fetal pulmonary maturity is elected, then a classical cesarean delivery is performed. Chemoradiation is administered after uterine involution. Women who elect to delay treatment, to provide quantifiable benefit to their fetuses, will have to accept an undefined risk of disease progression and impaired prognosis[1,8,48]. In patients with locally advanced disease or high-risk tumour neoadjuvant platinum-based chemotherapy, with or without paclitaxel can be an option[1,49]. Local response rates reported in pregnant patients with cervical cancer are similar to those recorded outside the pregnancy setting[49, 50].

Melanoma

The mainstay of treatment of melanoma is surgical resection. SLNB can be used during pregnancy using Technetium-99, rather than blue dye[1]. For metastatic disease, it is recommended interferon-a, due to lack of safety evidence during pregnancy for other agents such as ipilimumab, vemurafenib, dabrafenib, trametinib and cobimetinib[1, 9].

Ovarian cancer

The types of ovarian malignancy during pregnancy are different than in older women. In pregnant women the most common type is germ cell tumor. Management of ovarian cancer is similar to that of nonpregnant women. If frozen section analysis is positive for malignancy then surgical staging is done with inspection of all peritoneal surfaces, peritoneal washings are taken for cytology, biopsies are taken from diaphragmatic surface and peritoneum, omentectomy is done, and pelvic and paraortic lymphadenectomy is performed. Some of the surgical staging steps, especially lymphadenectomy, may not be technically feasible because of the enlarged uterus. In advanced disease bilateral andexectomy and omentectomy will reduce tumor burden. In early pregnancy, aggressive debulking may be elected with hysterectomy, but if optimal debulking is not possible then minimal debulking is performed and the operation is terminated. Chemotherapy can be given during pregnancy while awaiting pulmonary maturation. The recommended chemotherapy regimen for epithelial ovarian cancer is carboplatin with weekly paclitaxel after the first trimester of pregnancy and seems to be relatively safe[1,51]. The recommended combination for germ cell ovarian tumors is cisplatin and weekly paclitaxel, after the first trimester[1]. The BEP (bleomycin, etoposide, cisplatin) regimen typical used for the treatment of germ cell tumors, is not proposed due to the relatively increased risk of fetal intrauterine growth restriction and neonatal complications that have been reported[52-54].

Conclusion

Treatment of cancer during pregnancy is a difficult clinical condition as both mother and fetus may be affected. Data for the proper management of pregnant women with cancer are insufficient and guidelines are based on retrospective studies or case series. Treatment should be individualized and performed in specialized centers with great experience. This clinical situation should have a multidisciplinary approach from multiple specialists.

Conflict of interests

The authors declare that they have no conflict of interest.

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