Cancer in pregnancy: maternal and fetal implications

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Cancer is the second leading cause of death in women during their reproductive years, and complicates approximately 0.1% of all pregnancies. When cancer occurs during gestation it poses immense pressure on the pregnant patient, her relatives and her physicians. As cancer is diagnosed during gestation, it raises conflicts between optimal maternal therapy and fetal well-being. In this review, the available data are analysed regarding the impact of pregnancy on the course of the disease, and the effects of the malignant process and its treatment on both the mother and her fetus. Here, attention is focused on the most common malignancies associated with pregnancy; cervical and breast cancer, malignant melanoma and lymphoma. In addition, attention is focused on the available data regarding the impact of cytotoxic and radiation treatments on the mother and fetus.

Key words: breast cancer/cervical carcinoma/lymphoma/malignant melanoma/pregnancy

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Introduction

Cancer is the second most common cause of death during reproductive years (Murphey, 1999), and complicates between 0.02 and 0.1% of all pregnancies (Kennedy *et al.*, 1993). This incidence is expected to rise with the concomitant increasing age of child-bearing. 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 the tragedy of cancer raises many psychological and ethical problems. The most common malignant tumours associated with pregnancy include cervical and breast carcinomas, malignant melanoma and lymphoma. Here, the impact of pregnancy on these growing neoplasms, and that of the tumours 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.

Invasive cervical cancer

Pregnancy-associated cervical cancer (PACC) is the most common malignant tumour encountered throughout gestation (Nevin *et al.*, 1995), the estimated incidence ranging from 1 in 2000 to 1 in 13 000 pregnancies (Hacker *et al.*, 1982; Norstorm *et al.*, 1997). Furthermore, about 2–5% of these tumours are diagnosed during pregnancy (Duggan *et al.*, 1993; Sivanesaratnam *et al.*, 1993). The median age of women with cervical cancer diagnosed during pregnancy is in the early-thirties (about 10 years earlier than non-pregnant women), when many women are just beginning their family planning (Jones *et al.*, 1996). It seems that the earlier age of cervical neoplasm in pregnant women represents an accumulative peak incidence of pregnancy with that of cervical cancer.

The presenting symptoms of cervical cancer may vary depending mostly on the extent of the disease. Pregnancy itself, however, represents an ideal time for a routine physical and pelvic examination, and obtaining Papanicolaou (pap) smear for cytology. Indeed, most pregnant women with cervical cancer are asymptomatic, and are diagnosed when abnormal cytology is detected during routine screening (Dudan *et al.*, 1973; Lee *et al.*, 1981). It is noteworthy that several reports indicate that cervical cytology obtained during pregnancy is associated with higher rates of false-negative and false-positive results (Carter *et al.*, 1993; Guerra *et al.*, 1998; Cronje *et al.*, 2000). Although the results of colposcopy might also be falsely negative, it seems that colposcopically-directed biopsy or frequent follow-up visits for pregnant patients with an abnormal cytology should be recommended (Benedet *et al.*, 1987; Economos *et al.*, 1993). In some cases, colposcopically-directed brush cytology might become a safe substitute for directed biopsy in pregnant patients with abnormal pap smears (Lieberman *et al.*, 1999). The single most common symptom during pregnancy is vaginal bleeding (Method

and Brost, 1999), and this should call for a prompt evaluation of the cervix. When cervical pathology is suspected, colposcopic evaluation—including biopsies from suspicious lesions—is warranted. Some clinicians prefer to perform sequential colposcopic and cytological evaluations and to postpone biopsies to the second trimester. However, the risk of haemorrhage from colposcopically-directed biopsies is extremely low (Economos et al., 1993).

As for non-pregnant women, ~80–90% of tumours are classified as squamous or adenosquamous cell carcinoma (Sood et al., 1996; Method and Brost, 1999). Most cases (about 70%) of cervical cancer in pregnancy are identified in early stages, Ia, Ib and IIa (Hopkins and Morley, 1992; Nevin et al., 1995; Jones et al., 1996). These results represent a 2- to 3-fold higher probability of being diagnosed in an operable stage of the disease (Zemlickis et al., 1991). This difference may result from the routine examinations performed through prenatal care, or as a consequence of the age differences between pregnant and non-pregnant women. Moreover, an advanced stage of disease might prevent conception.

Unlike most pregnancy-related malignancies, initiation of treatment for cervical cancer cannot co-exist with preservation of fetal life (unless neoadjuvant chemotherapy is chosen). Therefore, when the tumour is detected in an early trimester, the medical staff and the patient have to decide whether to initiate therapy or to postpone treatment while monitoring tumour growth by pelvic examinations and imaging modalities. Delay of treatment for 11–17 weeks was first reported in 1965, when therapy was delayed in five women (delaying treatment until delivery) with pregnancy of >20 weeks duration (Prem et al., 1965). All five women were disease free 3–5 years post-partum. Since then, many studies have focused on the issue of postponing therapy for patients with the early stages of disease (Dudan et al., 1973; Thompson et al., 1975; Lee et al., 1981; Hacker et al., 1982; Greer et al., 1989; Zemlickis et al., 1991; Hopkins and Morley, 1992; Monk and Montz, 1992; Duggan et al., 1993; Sivanesaratnam et al., 1993; Sorosky et al., 1995; Sood et al., 1996). These reports summarize more than 82 patients, mostly with stage I disease, who chose to delay therapy for 1–32 weeks in order to reach fetal maturity. Although the duration of follow-up varies greatly in these reports, progression of the disease while expecting fetal maturity was described in only three patients (Dudan et al., 1973; Sorosky et al., 1995). Based on statistics of modern neonatal intensive care units (NICU) (Allen et al., 1993), which suggest that fetal viability and well-being can be expected by 36 weeks gestation, it seems that postponing therapy may be cautiously recommended (Hopkins and Lavin, 1996). According to the capabilities of each local NICU, when low morbidity rate can be obtained, earlier delivery (28–32 weeks gestation) should be carefully considered. Although data are limited, prognostic factors such as depth of invasion, histological type and lymphatic spread may enable an individualized therapeutic approach (Nevin et al., 1995). Neoadjuvant chemotherapy administration while postponing delivery was suggested, but the data regarding this possibility are extremely limited (Giacalone et al., 1996; Tewari et al., 1998).

The mode of delivery of patients with cervical cancer is controversial. Most reports suggest that survival is not affected significantly by the mode of delivery (Lee et al., 1981; Jones et al.,

1996). However, because of possible haemorrhage, dystocia and dissemination of tumour cells from a dilated untreated malignant cervix, most clinicians will recommend abdominal delivery (Method and Brost, 1999). It should be noted that recurrence was documented in few patients either at episiotomy site or at the abdominal incision of Caesarean operation (Sivanesaratnam et al., 1993; Cliby et al., 1994).

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 (Photopulos, 1990; Zemlickis et al., 1991; Hopkins and Morley, 1992; Monk and Montz, 1992; Duggan et al., 1993; Sivanesaratnam et al., 1993; Lewandowski et al., 1995; Nevin et al., 1995; Van der Vange et al., 1995; Method and Brost, 1999). Based on a case–control study, radical hysterectomy is not associated with higher complication rate in pregnant women (Sood et al., 1996). Other reports have also documented minimal operative complication rate and postoperative morbidity in pregnant women (Monk and Montz, 1992; Van der Vange et al., 1995). Recent studies recommend the use of concurrent radio-chemotherapy, followed by hysterectomy for bulky stage Ib carcinoma (Keys et al., 1999). However, this protocol was not evaluated in PACC.

Patients with an 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 (Rose et al., 1999). 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 situ. Most patients will have spontaneous abortion upon reaching a level of 40 Gy (Lee et al., 1981). Although data are scarce, most studies do not report significant differences in short- and long-term complications between pregnant and non-pregnant women treated with curative radiation (Sood et al., 1997).

Most studies agree that there is no difference in maternal survival between pregnant and non-pregnant women when matched by age, stage and the year of diagnosis (Sood and Sorosky, 1998; Method and Brost, 1999). Two case–control studies reported similar overall 5-year survival rates among pregnant and non-pregnant women with early-stage disease (Zemlickis et al., 1991; Van der Vange et al., 1995). Data regarding survival of patients with an advanced stage disease are limited, and most (but not all) studies found similar survival rates in pregnant women with advanced disease compared with those in unmatched controls (Bosch and Marcial, 1966; Nevin et al., 1995; Van der Vange et al., 1995). Few reports have reviewed fetal outcome in pregnancies associated with cervical neoplasm. Although there is a trend for lower birth weight among newborns of cervical cancer patients, these differences were not significant when presented by percentile of weight. There was also a trend toward higher stillbirth rate among treated patients (Zemlickis et al., 1991).

Gynaecological malignancies rarely spread to either the placenta or fetus, but most of those that do metastasize to products of conception are related to ovarian neoplasm. However, one case report exists of metastatic cervical squamous cell

Table I. Reciprocal relationships between pregnancy and cervical disease

Pregnancy provides an opportunity for performing pelvic examination and obtaining cervical cytology. However, false-negative rates are significant, and suspicious lesions should be evaluated by colposcopically directed biopsy.

Most studies found that pregnancy is often associated with lower stages of disease (compared with non-pregnant matched populations).

Pregnancy does not adversely affect the course of the disease. When matched by stage, age and year of diagnosis, it has no effect on survival.

Delay of surgical or radiation therapy might be considered in early stages while expecting fetal maturity. In such a case, a careful and frequent follow-up is indicated.

Cervical carcinoma rarely spreads to either the fetus or placenta.

Late stages of cervical cancer usually dictate immediate therapy, and often necessitate interruption of pregnancy.

The preferred mode of delivery is probably Caesarean section.

Upon delivery, cervical cancer does not adversely affect fetuses that reached maturity.

carcinoma that spread to the placenta (Dildy *et al.*, 1989). The reciprocal relationships between pregnancy and cervical disease are summarized in Table I.

Breast cancer

Pregnancy-associated breast cancer (PABC) is the second most common malignancy in pregnancy, complicating 1 in 1500 to 1 in 10 000 pregnancies (Anderson, 1979; Parente *et al.*, 1988; Cummings *et al.*, 1997). About 3% of all breast carcinomas are diagnosed during pregnancy; however, because nowadays child-bearing is delayed to later in life, breast cancer during pregnancy may become even more common (Treves and Holleb, 1958; Applewhite *et al.*, 1973; Nugent and O'Connell, 1985; Parente *et al.*, 1988; DiFronzo and O'Connell, 1996).

Some of the physiological alterations during pregnancy might be relevant to PABC. During pregnancy the breast becomes engorged as the vascular and lymphatic components grow. With regard to histological changes, the epithelial component of the breast matures to form the lobules and acinar epithelium. Pregnant women have substantially higher concentrations of oestrogen, human chorionic gonadotrophin (HCG), cortico-steroids and other endocrine modulators. Epidemiologically, pregnancy has a dual effect on breast cancer incidence. Early age at first full-term pregnancy and increasing parity are associated with a reduced risk of breast cancer (which might be related to a protective effect of HCG; Russo and Russo, 2000). On the other hand, pregnancy is associated with a transient post-partum increase in breast cancer risk (Surbone and Petrek, 1998; Chie *et al.*, 2000).

Most cases of PABC are asymptomatic. Up to 90% are detected by self-examination of a painless mass (Galenberg and Loprinzi, 1989). Although breast examination is an integral part of the initial prenatal examination, multiple series document significant (average 5–7 months) patient- and physician-related delays in the diagnosis of PABC. This delay has been attributed to several factors, including misinterpretation of the physical examination due to the hypervascular, engorged and nodular breast character-

istics of pregnancy (Petrek *et al.*, 1991; Petrek, 1995; Sorosky and Scott-Conner, 1998; Bernik *et al.*, 1999). These physiological changes of the breast are associated with an increase in radiographic density, thus limiting the sensitivity of mammo-graphy. Although mammography is not contraindicated during pregnancy (Bottles and Taylor, 1985), ultrasonography is more accurate (Ishida *et al.*, 1992). When a mass has been detected, the physician should promptly continue the work-up either by fine-needle aspiration (FNA) or by performing an open biopsy. The cytopathologist must be informed about the pregnancy due to the high rate of false-positive cytological findings (Sorosky and Scott-Conner, 1998).

In general, the metastatic work-up should be limited to those women in whom a detailed history and a comprehensive physical examination raise a high clinical suspicion of a widespread disease (Sorosky and Scott-Conner, 1998). The evaluation should consider the safety of the developing fetus. Chest radiographs are usually obtained with abdominal shielding. Either ultrasono-graphy or occasionally magnetic resonance imaging (MRI) should be used to look for liver involvement. Since the incidence of bone metastasis in stages I and II breast cancer is only 3% and 7% respectively, a bone scan is unnecessary. However, if bone metastasis is clinically suspected, or in stage III disease (associated with 25% bone metastasis) a technetium scan is preferred over skeletal films due to increased sensitivity, and lower radiation exposure to the fetus (Harbert, 1982; Fiorica, 1994; DiFronzo and O'Connell, 1996).

Many series reported an advanced stage at initial presentation, and consequently a higher rate of lymph node involvement in pregnant versus non-pregnant women (Nugent and O'Connell, 1985; Ribeiro *et al.*, 1986; Petrek *et al.*, 1991; Lethaby *et al.*, 1996; Gemignani *et al.*, 1999). In fact, pregnant women with breast cancer have a 2.5-fold higher risk of having a metastatic disease compared with non-pregnant women (Zemlickis *et al.*, 1992a). In theory, the advanced stage at diagnosis might represent either a diagnostic delay or a more biologically aggressive disease (Donegan, 1977). As discussed previously, diagnostic delay may be attributed to lack or misinterpretation of the physical

Table II. Reciprocal relationships between pregnancy and breast cancer

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Pregnancy-associated breast cancer (PABC) is often diagnosed in advanced stage of disease most probably due to delayed diagnosis.

PABC has an aggressive course, similar to that in non-pregnant, young breast-cancer patients.

PABC patients have similar survival rates (per stage) as non-pregnant patients.

The endocrine changes associated with pregnancy probably do not stimulate cancer growth. Therapeutic abortions do not influence the course of the disease.

Pregnancy may limit therapeutic options since breast-conserving surgery and radiotherapy are usually delayed until after delivery. Chemotherapy is relatively contraindicated during the first trimester.

An additional pregnancy after completion of therapy does not adversely affect the prognosis.

Placental metastases are very rare.

Breast cancer might be associated with significant lower fetal weights, and a higher, though not significant, rate of stillbirth.

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examination. The delay in diagnostic work-up and subsequent delay in appropriate therapy are considered major causes for the advanced stage at diagnosis. The possibility of biological differences between tumours diagnosed in pregnant versus non-pregnant women were evaluated by several groups. Some have found that PABC is characterized by several specific histopathological features such as 'cancerization' of lobules and high incidence of oestrogen receptor- and progesterone receptor-negative tumours (Shousha, 2000). However, most studies have concluded that the biological nature of the disease during pregnancy is no different than in age-matched, non-pregnant women (Galenberg and Loprinzi, 1989; Gemignani et al., 1999), and therefore is not relevant to the advanced stage of the disease at diagnosis. It has been documented that about 80% of breast cancers in young women, are oestrogen receptor-negative, regardless of gestational status (Nugent and O'Connell, 1985). These tumours have a biologically aggressive course, carry a poorer prognosis, and are probably hormone-independent (McGuire, 1978). Indeed, many studies have failed to show advantage in survival in women who underwent therapeutic abortions (Nugent and O'Connell, 1985). Thus, abortions are not indicated as a part of treatment strategy.

The mode of treatment for operable disease is usually modified radical mastectomy performed under general anaesthesia. Mastectomy is considered safe during pregnancy, and is associated with very small risk of fetal loss (Byrd et al., 1966). Breast-conserving surgery employs unacceptably large doses of postoperative radiation to the fetus, and therefore should be discouraged. This modality should be limited only to patients diagnosed late in pregnancy, in which post-lumpectomy radiation therapy should be administered after delivery. Women with lymph node metastasis will benefit from further treatment with adjuvant chemotherapy (Fisher et al., 1986; Berry et al., 1999; Gemignani et al., 1999). The main concerns associated with use of chemotherapy are discussed later.

Although PABC is generally diagnosed in more advanced stages, it has an equivalent prognosis to non-pregnant women when matched by age and stage at diagnosis (Riberio et al., 1986; Marchant, 1994). The reported 5-year survival rate was 82% for node-negative women (either pregnant or non-pregnant), and 47% and 59% for node-positive pregnant and non-pregnant patients respectively (Petrek et al., 1991). Others have also found no statistically significant difference in cause-specific survival between pregnant and non-pregnant patients (Nugent and O'Connell, 1985; Zemlickis et al., 1992a).

Children born to women with breast cancer are usually delivered earlier (often because of pre-term deliveries performed when pulmonary maturation is secured, in order to allow amplification of therapy). Furthermore, a study that assessed fetal outcome has shown a significant lower mean birth weight compared with that in matched controls. This difference remained valid when adjusted for gestational age. Since most patients in this study did not receive chemotherapy while pregnant, the relative lower birth weight is probably attributed to the disease itself. There was a trend for higher, non-significant, proportion of stillbirth (2.4%) among pregnant women with breast cancer (Zemlickis et al., 1992a). Another study which reviewed 24 cases of PABC treated by surgery and chemotherapy, found normal Apgar scores and birth weights as compared with the general population (Berry et al., 1999).

Although extremely rare, metastatic spread to the placenta was reported in association with an advanced disease (Dildy et al., 1989). Therefore, careful histological examination of the placenta is recommended in pregnancy-associated malignancies. Spread of breast cancer to the fetus has never been documented.

Adjuvant chemotherapy for breast cancer may induce drug-related amenorrhoea. However, ~50–60% of women aged <35 years will continue to menstruate after completion of adjuvant cytotoxic treatment (Sutton et al., 1990), and therefore a significant portion of young women treated with chemotherapy might subsequently become pregnant. The overall prognosis for women who become pregnant following completion of successful therapy is equivalent (or even superior) to those who did not conceive after remission (Peters, 1968; Kroman et al., 1997; Surbone and Petrek, 1998; Velentgas et al., 1999). In a review of several series that included 465 patients, the mean 5- and 10-year survival rates were 71.5 and 60.9% respectively (Danforth, 1991). Yet, since women with poor prognosis do not live long enough to

become pregnant, and since case–control studies were based on small numbers of women, a selection bias must be considered. Nevertheless, as recurrence peaks ~2 years after completion of treatment, avoidance of pregnancy during this period should be recommended (Sankila *et al*., 1994). The reciprocal relationships between pregnancy and breast cancer are summarized in Table II.

Malignant melanoma

The incidence of malignant melanoma has been increasing substantially during the past few decades, and it is now estimated that the individual lifetime risk for this tumour is about 1% (Rigel *et al*., 1987). The average age at presentation is 45 years, and about one-third of all women are of child-bearing age at diagnosis (Colbourn *et al*., 1989). Melanoma is considered one of the leading malignancies associated with pregnancy, accounting for about 8% of all cancers diagnosed during gestation (Potter and Schoeneman, 1970).

The staging system for malignant melanoma has incorporated criteria regarding tumour thickness, evidence of nodal metastasis, and involvement of advanced regional or distant metastasis (Balach and Milton, 1985). For patients with localized disease, the most significant prognostic factor is tumour thickness at diagnosis; the location of the primary tumour is also a determinant in survival. Tumours on the trunk, neck or head tend to have a poorer prognosis than lesions on the extremities (Wong and Strassnger, 1990).

It has been suggested that women have a better survival rate than men, even when matched for the extent of the disease (Shaw *et al*., 1980). The gender-related variations in survival have raised the possibility that the altered hormonal status throughout pregnancy might influence the course of the disease. Pregnancy is associated with hyperpigmentation that was ascribed to increased secretion of melanocyte-stimulating hormone (MSH) and other growth factors (Ances and Pomerantz, 1974). Moreover, several reports showed that melanocytes (extracted from melanoma specimens) were found to have oestrogen, progesterone and androgen receptors (McCarty *et al*., 1980; Kokoschka *et al*., 1982). Therefore, it was postulated that the gestational hyperoestrogenic state increases the risk of malignant melanoma. However, histopathological analysis showed that the number of oestrogen and progesterone receptors on melanoma cells is small, especially when compared with well-known hormone-dependent tumours (e.g. breast) (Chaudhuri *et al*., 1980; Flowers *et al*., 1987). Furthermore, recent clinical data regarding the use of oestrogenic agents (oral contraceptives) failed to show any association with increased risk in the incidence of melanoma (Green, 1991). Attempts to treat malignant melanoma by hormonal manipulation such as anti-oestrogenic drugs were disappointing (Adam *et al*., 1981; Bain *et al*., 1982; Holman *et al*., 1984).

The influence of pregnancy on malignant melanoma remains controversial. Since 1951, several reports have suggested that pregnancy may induce malignant melanoma or exacerbate its course (Pack and Scharnagel, 1951; Grin *et al*., 1996). Most of these studies, documenting altogether about 200 cases, were lacking stratification for tumour thickness, and some used inappropriate controls with unmatched prognostic factors. These studies suggested that patients diagnosed with malignant

melanoma during pregnancy had a more advanced stage of the disease. The pregnant patients were found to have a higher incidence of lesions on the trunk, and more regional and distant metastasis at time of diagnosis (Houghton *et al*., 1981). Nevertheless, most of these retrospective studies did not find any adverse effect on survival when appropriate matching was used (George *et al*., 1960; White *et al*., 1961; Colbourn *et al*., 1989). Others have found a worse prognosis and limited survival for women with pregnancy-associated melanoma (Sutherland *et al*., 1983). Another group have reported a worse prognosis during pregnancy limited only to patients with stage II disease (Shiu *et al*., 1976).

Recent studies addressed prognostic factors of the tumour, and used appropriate control groups to evaluate the contradictory conclusions of previous reports. These reports included more than 320 cases of stage I malignant melanoma, all matched with controls with similar prognostic factors. These studies have shown no significant difference in survival rates between women with stage I pregnancy-associated melanoma and matched non-pregnant controls (McManamny *et al*., 1989; Wong *et al*., 1989; MacKie *et al*., 1991). Nevertheless, several studies still report a significantly shorter disease-free interval (and 10-years survival) among pregnant patients, possibly attributed to a shortened time to nodal metastasis (Reintgen *et al*., 1985; Slingluff *et al*., 1990). Also, since most recurrences occurred within 3 years of treatment, avoiding further pregnancies during this time limit is recommended. Data relating to the higher stages of disease in pregnancy are limited.

Treatment of malignant melanoma is based on wide surgical excision with appropriate margins (depending on the thickness of the primary lesion) (Veronesi *et al*., 1988; Veronesi and Cascinelli, 1991). For most patients, this procedure can be performed under local anaesthesia, with little risk to the fetus. Using the blue dye technique, identification of sentinel lymph nodes is possible in 98% of cases. These nodes can be removed and then evaluated pathologically. When metastatic disease is evident, lymph node dissection is performed (Krag *et al*., 1995). Metastatic disease to lymph nodes and isolated metastases to the lungs, gastrointestinal tract and brain may be palliated by surgical removal, or (with limited success) by chemotherapy (Wornom *et al*., 1986). Chemotherapeutic agents used in metastatic melanoma include single-agent dacarbazine, and combinations such as tamoxifen, carmustine and cisplatin (DiPaola *et al*., 1997). Several case reports regarding treatment of metastatic melanoma during pregnancy have been published (Colbourn *et al*., 1989; Slingluff *et al*., 1990). The use of adjuvant interferon α-2b (INF) in patients with high-risk melanoma is controversial (Kirkwood *et al*., 1996; Kirkwood, 1998). INF has been used safely in pregnancy in order to treat hepatitis, myeloproliferative disorders and multiple myeloma (Baer, 1991; Sakata *et al*., 1995; Ruggiero *et al*., 1996). However, adjuvant INF for metastatic melanoma requires higher doses, which involve significant side effects such as influenza-like symptoms. The toxicity of this high-dose INF therapy in pregnant patients was not evaluated.

Malignant melanoma is the tumour that most frequently metastasizes either to the placenta or fetus, and accounts for >50% of all tumours with fetal involvement. These metastases have resulted in four infant deaths (Dildy *et al*., 1989; Brossard *et*

Table III. Reciprocal relationships between pregnancy and malignant melanoma

Pregnancy does not alter the prognosis of melanoma when compared with well-matched, non-pregnant women. However, several studies suggested a shorter disease-free interval in pregnant patients.
Several studies report that bad prognostic factors may occur more frequently during pregnancy.

Treatment is similar to that for non-pregnant women, but with specific considerations related to pregnancy.

Malignant melanoma accounts for more than one-half of the metastases to products of conception. The placenta and fetus should be examined thoroughly in these patients.

Table IV. Reciprocal relationships between pregnancy and Hodgkin's disease (HD)

Pregnancy neither exacerbates the disease, nor adversely affects the mean survival rate.
Most women present with a low-stage HD, and can be treated by either single-agent chemotherapy or modified supradiaphragmatic radiation.

Infants born to women with HD are not at risk for growth retardation or extreme prematurity.

There is a greater risk of stillbirth in this group.

al., 1994). The reciprocal relationships between pregnancy and malignant melanoma are summarized in Table III.

Lymphoma

Overall, lymphoma is the fourth most frequent malignancy diagnosed during pregnancy (Haas, 1984). Hodgkin's disease (HD) has a bimodal peak incidence, which primarily affects young adults, the mean age at diagnosis being 32 years. In contrast, non-Hodgkin's lymphoma (NHL) has an age-dependent incidence pattern with a mean age at diagnosis of 42 years (Ward and Weiss, 1989). Therefore, HD associated with pregnancy is not uncommon, occurring in from 1 in 1000 to 1 in 6000 deliveries (Lishner *et al.*, 1992). The incidence of pregnancy-associated NHL is quite low, although the experience is based on a small number of uncontrolled studies (Lishner *et al.*, 1994).

HD often presents with painless lymphadenopathy. Adequate biopsy is essential for diagnosis, and is considered safe during pregnancy. Staging procedures include chest X-radiography, abdominal ultrasound or MRI scanning, and bone marrow biopsy. Since the current therapeutic approach is initially to administer chemotherapy in most cases, staging may be limited. At early stages of pregnancy therapeutic abortion is evaluated due to the teratogenic effect of radio- and chemotherapy in the first trimester. This holds true especially for patients with advanced disease in whom delay of treatment may adversely affect the woman's survival (Jacobs *et al.*, 1981; Peleg and Ben-Ami, 1998). Therapeutic abortion should also be urged for patients with infra-diaphragmatic disease requiring pelvic irradiation. However, women with HD at the first trimester of pregnancy who refuse therapeutic abortion can be either treated by modified dose/field supradiaphragmatic radiation or by single-agent chemotherapy until the second trimester. Mantle irradiation, when modified by field and dose, usually does not exceed the 10 rad guidelines traditionally used as threshold for teratogenic risks. Selected cases can be followed at short intervals for signs of progression without any treatment (Ward and Weiss, 1989; Lishner *et al.*, 1992; Falkenberry, 1998). Patients who present in the second or third trimester can be safely treated with combination chemotherapy similar to the non-pregnant patients. Radiotherapy, especially to the subdiaphragmatic areas, is usually delayed and administered after delivery. When cytotoxic agents are used, delivery should be planned to avoid bone marrow depression at the time of labour.

For many years it was believed that pregnancy might exacerbate HD, and increase the relapse and mortality rate (Southman *et al.*, 1956). However, later publications have shown that pregnancy does not adversely affect survival rate (Barry *et al.*, 1962; Gobbi *et al.*, 1984; Nisce *et al.*, 1986). As for young non-pregnant women, about two-thirds of pregnant patients with HD present with stages I/II. A case–control analysis of 33 cases of HD associated with pregnancy showed a 20-year survival rate which was similar to that of 67 matched controls (Lishner *et al.*, 1996a). A report of 50 pregnancies associated with HD showed a 10% incidence of miscarriage and 4% stillbirth, though these values were not significantly different from findings in the general population. Furthermore, there was no significant difference in birth weight, mean gestational age and mode of delivery when compared with a group of matched healthy pregnant controls (Lishner *et al.*, 1992). The reciprocal relationships between pregnancy and HD are summarized in Table IV.

During pregnancy, most NHL patients present with lymph-adenopathy. Diagnosis is based on adequate pathological examination of the biopsies, although during pregnancy NHL may occasionally involve the breast, ovary or uterus (Gelb *et al.*, 1996). Although relatively few case reports and reviews exist regarding pregnancy-associated NHL, these cases might become more common due to the growing numbers of AIDS-related NHL cases (Serraino *et al.*, 1997). Most pregnant women present with an aggressive histology (Lishner *et al.*, 1994), and it has been suggested that these cases should be treated by aggressive combination chemotherapy. This strategy yields altogether less than 50% disease-free interval (Ward and Weiss, 1989; Aviles *et al.*, 1990; Gelb *et al.*, 1996). Burkitt's lymphoma and lymphoblastic lymphoma are associated with even higher mortality rates.

Table V. Reciprocal relationships between pregnancy and Non-Hodgkin's lymphoma (NHL)

Based on small series and case reports, it seems that NHL associated with pregnancy has a more aggressive histology and disseminated disease.

Treatment with aggressive combination chemotherapy is recommended, and results in a survival rate that is similar to that seen in non-pregnant women.

When administered after the first trimester, treatment of NHL has no deleterious fetal effects.

Patients with unfavourable histology, presenting in the first trimester, should be considered for a therapeutic abortion. When abortion is refused, a combined aggressive chemotherapy should be initiated since these lymphomas have an aggressive clinical course. Most pregnancies with a concomitant NHL diagnosed during the first and second trimester will result in healthy infants (Ward and Weiss, 1989; Aviles *et al*., 1990; Lishner *et al*., 1996b). Fetal survival is even higher for cases diagnosed during the third trimester. The few pregnant women presenting with a limited, low- to intermediate-grade disease could either be treated with localized radiation therapy, or observed until parturition followed by adequate staging and completion of therapy.

Several theories have been suggested to explain the aggressive nature of the disease in pregnant women. These theories focus either on the hormone-dependent growth observed in the rat model, or on the immunosuppressive effect of pregnancy (Ioachim and Morson, 1986), which facilitates tumour dissemination. Due to the small number of patients and the complexity of the disease, these theories remain unproven. The reciprocal relationships between pregnancy and Non-Hodgkin's disease are summarized in Table V.

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 results of animal studies cannot be extrapolated directly to humans however, as differences between animal and human outcomes following exposure to teratogenic drugs may be related to variations in dosage, gestational period and time of embryogenesis. Thus, studies in humans are needed to verify the risk of administration of chemotherapy during pregnancy. 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 (Nicholson, 1968a,b; Doll *et al*., 1988; Ebert *et al*., 1997). 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 to 12 weeks of gestation, when organogenesis takes place. The most toxic drugs during this period are aminopterin (no longer in use) and methotrexate. By the 12th week of gestation, organogenesis is completed 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 (Gililland and Weintein, 1983; Aviles and Niz, 1988; Aviles *et al*., 1991; Zemlickis *et al*., 1992b). Since chemotherapy may be associated with transient bone marrow suppression, delivery should be planned accordingly (Buekers and Lallas, 1998). 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*. These reports, as mentioned previously, were based on single cases and case–control studies and assessed more than 180 infants exposed to chemotherapy in different stages of gestation. The age of infant assessment ranged from 1 month to 22 years. The children were tested by a variety of conventional tests, including the Denver developmental screening tests, Wechsler and Bender–Gestalt cognitive tests, and reports from parents, school personnel and paediatricians. Altogether, these tests have shown that chemotherapy does not have a major impact on later neurodevelopment and cognitive capabilities. Moreover, the available data suggest that children exposed to chemotherapy *in utero* are not at increased risk for occurrence of malignancies or infertility (Koren, 1990; Zemlickis *et al*., 1993, 1996; Koren *et al*., 1996).

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 immediate post-implantation periods, radiation has an all-or-none effect, resulting in either embryonic death or further normal development. A dose of 200 cGy results in mouse embryonic death in 80% of cases (Rugh, 1963). 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 (Dekaban, 1968; Lione, 1987). The threshold seems to be about 5–25 cGy, with a downward shift of IQ in a dose-dependent manner (Otake *et al*., 1996). 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. For example, a distance of >30 cm from the edges of the field will yield a reasonable exposure of the fetus of only 4–20 cGy. 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.

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 fetal 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.

Summary

Malignant disease during pregnancy presents an extreme stress to both patient and physician, and its occurrence raises a conflict between optimal maternal therapy and fetal well-being. The most common malignancies (cervix, breast, lymphoma and melanoma) account for about 70–80% of pregnancy-associated tumours (Haas, 1984; Dildy et al., 1989). Many other sites of primary tumours have been reported in the literature, mainly leukaemia, ovary and thyroid carcinoma. Many reports and reviews have noted that pregnant patients tend to have a worse outcome when compared with non-pregnant women. Some have postulated that the altered hormonal environment of pregnancy may adversely influence the course of the disease. However, based on contemporary well-controlled studies, it seems that pregnancy per se should not be considered as a poor prognostic factor. However, since the gestational status might interfere with correct diagnosis and treatment, the result might be an inferior outcome. In this review, the main issues regarding four relatively common pregnancy-associated malignancies have been summarized, with especial focus on the dual relationship and the effect of pregnancy on tumour spread, and the effect of the tumour and anti-cancer therapy on the gestational state.

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