

Current Management of Patients with Melanoma who Are Pregnant, Want to Get Pregnant, or Do Not Want to Get Pregnant

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The number of pregnant women who are newly diagnosed with malignant disease annually in the U.S. is approximately 1 per 1000 population.¹ Melanoma, breast carcinoma, cervical carcinoma, leukemia, and lymphoma are the most common types of malignant disease that arise during pregnancy.^{2,3} The incidence of melanoma is rising at a rapid rate, and it is projected that 1 in 68 Americans born in the year 2002 will develop an invasive melanoma during their lifetime. Melanoma is the sixth most common malignancy in women. It is the most common malignancy in women ages 25–29 years, and it is associated with a younger age at the time of presentation.⁴ These trends suggest that approximately 35% of women with melanoma are of childbearing age.^{2,5} In this issue of *Cancer*, Daryanani et al. provide further evidence that pregnancy does not have an adverse effect on prognosis in patients with melanoma.⁶ The information from this single-institution study is valuable; however, the management of patients with melanoma with respect to pregnancy and hormonal contraception remains a challenge. The purpose of this editorial is to discuss the management of these patients and to enhance the information provided by Daryanani et al.⁶

It is clear that we will encounter increasing numbers of women of childbearing age who may be pregnant at the time of diagnosis of melanoma, who may desire to become pregnant after the diagnosis, or who may desire to use oral contraceptive pills to prevent pregnancy after a diagnosis of melanoma. In clinical practice, how these scenarios are approached may vary from institution to institution and from physician to physician. This is simply a reflection of the historic

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controversy that has surrounded the effect of pregnancy and hormones on melanoma and the appropriate management of melanoma in pregnant women and in women of childbearing age. Although no rigorous, randomized, prospective trials exist to answer all of these questions definitively, a wealth of epidemiologic data and controlled clinical studies provides consistent insight into optimal management approaches.

Pregnancy at the Time of Diagnosis

Numerous well controlled studies, such as that by Daryanani et al., have provided strong evidence that the clinical course, prognosis, and overall survival of pregnant women with melanoma (American Joint Committee on Cancer [AJCC] Stage I–II) is similar to that in nonpregnant women.^{2,3,5–9} The prognosis of pregnant women with melanoma still is dependent primarily on tumor thickness and ulceration status.¹⁰ Some studies have shown that thicker lesions are associated with pregnancy, presumably as a result of delayed diagnosis.⁸ Early detection is critical, and prompt biopsy of suspicious lesions is important and should not be deferred until after pregnancy. The earliest sign of a melanoma is a change in the size, shape, or color of a lesion. The earliest symptom is persistent itching of a lesion.¹¹ Biopsies and wide local excisions can be performed safely during pregnancy. Minor variations in logistics and techniques easily can accommodate the recommendations of the patient's obstetrician. For example, some of our obstetricians recommend recording fetal heart rate before and after the mother undergoes a wide local excision.

Can Pregnant Patients Undergo Sentinel Lymph Node Biopsy Safely?

Sentinel lymph node (SLN) mapping and biopsy represent one of the most significant advances in the management of patients with melanoma during the past decade. The most powerful prognostic factor related to recurrence and survival in patients with clinically localized melanoma is the status of the SLN.¹² We offer SLN biopsy at our institution to relatively healthy, nonpregnant patients with melanomas measuring ≥ 1.0 mm or < 1.0 mm with other adverse factors. This technique uses preoperative intradermal injection of ^{99m}Tc-sulfur colloid (1–3 millicuries [mCi]; CIS-US, Inc., Bedford, MA) and intraoperative, intradermal injection of isosulfan blue dye (Lymphazurin 1%; Hirsch Industries, Inc., Richmond, VA) around the intact tumor or biopsy site. Lymphatic mapping and SLN biopsy are performed with the aid of a hand-held gamma counter and visualization of blue lymph nodes.

Fetal doses < 100 milli-grays (mGy) of radiation

do not increase the incidence of fetal malformation. The Society of Nuclear Medicine recommends a pregnancy test in patients prior to any procedure that would expose a fetus to > 50 mGy. The dosages and radiopharmaceuticals used for lymphatic mapping deliver whole fetal doses of < 5 mGy. Therefore, these radiopharmaceuticals at dosages used for lymphatic mapping are not contraindicated in pregnant patients and carry negligible risk.^{13–15} The safety of isosulfan blue dye in pregnancy poses additional questions. The rate of allergic reactions to the dye reportedly is as high as 2%, and the incidence of life-threatening anaphylactic reaction requiring vigorous resuscitation is reported at 0.7–1.1%.^{16,17} Due to the risk of this rare but potentially catastrophic event of anaphylaxis in pregnant patients, we now use radiocolloid alone for SLN biopsy in pregnant patients at our institution. Alternatively, in women who are in middle to late pregnancy and who have undergone narrow excision of their primary melanoma with clear histologic margins, definitive wide local excision and SLN biopsy with radiocolloid and blue dye may be delayed until after delivery, with close clinical follow-up for the duration of the pregnancy.

Implications for the Fetus

What about the risk of metastasis to the placenta and fetus? Fortunately, placental and fetal metastasis from maternal malignant disease is an exceptionally rare event.¹⁸ However, melanoma is the most common type of malignancy to metastasize to the placenta and fetus, representing 30% of placental metastases and 58% of fetal metastases. Approximately 19 patients with melanoma placental metastasis have been reported, with maternal death in all patients: 80% within 3 months of delivery. Five patients with fetal metastasis have been reported, with four resulting in death. Therefore, although these occurrences are exceedingly rare, pregnant patients with melanoma at our institution are counseled, the placenta is sent for histologic evaluation, and the neonatal service is notified.

Pregnancy After Diagnosis

Although there is no clear evidence to suggest that prior, present, or subsequent pregnancy adversely affects the prognosis of patients with melanoma, there are no standard, defined guidelines for patients who desire to become pregnant after diagnosis and treatment of melanoma. Recommendations regarding the length of time to wait after a diagnosis vary from physician to physician, and some physicians recommend against getting pregnant. Significant proportions of patients with localized disease (AJCC Stage I–II) harbor occult disease and eventually develop re-

currences. It is not completely predictable who will and who will not develop recurrent disease. Many survival models demonstrate that tumor thickness is the single most important predictor of a probability of cure in patients who do not undergo SLN biopsy. Although approximately 50% of recurrences develop by 3 years in patients with thick lesions, late recurrences occur in some patients, even with thin lesions, longer than a decade after treatment.¹⁹ If recurrence develops during pregnancy, then it may be disastrous both medically and emotionally, potentially altering treatment options and with a risk of placental and fetal metastasis, although these are rare. The use of chemotherapy, radiation therapy, radiodiagnostic tests, and general anesthesia for extensive surgical procedures may have harmful effects on the fetus/newborn.

Our recommendation about how long to wait before becoming pregnant after a diagnosis of melanoma is on a case-by-case basis, depending primarily on the risk of recurrence (tumor thickness and tumor stage), age of the patient, and desire to become pregnant. There is no exact answer, and our approach is to educate patients completely about the risks to help them make informed decisions. At our institution, patients typically wait 0–5 years, depending on the aforementioned factors. For example, a woman age 40 years with a melanoma measuring 0.3 mm in thickness has only an approximate 1–3% risk of recurrence within 5 years, and we would not necessarily advise her to wait if she desires to become pregnant and finds this an acceptable risk. Alternatively, a woman age 21 years with a melanoma measuring 4.0 mm thick generally would be advised to wait for 3–5 years. Each patient is approached individually, with the patient ultimately making her own informed decision. If the patient does become pregnant, then self-examination of the skin and lymph nodes on a monthly basis is stressed.

Although controlled studies consistently demonstrate no statistically significant difference in survival for melanoma in pregnant patients compared with nonpregnant patients, the tragedy of a child losing their mother soon after birth is highlighted by clinical examples and case reports. Merkus et al. illustrated this point in their description of a couple who consulted the gynecologist repeatedly because of a primary fertility disorder.²⁰ A few days after the woman started the hormonal treatment that preceded the in vitro fertilization procedure, she noted swelling in the right groin area for which she consulted a surgeon. It was found that the swelling was a metastasis from a primary cutaneous melanoma that had been excised from her leg 6 months previously. Her first in vitro

fertilization treatment resulted in a pregnancy, which ended with the birth of a healthy boy. However, the placenta showed melanoma metastases, and the mother died 2 months after the birth of her son. Although recurrence and survival may not have been affected directly by pregnancy or hormonal treatment, the tragedy of this situation is readily apparent.

The Desire Not to Become Pregnant (Oral contraceptives)

Given the concerns that may face a woman of child-bearing age who has been diagnosed with melanoma, what about oral contraceptive use? Many studies with thousands of patients have demonstrated no significant increased risk for the development of melanoma associated with oral contraceptive use, including duration of use, age started, years since first or last use, or current use.²¹ There also is no evidence showing that hormone replacement therapy for menopause plays an etiologic role in the development or recurrence of melanoma. Because a very small risk of contraceptive or replacement hormones on recurrence has not been excluded in a prospective trial, some patients and/or physicians may choose not to accept even a theoretical risk and, instead, choose nonhormonal contraception or menopause symptom relief.

Conclusions

From previous studies, including that reported by Daryanani et al. in this issue of *Cancer*,⁶ we may conclude that pregnancy or hormone use before, during, or after a woman is diagnosed with melanoma does not appear to influence survival, which provides important information that should simplify the clinical management of these patients. However, generalized guidelines may not be applicable or appropriate because of patient variability. In clinical practice, this translates into individualized patient management. The patient with melanoma who is diagnosed during pregnancy is managed best by early and continual involvement of a multidisciplinary team with clinical and psychosocial expertise in melanoma therapy.

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