ACTA ONCOLOGICA

Vol. 32
No. 4

1993

MELANOMA AND PREGNANCY

A review

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In the last half-century the incidence of cutaneous malignant melanoma has increased all over the world according to available reports. No association between risk of melanoma and age at menarche, first birth, menopause or duration of reproductive period has been proven so far. Studies on the effect of parity on relative risk and survival have given divergent results with multiparous women possibly having a better prognosis than nullipara. Women with melanoma diagnosed during pregnancy tend to have thicker tumours, shorter disease-free interval and, maybe, lower 10-year survival rate than non-pregnant matched controls. There is no conclusive evidence that therapeutic abortion improves the cure rate. Multivariate analysis has failed to unveil impaired prognosis in women who become pregnant subsequent to diagnosis.

The precise etiology of cutaneous malignant melanoma is unknown, though there is little doubt that melanoma is the result of multiple interactions of various initiating and promoting factors. A dominant cause appears to be the relation between genetically determined susceptibility of the host and solar ultraviolet radiation. From present knowledge, particularly derived from epidemiologic studies, it appears that the risk to develop and die from melanoma is modulated by a considerable number of individual factors (Table 1).

In the last half-century, the age-standardized incidence rate of melanoma in Denmark has increased 6-fold, and a steep increase in risk has been seen for successively younger birth cohorts (1). The mortality rate has increased in the same period, but not as much as the incidence rate, which probably reflects earlier diagnosis and treatment (2–4). In 1989 a total of 388 Danish women developed melanoma and 40% of these women were of fertile age; the disease constituted 3% of all female cancer cases (5) and caused 1.6% of all female cancer deaths (6). When melanoma occurs in women of fertile age there is a need for advice to the patient. Does subsequent pregnancy increase the risk of recurrence? When melanoma is diagnosed during pregnancy several questions need to be answered. What is the effect of pregnancy on the outcome of the maternal disease? How does the melanoma affect the fetus, and how does the therapy affect mother and fetus?

The possible influence of reproductive or hormonal factors on the pathogenesis and biologic behaviour of melanoma have intrigued scientists and clinicians on the basis of clinical or anecdotic reports suggesting a detrimental influence of concurrent pregnancy. Likewise, pregnancy subsequent to the diagnosis of melanoma has been suspected to exert an ominous influence.

Although the association of melanoma with pregnancy is uncommon, this complication appears with an estimated incidence from 0.14 to 2.8 cases per 1 000 births (7) and has been reported to constitute 8% of all malignancy diagnosed during pregnancy (8). Melanoma accounted for 24.5% of all cases of malignancies in pregnant Swedish women in the period 1973–1984 (9). The distribution of malignant disease in pregnant women deviated from the distribution in fertile women generally, with an excess rate of melanoma and breast cancer in the pregnant group (9).

In Denmark the treatment of pregnant patients with melanoma has as a rule stuck to the following unwritten

Received 29 June 1992.
Accepted 20 February 1993.
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Table 1

Summary of risk factors for the development of cutaneous melanoma

Sun sensitivity
Ethnic fairness of the Caucasian race, freckling
Severe sunburns
Melanocytic nevi
Dysplastic nevus, congenital giant nevus, multiple nevi
Prior malignant melanoma
Familial melanoma
Concomitant disease—Immunodeficiency, immunosuppression
Xeroderma pigmentosum

guidelines: No extraordinary measures are taken in cases of stage I melanoma with tumour thickness <1 mm. If the tumour is >1 mm thick, recommendations regarding therapeutic abortion have been individualized on the basis of informed consent. A majority has favoured termination of pregnancy when dealing with stage II and III melanoma at the time of diagnosis. Advice to childbearing women after treatment of melanoma has been characterized by a certain reluctant attitude calling for abstinence from pregnancy for some years.

Sex differences and hormonal factors

Global melanoma incidence does not differ substantially between the sexes. In northern Europe a female predominance can be seen, with up to two female cases for each male case reported (3). In Denmark the age-standardized incidence rate was 10.6 for women and 8.5 for men in 1989 (5).

In women, however, the disease is reported to have a more favourable course. Sex was found to be an independent prognostic factor in a study based on almost 10% of the United States population (10) as well as in a study of all patients newly diagnosed in Sweden during the period 1960–1982 (11). This is thought to be a consequence of women presenting at an earlier clinical stage of disease with primary lesions confined to prognostically more favourable anatomic sites (12, 13). Compared to men, female patients have been found to have more favourable lesions with regard to primary lesion site, level of invasion, tumour thickness, and stage at time of diagnosis (14). The tumours seem to metastasize more slowly in women than in men (12), and survival after first evidence of distant metastases has been found to be significantly longer in women (15). Even when women have the same stage of disease, their survival is generally longer (7, 13, 16, 3). In elderly, however, there are almost equal survival rates in women and men (12, 15, 17).

These findings suggest that the hormonal background does not affect acquisition of melanoma, but may influence its anatomic localization and/or its subsequent spread. One report states a generally superior prognosis for female malignant disease in cases of melanoma, sarcoma, liver and colorectal cancer (18).

While generally melanoma is not regarded as a hormone-dependent neoplasm, circumstantial evidence suggests that certain endocrine factors may influence its biologic behaviour. Although some melanomas apparently present sex hormone-binding proteins, specific oestrogen, progesterone or androgen receptors at the surface of melanoma cells have not been demonstrated (3, 19–21).

Melanoma is rare in childhood. Above the age of 15, the incidence rate is almost 90-fold greater than in the younger age group (3). This could be related to the changing hormonal physiology which in this period of life normally leads to an increased degree of skin pigmentation (17) or could simply reflect absence of a carcinogenic stimulus and/or a long latent period.

No association between risk of melanoma and age at menarche, age at menopause or duration of reproductive period has been found so far (12, 22–26), with one exception where an unexplained association between melanoma and ovulatory life of greater length than 20 years are observed (27). A significantly better prognosis has been demonstrated for premenopausal women than for postmenopausal ones matched by age (12, 28).

Pregnancy before melanoma

Six case–control studies (21, 22, 24–27) have assessed the influence of parity on the risk of melanoma (Table 2). Two of these (21, 24) suggested that women with three or more children had lower melanoma risk than nulliparous women. In one of the studies (21), however, the association diminished substantially after adjustment for other risk correlates. A case–control study on uveal melanoma observed a decreased risk for women who had ever been pregnant and the protective effects increased with more live births after adjustment for confounding factors (29).

In 1989 (30), 5 398 American women responded to a detailed questionnaire accounting for medical and reproductive history. In this study it was found that diagnosis of melanoma was significantly associated with fewer pregnancies.

Also concerning the effect of parity on survival divergent findings have been reported. Parous women with three or more pregnancies prior to diagnosis have been claimed to have significantly higher 5-year survival rate than nulliparous women (12, 28, 31). Other reviews (16, 32–34), however, have found no significant association (Table 3).

Holly et al. (25) reported a non-significant positive association between the risk of melanoma and age at first birth after age 30, in contrast to other studies (21, 22, 24, 26, 27) in which no association has been reported.

Table 2

Influence of parity on relative risk of cutaneous malignant melanoma

Author	Ref. No.	Relative risk (All histologic types of melanomas)			
		Multiparous (5+)/nulliparous		(95% CI)	p-value
Holly et al. 1983	(25)	1.0	Age standardized	—	0.44
Holman et al. 1984	(26)	0.7	Odds ratio	(0.33–1.65)	0.76
Gallagher et al. 1985	(24)	0.3	RR-crude	—	0.02[a]
		0.3	RR-adjusted		
Green et al. 1985	(27)	2.3	—	(0.5–10.6)	0.29
Østerlind et al. 1988	(22)	0.9	RR-crude	(0.4–1.9)	0.36
		0.9	RR-adjusted	(0.5–1.7)	
Zanetti et al. 1990	(21)	0.3	Age-adjusted odds ratio	(0.16–0.70)	0.02
		0.6[b]	MLR odds ratio	(0.29–1.31)	0.22

[a] Test for trend over the categories 0/1-2/3-4/5+
[b] Multiple logistic regresion (MLR) equation including terms for age, education and sun exposure
Adopted from Francheschi et al. (1990) (23)

Table 3

Influence of parity prior to diagnosis of cutaneous malignant melanoma on 5-year survival

Author	Ref. No.	Parous		Nulliparous		p-value
		5-year survival rate %	No.	5-year survival rate %	No.	
Shiu et al. 1976	(16)[a]	70	170	76.6	47	—
Hersey et al. 1977	(31)[a]	77	330	68	113	$(0.025 < p < 0.05)$
Shaw et al. 1978	(12)[a]	81.6	388	73.8	254	(< 0.025)
Elwood et al. 1978	(32)[b]	61	254	63	51	(0.47)
Bork et al. 1981	(28)[c]	81.4	92	75.6	115	(0.07)[d]
Lederman et al. 1985	(33)[e]	83	119	87	92	NS
Trapeznikov et al. 1987	(34)	—	1260	—	119	NS

[a] All stages and ages
[b] Including ocular melanomas
[c] Stage I, age $\leqslant 50$
[d] Test for trend over the categories 0/1-2/3-4/5+
[e] Stage I, 9-year survival

Melanoma during pregnancy

Several women with melanoma diagnosed during pregnancy, described that the preexisting nevus presented itself during a previous pregnancy with irritation and/or growth. More than 10% of all pregnant women experienced signs of activation of nevi during the first trimester, which typically disappear after delivery. Histologically, however, this type of nevi is not different from the nevi of nonpregnant women (3). There is a suggestive, but not yet proven, relation between activation of nevi during pregnancy and development of malignant melanoma.

The reports on survival of patients with melanoma occurring during pregnancy (Table 4) show no significant difference in 5-year survival rates of pregnant patients compared to nonpregnant patients after adjustment for prognostic factors, specifically histopathological parameters (13, 16, 17, 19, 34–38). Before the middle of the 1980s complete reports on histological variables were not generally available and reports of clinical series without matched controls were not uncommon, making results difficult to compare. As shown by Houghton et al. (17) considerable confounding arose when working with a nonmatched control group as survival rate in controls changed from 83% before matching to 58% after matching for age, primary site and stage.

Trapeznikov et al. (34), Slingluff et al. (19) and MacKie et al. (35) reported more than 10 years' follow-up of pregnant melanoma patients and presented divergent 10-

Table 4

Survival rates of pregnant and non-pregnant women with cutaneous malignant melanoma stage I

Author	Ref. No.	Number		5-year survival (%)		10-year survival (%)	
		Pregnant	Non-pregnant	Pregnant	Non-pregnant	Pregnant	Non-pregnant
George et al. 1960	(38)	77	141[a]	78	61	—	—
Shiu et al. 1976	(16)	70	181[b]	74	86	—	—
Houghton et al. 1981	(17)*	12	175[b] 24[c]	55	83 ($p < 0.05$) 58 NS	—	—
Sutherland et al. 1983	(36)*	18	12[b]	31	70	—	—
Reitgen et al. 1985	(13)	58	585[d]	75	85	—	
Trapeznikov et al. 1987	(34)	102	599[e]	44.4	53.6	26.0	43.6 ($p = 0.05$)
Wong et al. 1989	(37)	66	619[b] 66[d]	86	87 NS 92 NS	—	—
Slingluff et al. 1990	(19)	100	86[d]	82	88	66	72
MacKie et al. 1991	(35)	92	296[a]	($p = 0.017$) ↓ ($p = 0.1$)[f]		—	—

* Histopathological micro staging was not available
[a] Age matched
[b] Non-matched
[c] Matched at age, primary site and stage
[d] Matched at age, primary site, stage and histopathologic variables
[e] Matched at age, primary site and histopathologic variables
[f] Log rank adjustment for tumour thickness

year survival rates. Trapeznikov et al. found no significant difference between 5-year survival rates of pregnant and non-pregnant melanoma patients but after a follow-up period of 10 years, the survival rate became significantly lower in the pregnant group. This finding suggests that a longer follow-up period is mandatory in order to reveal a possible negative effect of concurrent pregnancy on survival. Yet neither Slingluff et al. (19) nor MacKie et al. (35) could demonstrate any significant difference in survival after 10 and 20 years follow-up respectively. Of possible significance might be the fact that in the study by Slingluff et al. (19), unlike European practice, specific active immunotherapy was administrated to 83% of the patients and that 16% of them underwent elective lymph node dissection. In the WHO multicenter analysis (35) nulliparous women were not included in the control group, which consisted of parous women treated before, after, and between pregnancies.

Reitgen et al. (13), Slingluff et al. (19) and MacKie et al. (35) examined disease-free interval and survival of pregnant women with melanoma stage I. When disease-free intervals were plotted, both Reitgen et al. (13) and Slingluff et al. (19) found a significant difference between women who had melanoma appearing during pregnancy, when compared to their controls after 5 and 10 years of follow-up. Multivariate regression analysis demonstrated pregnancy at the time of diagnosis to be significantly positively associated with the development of metastatic disease, allowance being made for the influence of predictive factors as level of invasion, tumour thickness, ulceration, and anatomic site. MacKie et al. (35) found shorter survival and shorter disease-free interval for pregnant women, but after adjustment for tumour thickness, there was no significant difference between the pregnant and the non-pregnant groups.

In Table 5, the studies which also include site and stage are summarized. Slingluff et al. (19) found greater tumour thickness in pregnant patients and Reitgen et al. (13) reported generally more unfavourable histopathological features in the pregnant group. MacKie et al. (35) found that women who had melanomas diagnosed during pregnancy had significantly thicker primary tumours, while other possible confounding factors (site, age, growth pattern) did not differ between the pregnant and the non-pregnant groups. According to Table 5 there does not seem to be any obvious differences in primary tumour location between pregnant and non-pregnant melanoma patients. As to stage at time of diagnosis three reports before 1980

Table 5

Location and stage of cutaneous malignant melanoma in pregnant (P) and non-pregnant (N-P) women

Author	Ref. No.	Number		Location of primary melanoma (%)				Stage at diagnosis (%)			
		P	N-P	Trunk		Extremities		P		N-P	
				P	N-P	P	N-P	Local	Advanced	Local	Advanced
George et al. 1960	(38)	77	141[a]	—	—	—	—	55	45	70	30
Shiu et al. 1976	(16)	70	181[b]	37	25	56	66	54	46	70	30
Houghton et al. 1981	(17)*	12	175[b]/24[c]	42	32	50	58	67	33	88	12
Sutherland et al. 1983	(36)*	18	12[b]	22	25	56	67	—	—	—	—
Reitgen et al. 1985	(13)	50	585[a]	36	39	56	53			All stage I	
Trapeznikov et al. 1987	(34)	102	599[e]	—	—	—	—	80	20	80	18
Wong et al. 1989	(37)	66	619[b]/66[d]	41	32	48	57			All stage I	
Slingluff et al. 1990	(19)	100	86[d]	40	51	52	33	88	12	92	8
MacKie et al. 1991	(35)	92	296[a]	32	27	55	66			All stage I	

P = pregnant; N-P = non-pregnant
* Histopathological micro staging was not available
[a] Age mached
[b] No matching
[c] Matched at age, primary site and stage
[d] Matched at age, site, stage and histopathologic variables
[e] Logrank adjustment for tumour thickness

(16, 17, 38) give the impression that pregnant melanoma patients present at a more advanced stage, while two studies (34 and 19) published in the late 1980s indicate no such difference.

Since the report of Trapeznikov et al. (34) deals with several aspects of the impact of pregnancy on prognosis and clinical course of melanoma, this deserves a special comment. In this study 2 018 Russian women with melanoma were followed for more than 15 years; 102 women with melanoma occurring during pregnancy were compared to 599 non-pregnant melanoma patients after matching by age, tumour site and tumour thickness. A special group of 42 women who developed melanoma during lactation was also selected. The 3-, 5- and 10-year survival rates of pregnant women with melanoma stage I were 65.2%, 44.4% and 26.0% respectively, in comparison to 70.9%, 53.6% and 43.0% in the non-pregnant group. The differences are numerically suggestive, but statistically significant only for the 10-year survival rates. For advanced disease no survival differences were noted between pregnant and non-pregnant women. The survival rates of pregnant women with stage I melanoma were also analyzed in relation to whether they had a full-term pregnancy or an abortion before the 20th week. A significantly higher survival rate was observed in women who gave birth compared to those who underwent abortion; the 5-year survival rates were 66.5% and 33.5% respectively. In case of stage II melanoma, the data indicated that abortion before the 20th week might result in a better prognosis. Pregnant women with stage I melanoma diagnosed during the second half of pregnancy had significantly lower 5- and 10-year survival rates compared to non-pregnant counterparts. The 5- and 10-years rates were 27.0% and 18.0% compared to 53.6% and 43.0% respectively. Independent of stage, the survival rates were non-significantly lower when melanoma developed after the 20th week, compared to debut before the 20th week or during lactation.

In summary, it is an unsolved question why melanomas diagnosed during pregnancy are generally thicker and, probably as a consequence, carry a poorer prognosis. This tendency towards thicker tumours and maybe more advanced stage at presentation could be the result of an accelerating influence of pregnancy or be due to delay of diagnosis because of the increased pigmentation during pregnancy combined with the general physiological changes which could make the detection of a slight change in a molé more difficult.

Two out of three reports demonstrated significantly shorter disease-free intervals in patients with melanoma appearing during pregnancy and multivariate analysis has shown significant association between current pregnancy and risk of recurrence and metastasis. Intuitively, differences in disease-free interval should be reflected in survival differences. However, longer follow-up may be needed for the detection of a significant survival difference. As suggested by Slingluff et al. (19), another explanation might be in fact that the pregnant patients develop local or nodal matastases instead of more lethal distant metastases.

Metastatic spread of maternal cancer to the placenta or fetus is extremely rare. This phenomenon has been described in cases of lymphoma, leukaemia, breast, lung and stomach cancer, and malignant melanoma. Among the barely 100 cases reported from the literature malignant melanoma was the most common (30%) type of cancer (7, 8). In half the cases both placenta and the infant were involved. Spontaneous tumour regression has been described in infants born with transplacental metastases (7).

Pregnancy after melanoma

Recommendations given to young female melanoma patients have usually encouraged a delay of three years after diagnosis before pregnancy, since 80–90% of recurrences appear within this period (19). The main problems in this situation are the rise of reactivating maternal cancer, the remote possibility of transplacental transmission of metastatic disease to the infant (3), and the prospect of social complications for a bereaved child.

A retrospective study performed in 1985 dealt with 43 women (stage I) who subsequently became pregnant within 5 years from diagnosis (13). Since the standard recommendation was to advocate a delay of pregnancy with at least two years from diagnosis of stage I melanoma, 337 matched controls were selected whose course was not confounded by pregnancy nor recurrence within two years from diagnosis. The controls were matched with regard to age, anatomic site of primary lesion, melanoma stage, and pathologic factors (level of invasion, tumour thickness, ulceration, growth pattern). The two groups showed no statistically significant differences in 10-year disease-free interval or 10-year survival. This was confirmed by a multivariate regression analysis. These data suggest that pregnancy 2–5 years subsequent to diagnosis of primary melanoma has no pronounced effect on recurrence rate or survival.

The same year a follow-up study (39) was published concerning twenty-three women who conceived after melanoma therapy out of a total of 2 850 treated. To avoid a false conclusion due to the small number of patients, the data were presented diagrammatically. It was concluded that no exacerbation was seen in most of the female melanoma patients, who became pregnant subsequent to treatment.

Discussion

It is conceivable that the hormonal milieu of the premenopausal and non-parous period might exert some inhibitory influence on melanoma. With alteration of this milieu at the onset of menopause or, temporarily, as the result of pregnancy, this inhibitory influence might disappear. Such a theory could explain the sometimes observed spontaneous regression of melanoma after childbirth.

The well-known changes in pigmentation associated with pregnancy could delay diagnosis of early melanoma because of the temporarily darkening of pre-existing pigmented benign nevi. The demonstration of increased melanocyte-stimulating substances in pregnant women has increased the suspicion of an adverse influence, even though a direct association between melanocyte-stimulating hormone and melanoma has not been found (16). The same applies for a possible influence of oestrogen and progesterone and several attempts have failed to provide evidence of an effect on melanoma of these hormones (13, 18, 22, 24, 29, 30, 40, 41). There is at present no evidence suggesting a causal link between oral contraception and melanoma (3, 21, 22, 24, 29, 30, 42).

Another mechanism might be a possible deleterious influence of androgenic hormones on melanoma. This is suggested by the poorer prognosis of male patients, and the observation that large quantities of androgenic hormones are secreted during pregnancy. In vitro studies have favoured this hypothesis but cannot be extrapolated to the management of human melanoma (16). In casuistic reports orchidectomy have been reported with diverging results in cases of advanced melanoma (40, 43).

There is no conclusive evidence that termination of pregnancy, oophorectomy, adrenalectomy, or hypophysectomy can offer any benefit to the pregnant woman with a malignant melanoma (16, 34). Treatment of melanoma patients with oestrogens, anti-oestrogens, corticosteroids or androgens have, up to the present, been unsuccessful (3, 8, 13, 40).

The rising concentration of circulating growth hormone during pregnancy might possibly activate melanoma growth (35). The concentration of prolactin rises likewise during pregnancy, and prolactin has been suspected of possibly stimulating malignant cell transformation (26).

Human chorion gonadotropin (HCG) immunoactivity has been detected in sera from patients with several types of cancer, among these melanoma and carcinoma of the breast. In one patient HCG concentration in serum declined progressively with therapeutic response. Using radioimmunoassay technique an immunologic resemblance in tumour-secreted-HCG and HCG from sera of pregnant women have been demonstrated (44). Epidemiological as

well as experimental data show pregnancy to be a protective factor relative to the development of breast cancer. However, whether HCG has any relation to the development or behaviour of malignant melanoma is not known at present.

An immunological causal hypothesis has been suggested to explain why women with melanoma have a better prognosis than men, and previously pregnant women a better prognosis than nulligravida. Human melanoma is one of few malignant neoplasms capable of eliciting specific immune responses, probably because of high antigenicity (3). Some melanoma antigens resemble the antigens expressed on fetal tissue, and a maternal immunisation against fetal antigens during pregnancy may provide protection against the neoplasm. Exposure to fetal antigens during pregnancy could thus protect against the dissemination of cancer cells. Such a response to tumour-associated antigens might be effective in preventing spread of tumours rather than preventing their occurrence (31). Antibodies to antigens from various melanoma cell lines have been detected only in multiparous women, but these women with melanoma had no better prognosis than women with melanoma who had never been pregnant (3). Antibodies directed against a cultured melanoma cell line known to express an oncofetal antigen have been measured in sera obtained from patients with stage II melanomas. A positive correlation with disease-free interval/survival was detected among patients with high levels of IgM antibody (46). A study of the reactivity of blood leucocytes from melanoma patients, pregnant and non-pregnant women towards materials from fetal and melanomatous tissues has been carried out. It was found that only leucocytes from previously pregnant melanoma patients reacted, but they reacted both to melanoma- and fetal extracts, suggesting a cross-reactivity (47).

Another possible mechanism might be that during pregnancy fetal suppressor cells are present which affect maternal adult lymphocytes and alter the mother's immunological reactivity, preventing rejection of the fetal allograft. Changes in cellular and humoral immunity occur during pregnancy and are considered to be responsible for the improvement of autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis during pregnancy (41). A reduction in the normal proportion of circulating T-lymphocytes during early pregnancy and reduced reactivity of lymphocytes as well as the loss of germinal centres from lymph nodes point to a depression of cellular immunity during pregnancy (48).

ACKNOWLEDGEMENTS

We are grateful to Mrs. J. F. Larsen for excellent technical assistance.

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