

Section 1

Specific tumors during pregnancy

Chapter

1

Bone malignancies in pregnancy

Michael Lishner and Alla Osadchy

Introduction

Primary bone cancer is rarely associated with pregnancy [1,2]. The available information regarding its evaluation and management is very limited. A delay in diagnosis due to misinterpretation of tumor-related symptoms as those of normal pregnancy has been suggested [3].

Diagnosis

Although magnetic resonance imaging is the diagnostic method of choice [4] and can be repeated many times in pregnancy [5], ultrasound, biopsy to stage the tumor, and clinical examination remain equally safe and important in arriving at the diagnosis. Tests applying X-rays or gamma-rays (isotope scans) should be avoided [6]. Independence of bone tumors from hormonal regulation was shown [3]. The association of bone neoplasm with pregnancy may be fortuitous [7]. Rare cases of recurrent bone tumors diagnosed during pregnancy might be due to increased medical surveillance [8].

Treatment

Therapeutic considerations are complex, and a combined modality approach including surgery, radiation, and chemotherapy is often used and should be tailored to the individual patient. While surgical resections are generally regarded as safe during pregnancy, chemotherapy and radiation treatment are likely to be deferred until after delivery [6,9].

The decision-making analysis should include the type and site of the primary tumor, its growth rate and associated symptoms, the use of specific diagnostic tests, and appropriate treatment options [10]. Vaginal deliveries are possible [6,9]. In cases of bone malignancies involving the pelvis, cesarean section delivery might be considered to increase fetal safety [11]. Nevertheless, spontaneous vaginal deliveries after hemipelvectomy due to malignant tumors of the pelvis have been reported [12].

Prognosis

Although based on very limited data, it was suggested that pregnancy does not appear to exacerbate tumor growth or affect the outcome of the patients [9,13]. Based on small series, reproductive outcomes of long-term survivors of malignant bone tumors appear to be favorable, with a high rate of success to conceive and no birth defects in offspring reported [14,15].

Cancer in Pregnancy and Lactation: The Motherisk Guide ed. Gideon Koren and Michael Lishner.
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Section 1

Specific tumors during pregnancy

Chapter

2

Breast cancer and pregnancy

Liat Mlynarsky and Michael Lishner

Introduction

Breast cancer is the most commonly occurring malignancy among women of reproductive age and the second most common pregnancy-associated cancer, after cervical cancer [1,2]. Pregnancy-associated breast cancer (PABC) is defined as breast cancer diagnosed during pregnancy or within one year postpartum and it is estimated to account for up to 3% of all breast cancers. The prevalence of PABC is between 1 in 3,000 and 1 in 10,000 pregnancies.

Diagnosis

A high index of suspicion is required when evaluating a breast mass among pregnant and lactating women because of the substantial physiological changes of the female body during pregnancy. When a new breast mass is suspected, diagnostic evaluation must begin promptly.

Although mammography is the imaging of choice among nonpregnant women with a breast mass, its sensitivity declines among pregnant and lactating women due to the glandularity and the water content of the breast [1]. In one study, the false-negative mammography rate was significantly higher among pregnant women than among non-pregnant women (14% vs. 6%, respectively; $P < 0.0001$) [3]. Ultrasound is the modality of choice when PABC is suspected. It has been reported to distinguish solid from cystic lesions in 97% of cases [4], and with 100% sensitivity in a few studies [1,5,6].

There are insufficient evidence-based data regarding the efficacy of magnetic resonance imaging (MRI) and the safety of gadolinium during pregnancy. Thus, the international recommendations from an expert meeting summarized by Loibl *et al.* recommended against it [7].

When there is a palpable breast mass, the diagnostic procedure of choice is excisional biopsy under local anesthesia [8,9]. Fine needle aspiration can discriminate a cyst from a solid tumor, but the diagnostic value of cytology is diminished in pregnant or lactating women due to the presence of a hyperproliferative state which leads to a high false-positive rate.

Where there is a large mass, incisional biopsy should be considered. The yield of the biopsy is equivalent among pregnant and nonpregnant women, but the rate of complications is higher among pregnant or lactating women due to increased vascularity and the presence of breast milk as a culture medium. Another possible complication is milk fistula formation, more prevalent in central biopsies [8]. Some authors recommend emptying

the breast a week before the procedure by ceasing breast feeding, binding the breast, and placing ice packs. If it fails, bromocriptine can be used [4,10,11]. Nevertheless, there are no clear guidelines regarding prevention of biopsy-related complications.

Pathology

Invasive ductal carcinoma is the most commonly found histology in both pregnant and nonpregnant women of similar ages. It represents 75%–90% of the breast cancers in pregnant women [7,12,13]. The incidence of inflammatory breast cancer in pregnant women is 1.5%–4% [14]. However, as mentioned, pregnant women are more likely to present with larger, more poorly differentiated tumors, positive lymph nodes, and distant metastases than nonpregnant women [2,11,15]. Approximately 65%–90% of tumors diagnosed during pregnancy are at stage II or III, compared to 45%–66% diagnosed at these stages among nonpregnant women [2].

Estrogen receptor-negative and progesterone receptor-negative tumors, which correlate with poor prognoses, are more common among pregnant women than among age-matched controls, possibly due to receptor down-regulation in pregnancy [2,11,13,16]. The incidence of HER2 positivity was investigated in small studies; thus, it is not possible to conclude whether it is more common among pregnant women [17].

Metastases to the placenta and/or the fetus are very rare and account for 13% of all 81 known cases of maternal cancers with this type of distant metastasis [18]. Metastases to the fetus have been described only in cases of maternal metastatic melanoma, metastatic lung cancer, and hematologic malignancies [18]. A recent study published by our group demonstrated that the placenta impedes breast cancer cell growth in the area adjacent to it, probably through modifications of hormonal pathways and microenvironmental changes [19].

Therapeutic abortion

In the past, the belief was that hormonal changes during pregnancy endorse the growth of breast cancer. According to more recent literature, termination of pregnancy does not improve the prognosis of PABC [9]. Nevertheless, the decision should be made after multidisciplinary team discussion with the patient and her family.

Surgery

Surgical intervention during pregnancy is safe, but it should be postponed until after the 12th gestational week, because the risk for spontaneous abortion is higher in the first trimester [4,10]. Currently, the rate of mastectomy among pregnant women is higher than the rate of lumpectomy due to large tumor size and avoidance of adjuvant radiation, but breast-conserving surgery is becoming more frequent [20]. Kuerer and colleagues compared the outcomes of breast-conserving surgery and modified radical mastectomy in patients with stages I and II PABC and found no differences in disease-free and overall survival [21]. Lymphatic mapping (TC-99) to evaluate axillary involvement poses a low risk of radiation to the fetus, according to some studies [12]. On the other hand, isosulfan blue dye mapping is not recommended, because it is not FDA approved for the use in pregnant women and due to previous reports of anaphylaxis [7].

Radiotherapy

Radiation therapy administered either to complete breast-conserving surgery, as post-mastectomy adjuvant treatment in high-risk patients or as a palliative treatment for metastatic cancer, is contraindicated during pregnancy because of fetal exposure. As such, radiation must be postponed until after delivery [7].

Systemic therapy

All chemotherapeutic agents used to treat breast cancer are pregnancy category D, meaning teratogenicity was observed among humans. Nevertheless, when administered after the first trimester, standard protocols are safe and the rate of fetal malformations is not increased [22–25]. The incidence of fetal malformations from various cytotoxic drugs during the first trimester was reported to range from 14% to 19%, compared to only 1.3% in the second and third trimesters [26]. Other possible complications reported from the small prospective study by Berry *et al* [24], were preterm labor, transient tachypnea of newborn, low birth weight, hyaline membrane disease, and transient leukopenia.

In the Royal Marsden retrospective series [27], 28 women were treated with different chemotherapy protocols such as FAC (fluorouracil, doxorubicin, cyclophosphamide), AC (doxorubicin, cyclophosphamide), EC (epirubicin, cyclophosphamide), and CMF (cyclophosphamide, methotrexate, fluorouracil). The use of these protocols in the second and third trimesters was considered safe. The median gestational age at delivery was 37 weeks (range, 30 to 40 weeks), and the median birth weight was 3.0 kg (range, 1.4 to 3.5 kg). None of the infants had a birth weight lower than the 10th percentile for gestational age, and no fetal abnormalities were recorded.

In the largest prospective study to date, from M.D. Anderson [25], 57 women were treated with FAC chemotherapy and followed for a median of 38.5 months. No significant complications were observed when chemotherapy was administered during the second and third trimesters. No stillbirths, miscarriages, or perinatal deaths occurred. However, 3 deliveries were before the 34th week and 1 was before the 29th week, due to preeclampsia. One child was born with Down's syndrome and 1, born in the 38th week, had subarachnoid hemorrhage 2 days after delivery due to pancytopenia. Long-term results were not reported. Chemotherapy should be avoided 4 weeks before the anticipated delivery date to reduce the risk for infection, or hemorrhage due to pancytopenia [8].

The use of methotrexate during pregnancy is contraindicated, and tamoxifen is not recommended due to evidence of genital tract malformations [7]. Taxane use has only been described in case reports and thus the information is not reliable. Data regarding the effects of trastuzumab are very scarce; thus, it should be used with caution and careful monitoring of fetal growth and kidney function [8].

Prognosis

Comparisons between pregnant and nonpregnant women of matched age, nodal status, estrogen receptor status, and tumor histopathology and size yielded no differences in prognosis [7,23]. However, while breast cancer is usually diagnosed approximately 1 month after detection of a nodule among nonpregnant women, the diagnosis among pregnant and lactating women can be delayed for 9 to 15 months [8]. Indeed, pregnant women have a 2.5-fold higher risk for metastases at presentation than do nonpregnant women [2].

However, the true biological effects of the hormonal changes associated with pregnancy have also been suggested to induce more aggressive clinical behaviors. Thus, higher TNM stages are observed among pregnant women and result in worse metastasis-free survival and overall survival.

We believe that a pregnant woman with a breast lump should be evaluated promptly, to avoid diagnostic delay. The effects of the pregnant state on breast cancer cells should be studied, as this may provide biological insights that can lead to new therapeutic interventions.

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Section 1

Specific tumors during pregnancy

Chapter

3

Cervical cancer during pregnancy

Asnat Walfisch

Introduction

Cervical cancer is one of the most common cancers diagnosed during pregnancy, with an incidence of 1.5 to 12 per 100,000 pregnancies [1–3]. It is estimated that between 1% and 3% of patients with invasive cervical cancer are pregnant at the time of diagnosis [4,5].

The cervix plays an extremely important role in the continuation of a successful term pregnancy. This, together with the vulnerability of the fetus to common cancer treatment modalities, results in an exceedingly challenging dilemma for the physician and patient. Unfortunately, randomized controlled trials are almost impossible to perform due to the obvious ethical considerations and relative rarity of the disease. Thus, treatment guidelines are lacking. Most of the published data are composed of small series mainly focusing on evaluating treatment efficacy and safety. It is important to note that the progression of pre-invasive disease to cervical carcinoma during the course of a pregnancy is rare. In fact, the opposite process is more common. Nevertheless, it is imperative that a proper histologic diagnosis be made in situations of possible invasive disease.

Symptoms and signs

The majority of women with early cervical cancer are asymptomatic and are diagnosed by abnormal cytology [6,7]. Other patients may have symptoms similar to the nonpregnant population, that is, vaginal bleeding, discharge, and pain. Lee *et al* [8], reported no symptoms in any of the patients diagnosed with a stage IA lesion, and Smutek *et al* [9], reported vaginal discharge in 29% of patients and postcoital bleeding or spotting in 59% of patients with stage IB lesions during pregnancy. In another series, 63% of patients with stage I disease presented with an abnormal Papanicolaou (Pap) smear, whereas only 20% presented with postcoital bleeding [10]. Patients with advanced or disseminated disease can have a wide variety of symptoms including pelvic pain, flank pain, sciatica, chronic anemia, and even intestinal obstruction and/or respiratory distress. However, presentation at this late stage is increasingly less common [11].

Diagnosis

Pregnancy represents a unique opportunity for the early diagnosis of cervical cancer because visual inspection, cytologic examination of the cervix, and bimanual palpation are all considered part of routine antenatal care. Complete visualization of the transformation zone

Cancer in Pregnancy and Lactation: The Motherisk Guide ed. Gideon Koren and Michael Lishner.
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is usually possible due to the eversion of the squamo-columnar junction that occurs as part of the normal physiologic changes associated with the pregnant state. Interpretation of Pap smears obtained during pregnancy is somewhat problematic because several common physiologic changes associated with the gravid state can lead to false-positive results. For example, eversion of the transformation zone and exposure of columnar cells to the acid pH of the vagina causes squamous metaplasia, which may be interpreted as dysplasia. The Arias-Stella reaction may resemble an adenocarcinoma [12,13]. Trophoblast cells may be retrieved on the smear and resemble low grade dysplasia. It is essential that the cytopathologist be made aware that the smear has been obtained from a pregnant patient.

Evaluation of the cervix by Pap smear (including endocervical sampling) and biopsy of all suspicious lesions is mandatory in all pregnant patients. Cervical biopsy was not shown to be associated with excess bleeding or any pregnancy complications [14–17]. Thus, colposcopically directed biopsy should be performed in all indicated cases (suspected cervical intraepithelial neoplasia [CIN] \geq III). Endocervical curettage has not been definitively proven to cause complications in pregnancy; however, it has only been evaluated in small, nonrandomized trials and should be avoided [18]. Large-loop electro excision procedure of the transformation zone (LLETZ) and other excisional procedures must be used with caution [19]. Conization during pregnancy should be viewed as diagnostic and not therapeutic due to a high rate of positive margins and residual disease as demonstrated by Hannigan *et al* [20]. Other limitations of this procedure include complications such as bleeding, spontaneous abortion, infection, and preterm labor. Hemorrhage and miscarriage occur in a minority of patients, and perinatal death rates range from 3% to 6% [21].

Staging

Cervical carcinoma is clinically staged using the International Federation of Gynecology and Obstetrics (FIGO) classification [22], which is a summary of information derived mainly from the clinical examination and biopsy or cone histology and is no different during pregnancy. However, for the pregnant patient, pelvic examination may be less sensitive in detecting both size and extension of a cervical cancer. The clinical staging may also include plain film radiographs, an intravenous pyelogram (IVP), or a barium enema, but not findings at the time of surgery, computerized tomography (CT), or magnetic resonance imaging (MRI). During pregnancy, decisions regarding the use of radiological investigations must take into account the gestational age and the estimated dose of radiation delivered with the respective imaging study. CT scanning can be performed with minimal risk in the pregnant patient [23] and is helpful in determining the presence of lymphadenopathy or hydronephrosis. With an estimated fetal dose of 30 milligray (mGy), multiple scans should be avoided, particularly in the first trimester. In the pregnant patient, ultrasound and MRI should be considered as alternatives to CT scans because both are noninvasive and do not subject the fetus to ionizing radiation. Choi *et al.* [24,25] evaluated 115 patients with cervical cancer using MRI before undergoing radical hysterectomy. They reported a negative predictive value of 95%, 96%, and 93% for predicting invasion into the parametria, vagina, and pelvic lymph nodes, respectively.

Other authors have also advocated the increasing role that MRI plays in cervical cancer staging [26]. The effects of positron emission tomography (PET) and the radioactive isotopes it uses on the developing fetus are unknown, and as such, the test is contraindicated in pregnancy.

Pathology and biology

Similar to the nonpregnant population, the majority of invasive cervical cancer cases have a squamous histology (>80%). Of the remaining cases, the majority are adenocarcinomas [27]. Other, less common, histologies such as neuroendocrine tumor of the cervix have been described [28]. There is no conclusive evidence that the pregnant state alters the biology of cervical cancer. However, some authors have found a higher proportion of early stage tumors in pregnant patients, which is likely a consequence of the increased cervical cancer screening performed during routine antenatal care [4,29]. In a series of 28 pregnant patients with invasive disease, Takushi *et al.* found 22 patients (79%) presenting with stage I disease and 6 (21%) with stage II or III [30].

Treatment

The initial evaluation of the pregnant patient with cervical cancer must include a thorough and complete assessment of the fetus, including accurate gestational age, a thorough ultrasound examination of the fetus for presence of anomalies and growth, as well as, obtaining results of serum markers for aneuploidy, if possible. Once the diagnosis, stage, and extent of invasive cervical cancer have been established, a multidisciplinary team should discuss appropriate treatment strategies. This team should, ideally, include specialists in maternal-fetal medicine, gynecologic oncology, neonatology, social work, and radiation oncology.

Whereas in the nonpregnant patient population the decision to proceed with either surgical excision or radiation with chemotherapy is based almost exclusively on the stage, in the pregnant patient, other considerations are involved. The decision to initiate or delay treatment has ethical, moral, cultural, and religious implications that need to be carefully addressed. The patient should decide whether the present pregnancy, and future fertility, are desired. At times, a decision must be made of whether to terminate the pregnancy or depart from standard treatment modalities. An alternative treatment path can be cautiously decided upon, based on a lower level of evidence.

Noninvasive cervical carcinoma

Treatment of noninvasive carcinoma can safely be deferred to the postpartum period, provided that a careful colposcopic evaluation is performed in addition to cytology [4,31].

Invasive cervical carcinoma

FIGO stage IA

Controversy persists regarding the management of patients with IA1 squamous cell carcinoma of the cervix. In the nonpregnant population, excisional procedures are reserved for patients in whom occult malignancy cannot be ruled out. Extra-fascial hysterectomy remains the treatment of choice for the nonpregnant patient with no desire for future fertility. Fertility-sparing alternatives to hysterectomy have been explored and debated [32].

For the pregnant patient who desires immediate treatment of a IA1 lesion, with the intent on ending the pregnancy, choices include termination followed by hysterectomy or removal of the uterus with the fetus in situ. Delaying the treatment of an occult lesion during pregnancy may have no impact on survival. Thus, excisional