

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

Jennifer L. Schwartz, M.D.¹

Ellen L. Mozurkewich, M.D.²

Timothy M. Johnson, M.D.^{1,3,4}

¹ Department of Dermatology, University of Michigan Medical School and Comprehensive Cancer Center Melanoma Program, Ann Arbor, Michigan.

² Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, University of Michigan Medical School and Comprehensive Cancer Center Melanoma Program, Ann Arbor, Michigan.

³ Department of Otorhinolaryngology, University of Michigan Medical School and Comprehensive Cancer Center Melanoma Program, Ann Arbor, Michigan.

⁴ Department of Surgery, Division of Plastic Surgery, University of Michigan Medical School and Comprehensive Cancer Center Melanoma Program, Ann Arbor, Michigan.

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

See referenced original article on pages 2248–53, this issue.

Address for reprints: Jennifer L. Schwartz, Department of Dermatology, University of Michigan, 1910 Taubman Center, Ann Arbor, MI 48109-0314; Fax: (734) 936-6395; E-mail: jennschw@umich.edu

Received December 2, 2002, revision received January 13, 2003; accepted January 17, 2003.

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.

REFERENCES

1. Wingo PA, Tong T, Bolden S. Cancer statistics, 1995. *CA Cancer J Clin.* 1995;45:8–30.
2. Pavlidis NA. Coexistence of pregnancy and malignancy. *Onco-gologist.* 2002;7:279–287.
3. Antonelli NM, Dotters DJ, Katz VL, Kuller JA. Cancer in pregnancy: a review of the literature. Part I–II. *Obstet Gynecol Surv.* 1996;51:125–142.
4. American Cancer Society. ACS 2002 facts and figures. Available from URL: http://www.cancer.org/docroot/STT/stt_0.asp [accessed November 23, 2002].
5. Teplitzky S, Sabates B, Yu K, Beech DJ. Melanoma during pregnancy: a case report and review of the literature. *J LA State Med Soc.* 1998;150:539–543.

6. Daryanani D, Plukker JTh, De Hullu JA, Kuiper H, Nap RE, Hoekstra HJ. Pregnancy and early-stage melanoma. *Cancer*. 2003;97:2248–2253.
7. MacKie RM. Pregnancy and exogenous hormones in patients with cutaneous malignant melanoma. *Curr Opin Oncol*. 1999;11:129–131.
8. Wrone DA, Duncan LM, Sober AJ. Melanoma and pregnancy: eight questions with discussion. *J Gender Specif Med*. 1999;2:52–54.
9. Grin CM, Driscoll MS, Grant-Kels JM. The relationship of pregnancy, hormones, and melanoma. *Semin Cutaneous Med Surg*. 1998;17:167–171.
10. Balch CM, Soong SJ, Gershenwald JE, et al. A prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint Committee on Cancer melanoma staging system. *J Clin Oncol*. 2001;19:3622–3634.
11. Schwartz JL, Wang TS, Hamilton TA, Lowe L, Sondak VK, Johnson TM. Thin primary cutaneous melanomas: associated detection patterns, lesion characteristics, and patient characteristics. *Cancer*. 2002;95:1562–1568.
12. Gershenwald JE, Thompson W, Mansfield PF, et al. Multi-institutional melanoma lymphatic mapping experience: the prognostic value of sentinel lymph node status in 612 Stage I or II melanoma patients. *J Clin Oncol*. 1999;17:976–983.
13. Adelstein SJ. Administered radionuclides in pregnancy. *Teratology*. 1999;59:236–239.
14. Steenvoorde P, Pauwels EK, Harding LK, et al. Diagnostic nuclear medicine and risk for the fetus. *Eur J Nucl Med*. 1998;25:193–199.
15. Timins JK. Radiation during pregnancy. *NJ Med*. 2001;98:29–33.
16. Cimmino VM, Brown AC, Szocik JF, et al. Allergic reactions to isosulfan blue during sentinel node biopsy—a common event. *Surgery*. 2001;130:439–442.
17. Albo D, Wayne JD, Hunt KK, et al. Anaphylactic reactions to isosulfan blue dye during sentinel lymph node biopsy for breast cancer. *Am J Surg*. 2001;182:393–398.
18. Altman JF, Lowe L, Redman B, et al. Placental metastasis of maternal melanoma. *J Am Acad Dermatol*. In press.
19. Gamel JW, George SL, Edwards MJ, Seigler HF. The long-term clinical course of patients with cutaneous melanoma. *Cancer*. 2002;95:1286–1293.
20. Merkus JM, Teepen JL. The indispensable anamnesis: in-vitro fertilization in a woman under treatment for melanoma. *Ned Tijdschr Geneesk*. 1998;142:2073–2075.
21. Karagas MR, Stukel TA, Dykes J, et al. A pooled analysis of 10 case-control studies of melanoma and oral contraceptive use. *Br J Cancer*. 2002;86:1085–1092.

Pregnancy and Early-Stage Melanoma

Deepu Daryanani, M.D.¹

John T. Plukker, M.D., Ph.D.¹

Joanne A. De Hullu, M.D., Ph.D.²

Hilde Kuiper, M.D.³

Raoul E. Nap, M.Sc.¹

Harald J. Hoekstra, M.D., Ph.D.¹

¹ Division of Surgical Oncology, University Medical Center Groningen, Groningen, The Netherlands.

² Department of Obstetrics and Gynecology, University Medical Center Groningen, Groningen, The Netherlands.

³ Department of Pathology, University Medical Center Groningen, Groningen, The Netherlands.

See related editorial on pages 2130–3, this issue.

Presented at the biannual meeting of the European Cancer Conference (ECCO11), Lisbon, Portugal, October 21–25, 2001.

Groningen melanoma data base was supported by a grant from the Research Foundation IJsselmond, The Netherlands.

A large amount of the data was provided kindly by the former head of the Division of Surgical Oncology of the University Medical Center, Groningen Prof. Dr. H. Schraffordt Koops.

Address for reprints: Harald J. Hoekstra, M.D., Ph.D., Division of Surgical Oncology, Department of Surgery, University Medical Center Groningen, P.O. Box 30.001; 9700 RB Groningen, The Netherlands; Fax: 011 (31) 503614873; E-mail: h.j.hoekstra@chir.azg.nl

Received August 30, 2002; revision received November 13, 2002; accepted November 15, 2002.

BACKGROUND. Cutaneous melanomas are aggressive tumors with an unpredictable biologic behavior. It has been suggested that women who present with melanoma during pregnancy have a worse prognosis due to more aggressive behavior of the melanoma. The objective of the current study was to evaluate the long-term effect of pregnancy on disease progression in women with Stage I–II melanoma.

METHODS. From 1965 to 2001, 46 pregnant women were treated for a Stage I–II melanoma at the University Medical Center Groningen. These patients were compared with an age-matched and gender-matched control group (nonpregnant) of 368 women with Stage I–II melanoma. The patients were staged according to the 2002 American Joint Committee on Cancer TNM classification system for melanoma. The 10-year disease-free survival (DFS) and 10-year overall survival (OS) rates were calculated using logistic regression analysis.

RESULTS. The median age of patients in the pregnant group was 30 years (range, 18–46 years), and the median age of patients in the nonpregnant group was 36 years (range, 17–45 years). The median follow-up was 109 months (range, 1–356 months). Pregnant patients presented more often with thicker melanomas (median, 2.0 mm vs. 1.7 mm; not statistically significant). No differences with regard to tumor location, histologic subtype, tumor ulceration, or vascular invasion were detected between the pregnant group and the nonpregnant group. There was no statistical difference in the 10-year DFS and 10-year OS rates between the two groups. The 10-year DFS rates for patients in the pregnant and nonpregnant groups, respectively, were 88% versus 86% for patients with Stage I melanoma and 67% versus 73% for patients with Stage II melanoma. The 10-year OS rates for patients in the pregnant and nonpregnant groups, respectively, were 94% versus 90% for patients with Stage I melanoma and 82% versus 81% for patients with Stage II melanoma.

CONCLUSIONS. Pregnancy does not appear to have an adverse, long-term effect on survival in patients with clinically localized melanoma. Further studies should address whether pregnant patients present with thicker lesions and/or whether they have decreased DFS compared with nonpregnant women. The prognosis for women with melanoma during pregnancy, as it relates to survival, still is dependent on tumor thickness and ulceration. *Cancer* 2003;97:2248–53.

© 2003 American Cancer Society.

DOI 10.1002/cncr.11321

KEYWORDS: melanoma, staging, pregnancy, survival.

Melanoma often is diagnosed in young adults, and a significant number of these patients are women in their reproductive phase of life. The real incidence of melanoma during pregnancy is unknown. In 1969, Smith and Randall reported an incidence of 2.8 per 1000 deliveries.¹ The influence of pregnancy on the prognosis of women with melanoma has been a controversy since 1951, when Pack and Scharnagel reported on 10 pregnant patients with malignant melanoma, 5 of whom died within 30 months after diagnosis.² Since that

report, numerous case reports also have been presented demonstrating a worse prognosis for pregnant women compared with nonpregnant women with melanoma and the dilemmas in treatment policies.^{3,4} However, in 1985 the World Health Organization Melanoma Program initiated a retrospective study of patients with melanoma in relation to pregnancy. That study showed that there were no survival differences between pregnant and nonpregnant women with Stage I melanoma after correcting for tumor thickness.⁵ Thus, the literature is confusing, and reports are contradictory on the behavior of melanoma.

It has been hypothesized that the frequency and prognosis of melanomas in women are influenced by hormonal or reproductive factors. However, previous studies failed to prove that the presence of hormone receptors in human melanoma cells carried a poorer prognosis.^{6–8} Traditional quantitative analyses suggest that a proportion of melanoma cells carry a type II estrogen receptor; however, the absence or presence of this receptor did not appear to affect the individual outcome of the patient.⁸ This was underlined in recent reports in which the relation between the use of oral contraceptives and prognosis also was not proven.^{9–11}

The objective of the current study was to report our single institution's experience with melanoma arising during pregnancy. Specific goals of the study were to determine the disease-free survival (DFS) and overall survival (OS) rates for this group of patients over a long-term follow-up. Furthermore, the impact of Breslow thickness, ulceration, vascular invasion, histologic subtype, and tumor location on DFS and OS was studied.

MATERIALS AND METHODS

Between 1965 and 2001, a total of 2567 patients were diagnosed and treated for cutaneous malignant melanoma at the University Medical Center Groningen. The population consisted of 991 male patients (39%) and 1576 female patients (61%). For the purposes of this study, 46 female patients with melanoma with a median age of 30 years (range, 18–46 years) were identified as pregnant and were diagnosed with Stage I–II melanoma according to the American Joint Committee on Cancer (AJCC) TNM classification system (Table 1).¹² This pregnant group was compared with a nonpregnant control group. The age-matched and gender-matched control population was selected from women with Stage I–II cutaneous melanoma between the ages of 16 years and 46 years who were not pregnant at the time of diagnosis. The subgroup of selected patients for the control group consisted of 368 nonpregnant women with Stage I–II melanoma with a median age of 36 years (range, 17–45 years). The clin-

TABLE 1
The 2002 American Joint Committee on Cancer TNM Melanoma Staging System^a

Stage/T classification ^b	Thickness (mm) ^c	Ulceration status
IA		
T1A	≤1.0	Without ulceration
IB		
T1B	≤1.0	With ulceration
T2A	1.01–2.0	Without ulceration
IIA		
T2B	1.01–2.0	With ulceration
T3A	2.01–4.0	Without ulceration
IIB		
T3B	2.01–4.0	With ulceration
T4A	>4.0	Without ulceration
IIIC		
T4B	>4.0	With ulceration

^a See Balch et al.¹²

^b 2002 American Joint Committee on Cancer classification system.

^c Thickness according to Breslow.

ical data retrieved from the Groningen melanoma data base included age at diagnosis, site of the primary tumor, and stage at diagnosis. All histologic slides were reviewed at our institution. The histopathologic characteristics recorded included the histologic subtype of melanoma (superficial spreading, nodular, or unknown), tumor ulceration, Breslow depth of invasion (in millimeters), and the presence or absence of vascular invasion.

Treatment

All patients were treated according to the guidelines of the Dutch Melanoma Working Party.¹³ Most patients who were referred to our institution underwent diagnostic excision of their primary lesions elsewhere. The patients were referred for further treatment, which consisted mostly of wide excision only. Sentinel lymph node biopsy was performed from 1995 onward in six patients, all of whom were postpartum. Fifteen patients (33%) in the pregnant group (all postpartum) received adjuvant, hyperthermic, isolated limb perfusion with melphalan compared with 144 patients (39%) in the nonpregnant group. In the past, the adjuvant limb perfusion was part of an institutional protocol or was part of the European Organization for Research and Treatment of Cancer study on adjuvant limb perfusion in patients with Stage I melanoma.

Follow-Up

All patients were followed regularly in the outpatient clinic for regional and/or distant failures. The follow-up scheme included only annual chest X-rays and did

not include laboratory controls. Regional failure was defined by the histologic or cytologic confirmation of tumor cells at the site of the primary tumor and/or along its lymphatic drainage pathway to the first lymph node basin. Distant failure was defined by radiologic detection of suspected lesions by means of computer tomography (lungs and brain), ultrasound (liver), and bone scintigraphy. Histologic confirmation of distant failure was not obtained for all patients. Appropriate treatment for patients who developed recurrent disease depended of the type and site of recurrence. No patient received any kind of adjuvant, systemic treatment.

Statistical Analysis

The SPSS software package (version 10.0 for Windows; SPSS, Inc., Chicago, IL) was used for statistical analysis. To compare the two groups with regard to Breslow thickness, the Mann-Whitney *U* test was used. DFS was defined as the time between the date of diagnosis and the date of first recurrence. Follow-up was defined as the time between the date of diagnosis and the date of disease specific death or the last visit to the outpatient clinic. Kaplan-Meier, Cox regression, and logistic regression analyses were performed to identify the risk factors and to calculate the 10-year DFS and 10-year OS curves with the date of diagnosis, first recurrence, or death acting as endpoints. To compare the distribution of survival between the pregnant group and the nonpregnant group, a log-rank test was used. Potential prognostic factors were calculated using univariate and multivariate analyses. *P* values < 0.05 was considered significant.

RESULTS

Clinical Data

Data concerning 610 consecutive women of childbearing age with cutaneous melanoma were analyzed. Fifty-seven patients were pregnant at the time of diagnosis (46 women with Stage I-II melanoma, 8 women with Stage III melanoma, and 3 women with Stage IV melanoma). The number of women with Stage III and IV was not sufficient for statistical analysis; thus, Stage III-IV disease was not considered. The nonpregnant control group consisted of 368 of 610 women of childbearing age who had sufficient clinical and pathologic available. The clinical variables of women in the pregnant group and the nonpregnant group with Stage I-II melanoma are presented in Table 2. The median follow-up was similar for both groups: The median follow-up was 106 months (range, 3-260, months) for patients in the pregnant group and 109 months (range, 1-356 months) for patients in the nonpregnant group. Primary melanomas of an extremity predomi-

TABLE 2
Demographic Data on Patients with Melanoma in the Pregnant Group and the Nonpregnant Group with Logistic Regression Analysis of Disease Free Survival and Overall Survival

	Pregnant group		Nonpregnant group		Logistic regression	
	No.	%	No.	%	DFS	OS
Total group						
Patients (<i>n</i> = 414)	46	11	368	89	—	—
Age (yrs)						
Median	30	—	36	—	—	—
Range	18-46	—	17-45	—	NS	NS
Melanoma site						
Upper extremity	8	17	51	14	<i>P</i> < 0.004	NS
Lower extremity	28	61	229	62		
Trunk	7	15	66	18	NS	NS
Head and neck	3	7	22	6	NS	NS

DFS: disease-free survival; OS: overall survival; NS: not statistically significant.

TABLE 3
Staging of Patients with Melanoma in the Pregnant Group and the Nonpregnant Group According to the 2002 American Joint Committee on Cancer TNM Classification System^a

Stage ^b	Pregnant group		Nonpregnant group	
	No.	%	No.	%
IA	11	24	113	31
IB	13	28	96	26
IIA	13	28	94	26
IIB	5	11	45	12
IIC	4	9	20	5

^a See Balch et al.¹²

^b 2002 American Joint Committee on Cancer Classification System.

nated in this group of patients. In the pregnant group, 36 patients (78%) had melanomas of an extremity, 28 of whom had disease that originated in the lower extremities (61%). Seven patients (15%) had melanomas of the trunk (thorax, abdomen, and back), and 3 patients (7%) had melanomas of the head and neck. In the nonpregnant group, the corresponding percentages were 76%, 18%, and 6%, respectively. For a summary of the primary tumor locations, see Table 2. Patients were staged according to the 2002 AJCC TNM classification system, as presented in Table 3.¹²

Histopathologic Data

All primary tumors were classified histologically according to histologic subtype, Breslow thickness, vascular invasion, and tumor ulceration and are summarized in Table 4. There was no significant difference between the two groups in histologic subtype. The

TABLE 4
Histopathologic Data on Primary Tumors and Logistic Regression Analysis of Disease Free Survival and Overall Survival

Variable	Pregnant group		Nonpregnant group		Logistic regression (<i>P</i> value)	
	No.	%	No.	%	DFS	OS
Histologic subtype	—	—	—	—	<0.002	NS
Unknown/other	17	37	145	39	—	—
SSM	20	43	177	48	—	—
Nodular	9	20	46	13	—	—
Breslow thickness (mm) ^a	—	—	—	—	<0.006	<0.005
0–0.75	12	26	116	32	—	—
0.76–1.50	14	30	122	33	—	—
1.51–4.0	14	30	97	26	—	—
>4.0	6	13	33	9	—	—
Vascular invasion	—	—	—	—	NS (0.076)	NS
Absent	39	85	328	89	—	—
Lymphatic	2	4	15	4	—	—
Blood vessel	4	9	8	2	—	—
Unknown	1	2	17	5	—	—
Ulceration	—	—	—	—	<0.010	<0.036
Yes	10	22	84	23	—	—
No	36	78	284	77	—	—

DFS: disease-free survival; OS: overall survival; NS: not statistically significant; SSM: superficial spreading melanoma.

^a The sum of percentages may not add up to 100% due to rounding.

majority of tumors were superficial, spreading melanomas: (43% in the pregnant group compared with 48% in the nonpregnant group). There also was no difference in the frequency of nodular type melanoma (20% in the pregnant group compared with 13% nonpregnant group; not statistically significant). In the pregnant group, the median Breslow thickness was 2.0 mm compared with 1.7 mm in the nonpregnant group (not statistically significant; $P = 0.119$; Mann–Whitney U test). In the pregnant group, the incidence of blood vessel invasion was 9% compared with 2% in the nonpregnant group (not statistically significant; $P > 0.05$). The numbers of tumors that were classified as ulcerating also were comparable in both groups.

DFS and OS

For patients with Stage I melanomas, the 10-year DFS rate was 88% in the pregnant group compared with 86% in the nonpregnant patients ($P = 0.6541$). The 10-year OS rates were 94% and 90%, respectively ($P = 0.6977$). Pregnant patients with Stage II melanomas had a 10-year DFS rate of 67% compared with 73% for nonpregnant patients with Stage II melanomas ($P = 0.7322$). The OS rates for patients with Stage II melanomas were 82% and 81%, respectively ($P = 0.7162$) (see Figs. 1, 2).

Logistic regression analysis showed that increasing Breslow thickness ($P < 0.005$) and the presence of ulceration ($P < 0.036$) significantly led to a higher

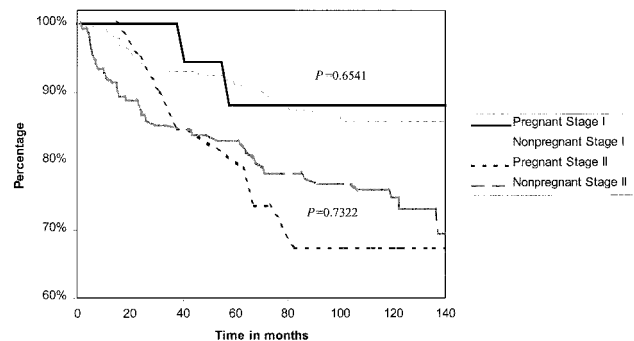


FIGURE 1. Disease free survival of pregnant patients versus nonpregnant patients with Stage I and Stage II melanoma according to the American Joint Committee on Cancer TNM classification system.

mortality. No significant effect on OS of vascular invasion, tumor type, tumor location, or pregnancy was detected. Logistic regression analysis with DFS as a dependent variable revealed that the length of DFS was related to increasing Breslow thickness ($P < 0.006$), ulceration ($P < 0.010$), tumor location (extremity melanoma; $P < 0.004$), and histologic subtype (nodular melanoma) ($P < 0.002$) but was not related to vascular invasion (not statistically significant; $P = 0.076$) (Tables 2, 4). In this model, 30% of the variance in the DFS could be explained by the model. Although pregnancy showed no significant effect on

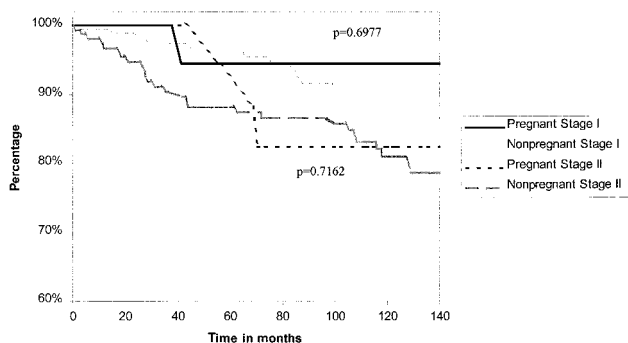


FIGURE 2. Overall survival of pregnant patients versus nonpregnant patients with Stage I and Stage II melanoma according to the American Joint Committee on Cancer TNM classification system.

DFS, it did reveal a trend toward a longer DFS in the nonpregnant group.

DISCUSSION

The possible influence of hormonal factors on the pathogenesis and biologic behavior of melanoma has intrigued scientists and clinicians on the basis of clinical or anecdotal reports suggesting a detrimental influence of concurrent pregnancy. The earlier hypothesis was that, during pregnancy, there was an increase in melanin-stimulating hormone, estrogen, and progesterone that, in turn, lead to increased pigmentation and size of benign nevi and even to possible malignant transformation.¹⁴ However, recent reports have denied the expression of estrogen receptors on human melanoma cells that affect the outcome of the disease.^{7,15} In a large cohort study of subfertile women, Venn et al. reported no evidence of an increased risk of melanoma in women who received exogenous hormones for in vitro fertilization compared with a control group.¹⁶ Thus, to date, there are no clear indications that exogenous hormone stimulation or hormonal changes during pregnancy stimulate the growth of the primary tumor or of potential micrometastases. Furthermore, there is no evidence showing that exogenous hormones, such as oral contraceptive medication, are contraindicated after treatment for melanoma.

In our research, the effect of pregnancy on disease progression in patients with melanoma was determined by comparing the 10-year DFS and OS rates in pregnant and nonpregnant patients of childbearing age at the time they were diagnosed with clinically localized melanoma. Our study showed no difference in the 10-year DFS rate between the pregnant and nonpregnant groups (Stage I, 88% vs. 86%, respectively; Stage II, 67% vs. 73%, respectively) and no significant difference in the 10-year OS rate (Stage I, 94%

vs. 90%, respectively; Stage II, 82% vs. 81%, respectively) (Figs. 1, 2). Several large international studies, including a report from the World Health Organization, attempted to answer the same question approximately 10 years ago using multivariate regression analyses.^{5,17-21} Data from those studies suggested that pregnant women who had their Stage I and II melanoma classified according to the previous AJCC staging system (primary site only with any tumor thickness) did not show any survival or DFS difference if they were treated promptly and appropriately. However, the majority of those studies failed to mention the length of follow-up. Two similar reports published by Duke University showed a significantly shorter DFS in the pregnant group without any detrimental effect on OS.^{22,23} The Duke University authors reported that 51% of patients in their pregnant group and 68% of patients in their control group remained disease free at 10 years. However, although pregnancy showed no significant effect on the DFS in that series, it did reveal a possibly longer DFS in the nonpregnant group.

An interesting phenomenon is the slightly increased median thickness of primary melanomas in the pregnant group compared with the nonpregnant group in the current study and in other studies.^{5,19,23} In the current series, we noted thicker primary tumors (median, 2.0 mm vs. 1.7 mm; $P = 0.119$) in the pregnant group, but we failed to show a significant effect on DFS or OS. Overall, it is believed generally that nevi enlarge or that new nevi arise during pregnancy. The hypothesis is that salient signs of early melanoma, growth and change, initially may be misinterpreted as physiologic, pregnancy-related changes leading to a change in diagnosis.²⁴ However, Pennoyer et al. recently reported that only a small proportion of nevi (6%) showed a change during pregnancy.²⁵ Further research will be necessary to confirm these results in a larger study population. If this is confirmed, then it would mean that advice to pregnant women should be the same as advice to nonpregnant women: Timely biopsy of all suspicious nevi should be performed and should not be deferred until after delivery.²⁴

Our study also focused on the effect of Breslow thickness, ulceration, vascular invasion, histologic subtype, and tumor location on DFS and OS in the pregnant and nonpregnant groups. There was no difference for either group in the presence of ulceration, vascular invasion, or primary tumor location. Primary tumor locations were comparable with the literature, which indicates that extremity melanomas predominate in this group of patients.²⁶ Logistic regression analysis of mortality and DFS showed that increasing Breslow thickness (OS, $P < 0.005$; DFS, $P < 0.006$) and the presence of ulceration (OS, $P < 0.036$; DFS, P

< 0.010) were identified as independent prognostic factors. This was reported previously in the literature and was the foundation for the 2002 AJCC TNM classification system.¹² Furthermore, logistic regression analysis of DFS also showed that extremity melanoma ($P < 0.004$) and nodular type melanoma ($P < 0.002$) are unfavorable prognostic factors for patients with Stage I–II melanoma. Although we could not confirm vascular invasion as a prognostic factor, we did establish a trend toward a poorer prognosis ($P = 0.076$).

Based on the results of the current study and a critical review of the literature, pregnancy at the time of diagnosis of clinically localized invasive melanoma does not appear to be a risk factor for disease progression. Pregnant patients may present with thicker melanomas, and pregnancy may decrease disease free survival, but neither melanoma thickness nor disease free survival differed significantly between pregnant and nonpregnant patients in this study. In patients with melanoma who are pregnant at the time of diagnosis, survival still is dependent on tumor thickness and the absence or presence of ulceration. Therefore, patients should be counseled regarding these factors and not regarding the pregnancy.

REFERENCES

- Smith RS, Randall P. Melanoma during pregnancy. *Obstet Gynecol.* 1969;34:825–829.
- Pack GT, Scharnagel IM. The prognosis for malignant melanoma in the pregnant woman. *Cancer.* 1951;4:324–334.
- Baergen RN, Johnson D, Moore T, Benirschke K. Maternal melanoma metastatic to the placenta: a case report and review of the literature. *Arch Pathol Lab Med.* 1997;121:508–511.
- Johnston SR, Broadley K, Henson G, Fisher C, Henk M, Gore ME. Management of metastatic melanoma during pregnancy. *BMJ.* 1998;316:848–849.
- MacKie RM, Bufalino R, Morabito A, Sutherland C, Cascinelli N. Lack of effect of pregnancy on outcome of melanoma. For the World Health Organisation Melanoma Programme. *Lancet.* 1991;337:653–655.
- Lecavalier MA, From L, Gaid N. Absence of estrogen receptors in dysplastic nevi and malignant melanoma. *J Am Acad Dermatol.* 1990;23:242–246.
- Flowers JL, Seigler HF, McCarty KS, Konrath J, McCarty KS Jr. Absence of estrogen receptor in human melanoma as evaluated by monoclonal antiestrogen receptor antibody. *Arch Dermatol.* 1987;123:764–765.
- Neifeld JP, Lippman ME. Steroid hormone receptors and melanoma. *J Invest Dermatol.* 1980;379–381.
- Gefeller O, Hassan K, Willie L. Cutaneous malignant melanoma in women and the role of oral contraceptives. *Br J Dermatol.* 1998;138:122–124.
- Grin CM, Driscoll MS, Grant-Kels JM. The relationship of pregnancy, hormones, and melanoma. *Semin Cutaneous Med Surg.* 1998;17:167–171.
- Pfahlerberg A. Systematic review of case control studies: oral contraceptives show no effect on melanoma risk. *Public Health Rev.* 1997;25:309–315.
- Balch CM, Buzaid AC, Soong SJ, et al. Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma. *J Clin Oncol.* 2001;19:3635–3648.
- Kroon BB, Bergman W, Coebergh JW, Ruiter DJ. Consensus on the management of malignant melanoma of the skin in The Netherlands. Dutch Melanoma Working Party. *Melanoma Res.* 1999;9:207–212.
- Winton GB, Lewis CW. Dermatoses of pregnancy. *J Am Acad Dermatol.* 1980;6:977–998.
- Miller JG, Gee J, Price A. Investigation of oestrogen receptors, sex steroids and soluble adhesion molecules in the progression of malignant melanoma. *Melanoma Res.* 1997;7:197–208.
- Venn A, Watson L, Lumley J, Giles G, King C, Healy D. Breast and ovarian cancer incidence after infertility and in vitro fertilisation. *Lancet.* 1995;346:995–1000.
- McManamny DS, Moss AL, Pocock PV, Briggs JC. Melanoma and pregnancy: a long-term follow-up. *Br J Obstet Gynaecol.* 1989;96:1419–1423.
- Slingluff CL Jr., Seigler HF. Malignant melanoma and pregnancy. *Ann Plast Surg.* 1992;28:95–99.
- Travers RL, Sober AJ, Berwick M, Mihm MC Jr., Barnhill RL, Duncan LM. Increased thickness of pregnancy-associated melanoma. *Br J Dermatol.* 1995;132:876–883.
- Wong DJ, Strassner HT. Melanoma in pregnancy. *Clin Obstet Gynecol.* 1990;33:782–791.
- Wong JH, Sterns EE, Kopald KH, Nizze JA, Morton DL. Prognostic significance of pregnancy in Stage I melanoma. *Arch Surg.* 1989;124:1227–1230.
- Reintgen DS, McCarty KS Jr., Vollmer R, Cox E, Seigler HF. Malignant melanoma and pregnancy. *Cancer.* 1985;55:1340–1344.
- Slingluff CL Jr., Reintgen DS, Vollmer RT, Seigler HF. Malignant melanoma arising during pregnancy. A study of 100 patients. *Ann Surg.* 1990;211:552–557.
- MacKie RM. Pregnancy and exogenous hormones in patients with cutaneous malignant melanoma. *Curr Opin Oncol.* 1999;11:129–131.
- Pennoyer JW, Grin CM, Driscoll, et al. Changes in size of melanocytic nevi during pregnancy. *J Am Acad Dermatol.* 1997;36:378–382.
- Chang AE, Karnell LH, Menck HR. The National Cancer Data Base report on cutaneous and noncutaneous melanoma: a summary of 84,836 cases from the past decade. The American College of Surgeons Commission on Cancer and the American Cancer Society. *Cancer.* 1998;83:1664–1678.