Cancer in pregnancy

M. Lishner

Meir Hospital, Kfar Saba, Israel

Cancer is the second most common cause of death in women during their reproductive years, and complicates between 0.02% and 0.1% of all pregnancies. This incidence is expected to rise with the concomitant increase in age of childbearing. The most common malignant tumors associated with pregnancy include cervical and breast carcinomas, malignant melanoma and lymphoma. The relatively rare occurrence of cancer during pregnancy precludes conducting large, prospective studies to examine diagnostic, management and outcome issues. The literature on cancer during pregnancy is largely composed of case reports and small, uncontrolled studies.

Cancer diagnosed during pregnancy poses a very difficult challenge to the woman, her family and the medical staff. The void between creation of a new life and tragedy of cancer raises many psychological and ethical problems. The benefits of the diagnostic work-up and use of chemotherapy, radiotherapy and surgery have to be weighed carefully against their risk to the unborn baby. This often results in conflict over benefit to mother or infant.

Here the impact of pregnancy on these growing neoplasms and that of the tumors on the developing fetus will be reviewed. The short- and long-term sequelae associated with the treatment of cancer in pregnancy on the newborn will also be discussed.

Breast cancer in pregnancy

Diagnosis

A high index of suspicion is required in the evaluation of a mass in the breast of a pregnant woman. During pregnancy, a woman’s body undergoes substantial physiological changes, including enlargement of the breasts, which makes it more difficult to notice the small lumps that forewarn one of cancer. Also, it is probable that women and their physicians relate findings consistent with breast cancer to pregnancy-induced engorgement. It has been reported that the average delay from first symptoms to treatment exceeds 5 months [1]. Also, we reported that a pregnant woman has a 2.5-fold higher risk of being diagnosed with metastatic breast cancer and a decreased chance of diagnosis of stage I [2]. Similar findings have also been reported by other authors [3, 4].

To detect breast cancer, pregnant and lactating women should practice self-examination and be examined by a physician as a part of routine prenatal care. The finding of a suspicious mass should lead, without delay, to a diagnostic evaluation. Mammograms are not performed routinely due to concern about fetal irradiation. However, a bilateral mammographic examination of both breasts with modern equipment would yield less than 50 mrad (500 μGy) to the human embryo [5], which is well below the 10 Rad (100 mGy) toxic level. However, it is likely that the sensitivity of mammography is diminished during pregnancy due to increased glandularity and water content of the breast [6, 7]. Breast ultrasonography is accurate and safe in differentiating cysts from solid tumors [6]. Thus the shortcomings of the non-invasive diagnostic procedures mandate proper tissue sampling, in a timely manner, in most patients with a suspicious lesion.

Fine needle aspiration (FNA) of a suspected lesion in the breast carries the risk of both false-positive and -negative results. The hyperproliferative cellular state of the mammary tissue leads to the possibility of false-positive diagnosis of malignancy. On the other hand, the needle technique runs the risk of missing the mass [8]. Although excisional biopsy under local anesthesia during pregnancy may be problematic because of hypervascularity and edema, with risks of post-operative hematoma, infection and milk fistula, it should still be performed. There is no evidence to suggest that a breast biopsy constitutes a risk to the mother or the fetus. Determination of receptor hormonal status using immunochemistry techniques is indicated for treatment accuracy.

Therapeutic abortion

Most recent reports do not show an advantage in survival after therapeutic abortion [8].

Preoperative staging

Metastatic work-up can be performed during pregnancy but should be limited to those situations in which there is a high suspicion of metastasis and their establishment would alter the course of therapy. This problem is complicated by the fact that some tests utilized for staging require ionizing radiation, which may be harmful to the developing fetus.

Pathology and biology

The pathology is identical to that found in non-pregnant women, including an incidence of inflammatory carcinoma of 1.5–4% [9]. However, recent histopathological reports of 14 cases found that breast carcinomas diagnosed in pregnancy are mostly estrogen- and progesterone-receptor negative with a higher incidence of cancerization of lobus and of grade 3 invasive ductal carcinomas [10]. The stage distribution at the time of presentation is as follows: stage 1, 28%; stage 2, 30%; and stages 3 and 4, 42% [11]. Very little information is available about the accuracy and value of steroid hormone receptor status during pregnancy. Most probably, pregnant women, like most young patients, are estrogen- and progesterone-receptor negative. No data on pregnant patients with accurate hormone receptor status exist for formulating recom-
The biological effects of radiation on the embryo are expected if controls and by the lack of survival benefit with termination of delayed until the second trimester. If adjuvant chemotherapy is considered necessary, it should be supported by the similar survival of matched non-pregnant controls and by the lack of survival benefit with termination of pregnancy. If adjuvant chemotherapy is considered necessary, it should be delayed until the second trimester.

**Late stage cancer: stages III and IV**

Advanced stage III and IV breast cancer usually requires chemotherapy after surgical resection of the tumor. Radiation treatment may be necessary for local control, but should probably be administered after labor.

**Fertility**

Despite limited data, it appears that in utero exposure to chemotherapy is not associated with significant gonadal dysfunction. Secondary sexual development signs in different research cohorts and direct evidence of normal fertility in a few cases indicate that there are no adverse effects of exposure to chemotherapy during fetal life on fertility during adolescence.

**Cervical cancer in pregnancy**

Reports suggest that the majority of women with early cervical cancer are asymptomatic and are diagnosed by abnormal cytology. Other patients may have symptoms similar to the non-pregnant population, i.e. vaginal bleeding, discharge and pain.

Evaluation of the cervix by Papanicolaou (Pap) smear (including endocervical sampling) and biopsy of all suspicious lesions is mandatory in all pregnant patients. Complete visualization of the transformation zone is usually possible due to the eversion of the squamocolumnar junction that occurs as part of the normal physiological changes associated with the pregnant state. Interpretation of Pap smears obtained during pregnancy is somewhat problematic, since several common physiological changes associated with the gravid state can lead to false-positive results. It is essential that the cytopathologist be made aware that the smear has been obtained from a pregnant patient.

A patient with an abnormal Pap test and a normal cervix on routine examination should undergo colposcopy. The technique of colposcopic-directed biopsies has been shown to be a less morbid yet accurate alternative to the traditional practice of random biopsies and conization. Conization is indicated in those cases where colposcopy is unsatisfactory and cytology is highly suggestive of invasive cancer. 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. [23]. Other limitations to this procedure include complications such as bleeding, spontaneous abortion, infection and preterm labor. Studies suggest that hemorrhage and miscarriage occur in a minority of patients and perinatal death rates range from 3% to 6% [24].
Staging

Cervical carcinoma is clinically staged using the International Federation of Gynecology and Obstetrics (FIGO) classification [25], which is a summary of information derived mainly from physical examination and radiological investigations. During pregnancy, decisions regarding the use of radiological investigations must take into account the age of the fetus and the estimated dose of radiation delivered with the respective imaging study. In the pregnant patient, ultrasound and magnetic resonance imaging (MRI) should be considered as alternatives to computed tomography (CT) scans, since both are non-invasive and are not associated with ionizing radiation [26].

Pathology and biology

Similar to the non-pregnant population, the majority of cases of invasive cervical cancer have a squamous histology (>80%). Of the remaining cases, the majority are adenocarcinomas [27].

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 to be a consequence of the increased frequency of cervical cancer screening performed during routine antenatal care [28, 29]. In contrast, studies suggest that those cases diagnosed late in the pregnancy or postpartum tend to be associated with a more advanced clinical stage and worse prognosis [30].

Treatment

Early stages of the disease (I and IIa) are usually treated either by radical hysterectomy and pelvic lymph node dissection, or by radiation. Surgery is associated with low morbidity, acceptable survival (80–95%) and preservation of ovarian function.

Based on a case–control study, radical hysterectomy is not associated with higher complication rates in pregnant women. Other reports have also documented minimal operative complication rates and postoperative morbidity in pregnant women. Recent studies recommend the use of concurrent radiochemotherapy, followed by hysterectomy for bulky stage Ib carcinoma. However, this protocol was not evaluated in pregnancy associated cervical cancer [31, 32].

Patients with advanced disease (stage IIb and higher) are usually treated by radiation. Recent studies have demonstrated improved survival rate with the use of concurrent radiotherapy and cisplatinum-based chemotherapy. However, to the best of our knowledge, pregnant women were not included in these studies. When the fetus is viable, delivery by Caesarean section is performed prior to initiation of therapy, otherwise the fetus will be lost in utero. Most patients will have spontaneous abortion upon reaching a level of 40 Gy. Although data are scare, most studies do not report significant differences in short- and long-term complications between pregnant and non-pregnant women treated with curative radiation.

Mode of delivery

Little data exists examining the safety of Caesarean section versus vaginal delivery. Non-randomized studies suggest that there is no difference in survival rates [28]. However, the risks of obstructed labor, hemorrhage and episiotomy site recurrence with vaginal delivery has led to the recommendation of Caesarean delivery as the preferred method.

Prognosis

Due to small numbers and methodological flaws of the existing literature, the effect of pregnancy on prognosis is controversial, especially in the higher stages of disease. It appears that pregnancy-associated cervical carcinoma has an overall better prognosis than in the non-pregnant population due to the relatively high proportion of patients with early stage disease. After stratifying for stage, survival analyses generally do not show a difference between the two groups [32]. Treatment of non-invasive cervical cancer can be postponed until postpartum. Due to diagnostic and therapeutic difficulties associated with it in pregnancy, re-evaluation after delivery is crucial.

Fetal outcome

Cervical cancer does not appear to affect the outcome of pregnancy. Laser vapourisation of the uterine cervix does not influence the outcome of subsequent pregnancy. In a study performed by Zemlickis et al. [28] no statistically significant differences in mean gestational age or proportion of preterm deliveries were seen when infants born to women with invasive cervical cancer were compared with controls. Also, the risk of prematurity increased after conization for carcinoma in situ (CIS) and did not increase when women with CIS had other procedures. Mean birth weight was slightly lower for infants in the cancer group. None of the infants were exposed to therapy in utero [33].

Malignant melanoma and pregnancy

Introduction

Malignant melanoma is a serious health problem worldwide and is increasing at a rate that exceeds all other solid tumors [34]. The increasing incidence is accompanied by an associated decrease in age at presentation. Malignant melanoma during pregnancy has an estimated incidence of between 0.14 and 2.8 cases per 1000 births [35] and represents 8% of malignancies diagnosed during pregnancy [36].

Diagnosis

The signs and symptoms of melanoma are similar to the non-pregnant population and the anatomic location of the primary tumor does not differ between pregnant and non-pregnant women. Changes in size, color and configuration of any pigmented lesion suggest a malignant change and the need for further investigation. Two-thirds of melanomas occur in pre-existing nevi. However, some degree of hyper-pigmentation during pregnancy is experienced by most women. It has been suggested that this hyper-pigmentation may lead to a delay in diagnosis of the disease [34]. A growing number of reports suggest minimal changes in size occur during pregnancy [37]. Bleeding and ulceration are more
ominous signs and require immediate attention. Excisional biopsy is the recommended procedure for any suspicious lesions.

**Staging**
Clinical staging traditionally has included assessment of the local tumor site and adjacent skin, regional lymph node areas and distant organs that are frequently the site of metastatic disease. The decision to perform radiological investigations in the pregnant patient should be based on the presence of symptoms, the stage of pregnancy, the specific test needed and the estimated dose of ionizing radiation and risks associated with that dose. Intensive radiological investigation(s) is not required for patients with early disease. Routine elective lymph node dissection is controversial and has not been shown to have a consistent impact on survival [37]. The use of blue dye or a radiolabeled tracer injected at the primary tumor site to identify the draining or ‘sentinal lymph node’ has been shown to be accurate with little morbidity and high accuracy. During pregnancy, the radiolabeled technique should be avoided due to the risk of radiation exposure of the fetus.

**Therapeutic abortion and contraception**
There is no conclusive evidence that regression of melanoma occurs after therapeutic abortion [38–40]. Since the influence of pregnancy or hormones on melanoma has not been observed, the general consensus is that oral contraceptives are not contraindicated in patients with a prior history of melanoma, regardless of the duration of their use [35].

**Pathology and biology**
The effect of pregnancy on melanocytic nevi is unclear. Previous studies have suggested that patients may overestimate changes in melanocytic nevi. A recent prospective study of 22 patients using photographs and objective measurements failed to demonstrate any significant change in size of nevi from the first to the third trimester [37]. Another area of controversy exists regarding the effect of pregnancy on site of presentation. Some studies have suggested an increased risk in pregnancy of lesions in areas associated with a worse prognosis, such as the head and neck and truncal regions, while others have not found this association [35]. Similarly, there is debate as to whether pregnancy is associated with increased tumor thickness [36]. Stage of the disease at diagnosis and not pregnancy is the only consistent factor influencing the prognosis in terms of survival and disease-free interval.

**Prognosis**
The effect of pregnancy on prognosis of melanoma has been a focus of interest in the medical literature for years. When matched for age, anatomical site and stage, most studies have not demonstrated a difference in survival. However, some studies have demonstrated a shorter disease-free interval in pregnant patients compared with controls [35].

**Fetal outcome**
Metastases to the placenta and fetus are rare but have been documented with hematological as well as solid tumors. Malignant melanoma is the tumor that most frequently metastasizes to the placenta or fetus. Therefore, the placenta should be thoroughly examined for metastasis. If present, the infant should be monitored for development of malignant disease. Of the 17 reported cases, only four have resulted in fetal death [41].

**Fertility**
There is no evidence that a diagnosis of melanoma adversely affects fertility.

**Hodgkin’s disease in pregnancy**

**Introduction**
Since the peak incidence of Hodgkin’s disease (HD) is in the age range from 20 to 40 years, its association with pregnancy is not uncommon, occurring in 1:1000 to 1:6000 deliveries [42]. Therefore the guidelines for evaluation and treatment of HD in pregnancy are not well established.

**Diagnosis**
Since tomographic scans and isotope are not recommended during pregnancy and since the current trend is to administer chemotherapy initially even in early stages (stages I and II) of Hodgkin’s disease, a limited initial staging work-up is suggested.

It should include history, physical examination, routine blood tests, bone marrow biopsies, chest X-ray with abdominal shielding, abdominal ultrasound and possibly MRI. The clinical behavior of HD during pregnancy does not appear to differ from that outside of this setting and pregnant women are not more likely to present at a higher stage than women of reproductive age in general [43, 44]. Also, the histological subtypes of HD in pregnancy are not different from that of non-pregnant women younger than 40 years [43].

**Treatment**
Due to the limited availability of treatment information it is not feasible to make specific recommendations regarding patient management. In general, it is recommended to avoid chemotherapy during the first 12–16 weeks of pregnancy if possible and to postpone radiotherapy until after the delivery [43]. If combination chemotherapy is considered, the recommended protocol is probably adriamycin, bleomycin, vinblastine and dacarbazine (ABVD).

**Prognosis and fetal consequences**
There is no effect of pregnancy on survival of women with HD [43, 44]. Infants born to women with HD during pregnancy do not have a higher risk for prematurity or intrauterine growth retardation [44]. In the cases reported by Anselmo et al. [45], pregnant women affected by HD safely carried their pregnancies to term and gave birth to healthy children. The association of HD with pregnancy is not, on its own, an indication for a therapeutic abortion. Recommendations regarding abortion should be individualized based on potential harm of staging procedures, chemotherapy or radiotherapy to the fetus [46].
Induction of labor should be performed when there is a viable fetus and the mother’s blood counts are not compromised by a recent cytotoxic treatment. Breast feeding is contraindicated during active treatment of HD. There are no reports of HD metastatic to the placenta or to the fetus.

**Effect of cytotoxic and radiation therapy on the developing fetus**

Most patients with a pregnancy-associated malignancy, who choose to continue pregnancy, are treated with chemotherapy. However, to date there are no prospective clinical studies assessing the short- and long-term effects of chemotherapy during pregnancy. Therefore, all available information is reliant upon case reports and small retrospective case-controlled studies.

Chemotherapeutic agents are highly teratogenic, and all agents were first studied using animal models. The estimated risk of malformations when a single agent is administered during the first trimester ranges from 7.5% to 17%, the teratogenic risk being estimated to increase when combination chemotherapy is used [47]. Possible outcome depends on the particular drug or combination of drugs used, and the gestational age. Significant exposure to cytotoxic agents during the first 4 weeks of gestation may result in spontaneous abortion. The risk of birth defects increases if the exposure occurred during 5–12 weeks of gestation, when organogenesis takes place. The most toxic drugs during this period are aminopterin (no longer in use) and methotrexate. By week 12 of gestation, organogenesis is complete with the exception of the brain and gonads. Exposure to these drugs during the second and third trimesters is not associated with teratogenic effects, but may further result in intrauterine growth retardation, prematurity and stillbirth [18]. Since chemotherapy may be associated with transient bone marrow suppression, delivery should be planned accordingly. Although information regarding specific cytotoxic drugs is limited, the scope of this review is too brief to include specific details.

Since the brain develops throughout pregnancy, several studies have focused on the neurodevelopment and cognitive capacities of children exposed to chemotherapy in utero. Altogether, these tests have shown that chemotherapy does not have a major impact on later neurodevelopment and cognitive capabilities [19, 50]. Moreover, the available data suggest that children exposed to chemotherapy in utero are not at increased risk for occurrence of malignancies or infertility [51–53].

Radiation is commonly used for diagnostic and therapeutic purposes in cancer patients. The developing embryo and fetus are extremely sensitive to ionizing radiation, and the human brain seems to be the most sensitive organ. During the peri-implantation and post-implantation periods, radiation has an all-or-none effect, resulting in either embryonic death or further normal development. Later in pregnancy, radiation may cause mental retardation, microcephaly, intrauterine growth retardation and other abnormalities. Based on the Hiroshima and Nagasaki radiation survivors, the highest risk of brain damage and consequent mental retardation occurs between 8 and 15 weeks of gestation. The threshold seems to be about 5−25 cGy, with a downward shift of IQ in a dose-dependent manner. Most diagnostic imaging modalities expose the fetus to very small doses of irradiation much less than the 5−10 cGy (even without abdominal shielding) that are the recommended safe limits. For example, thousands of skull, dental, chest and extremities radiographs are needed to reach a dangerous cumulative dose of 5 cGy. However, several procedures such as intravenous pyelograms (IVP; ~1.4 cGy), abdominal computed tomography and barium enemas (2.5–4.0 cGy) are dangerously close to the limits of the allowed dose. Radiation doses used in cancer therapy are in the range of 3000−7000 cGy. However, the effective fetal dose depends on the size of the radiation fields, the target dose and the distance from the embryo/fetus to the edges of the radiation field and the specific radiation machine and its leakage. Thus, this modality can be used to treat head, neck, breast and extremities without significantly irradiating the fetus. Before initiation of radiotherapy during pregnancy, an experienced medical physicist and radiation oncologist should be consulted [54].

To conclude, chemotherapy administered during the first trimester is associated with significant teratogenic effects. The risks of birth defects when cytotoxic drugs are administered during second and third trimesters are similar to those of the general population. As for exposure to X-radiation, the accepted dose limits of radiation are about 5 cGy, and most radiographic imaging techniques employs doses well below these safe limits. Therapeutic radiation, which involves exposure to much higher doses, is only considered acceptable (when well-being is to be preserved) for the treatment of areas at a correct distance from the fetus, and after consultation with an experienced radiation oncologist.

**References**


