DISCLOSURE OF RELATIONSHIPS WITH INDUSTRY

Emily Y. Chu, MD PhD

F023: Practical Considerations for Patients with Melanoma or Dysplastic Nevi

DISCLOSURES

I do not have any relevant relationships with industry.
Pregnant woman dies after abdominal pain turns out to be skin cancer

A frightening case of melanoma is putting the spotlight on skin cancer and pregnancy.

A young mom who discovered that melanoma had spread throughout her body while carrying her second child died three weeks after her diagnosis.

Danielle Janofsky of Williamstown, New Jersey, was six months pregnant when she went to the hospital complaining of abdominal pains on Feb. 8. Doctors found melanoma that had spread to her liver, kidney, stomach and brain, according to a fundraising page set up for her family.

Her son was delivered via C-section about two weeks later, with Janofsky apparently waiting as long as she could for the birth so the baby could develop.
If melanoma is diagnosed before pregnancy, is the patient’s prognosis negatively impacted?
Effect of Pregnancy on Survival in Women With Cutaneous Malignant Melanoma
Marko B. Lens, Inger Rossahl, Anders Alfredson, Bahman Y. Farahmand, Ingrid Syversen, Bernt Boeck, and Julius A. Newton Bishop

ABSTRACT
Purpose
An adverse influence of pregnancy on the risk of death in women with cutaneous melanoma was suggested historically by anecdotal reports. Previous studies included small numbers of women observed for short periods.

Methods
Using data from the Swedish National and Regional Registries, we performed a retrospective cohort study of all Swedish women who were diagnosed with cutaneous melanoma during their reproductive period, from January 1, 1958, to December 31, 1999. The relationship between pregnancy status at the diagnosis of melanoma and overall survival was examined in multivariable proportional-hazards models.

Results
The cohort comprised 185 women (3.3%) diagnosed with melanoma during pregnancy and 5348 (96.7%) women of the same childbearing age diagnosed with melanoma while not pregnant. There was no statistically significant difference in overall survival between pregnant and nonpregnant groups (log-rank $\chi^2(1) = 0.84, P = .36$). Pregnancy status at the time of diagnosis of melanoma was not related to survival in a multivariable Cox model in the 2,101 women (hazard ratio for the pregnant group was 1.08; 95% CI, 0.60 to 1.93). In the multivariable analysis, pregnancy status after diagnosis of melanoma was not a significant predictor of survival (hazard ratio for death in women who had pregnancy subsequent to the diagnosis of melanoma was 0.55; 95% CI, 0.22 to 1.06).

Conclusion
The survival of pregnant women with melanoma is not worse than the survival of nonpregnant women with melanoma. Pregnancy subsequent to the diagnosis of primary melanoma was not associated with an increased risk of death.

Table 4. Multivariable Cox Regression Analysis for 2,101 Women With Melanoma (results from the secondary analysis)

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy subsequent to the diagnosis of primary melanoma*</td>
<td>0.58</td>
<td>0.32 to 1.05</td>
<td>.07</td>
</tr>
<tr>
<td>Breslow thickness (per additional category)</td>
<td>2.14</td>
<td>1.75 to 2.66</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Axial site v limb site of primary melanoma</td>
<td>2.56</td>
<td>1.81 to 3.63</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Clark’s level (&gt; 3 v ≤ 3)</td>
<td>1.40</td>
<td>0.92 to 2.15</td>
<td>.118</td>
</tr>
<tr>
<td>Age (per year increase)</td>
<td>1.01</td>
<td>0.99 to 1.04</td>
<td>.278</td>
</tr>
</tbody>
</table>

Abbreviation: HR, hazard ratio.

*Pregnant women at the time of diagnosis of melanoma versus nonpregnant women at the time of diagnosis of melanoma.
Lack of effect of pregnancy on outcome of melanoma

RISE M. MacKie, ROSARIO BULJALONO, A. MORAFIO, C. SUTHERLAND, N. CASCINELLI

For the World Health Organisation Melanoma Programme

To determine the effect of pregnancy on prognosis in melanoma we investigated 386 women treated for stage 1 primary cutaneous disease during their childbearing years. 85 women had been treated before any pregnancy, 92 during pregnancy, and 68 after they had completed all pregnancies. Women who had received treatment while pregnant had primary tumours of significantly greater thickness than did those in the other three groups (p = 0.002). Other possible confounding factors (site, age, parity) did not differ between the groups. Overall, tumour thickness was controlled for, survival rate of women in whom melanoma was diagnosed and treated while they were pregnant did not differ from that in the other three groups. Cox regression analysis showed no differences between the three groups of women who were not pregnant at diagnosis. Women with melanoma should be advised about pregnancy on the basis of thickness and site of tumour and evidence of vascular spread, and not hormonal status.

If melanoma is diagnosed before pregnancy, is the patient’s prognosis negatively impacted?

Based on studies to date: No
Do melanomas diagnosed during pregnancy have a worse prognosis than those in non-pregnant patients?

(Also, what is the definition of pregnancy-associated melanoma?)
Single institution study retrospective study of 462 patients

41 patients with pregnancy-associated melanoma

PAM patients found to have worse prognosis than non-PAM, with 9-fold increase in recurrence, 7-fold increase in metastasis, 5-fold increase in mortality
Melanoma during pregnancy: Level of evidence and principles of precaution

To the Editor: For many years, the outcome of melanoma during pregnancy has been subject to debate. This is an ever-increasing medical issue as melanoma ranks first among malignancies discovered during pregnancy and postpartum in many parts of the world. A major discussion point has been whether analysis of the association with mortality should be adjusted for tumor thickness, a major prognostic factor, because some large population cohorts observed that melanomas during pregnancy and the first year postpartum are significantly thicker. However, whether or not pregnancy-associated melanoma is an independent criterion for poor prognosis, it remains obvious that, because of the increased thickness of their tumor lymphangiogenesis among other hormonal theories.

In their study, Tellez et al add another piece to the available evidence suggesting that pregnancy significantly affects melanoma outcome. This is a single-institution study with a small number of cases (41 pregnancy-associated melanomas) and underestimates substantial limitations regarding design and analysis, as pointed out by Martires et al in their letter to the editor. We also contend that the persistent debate on statistical methodology and adjustment for different variables is important to conduct large population-level studies that allow comparing mortality of pregnancy-associated melanomas to melanomas in other women from the same age group without the need for adjustment and therefore reflecting the reality of the disease course. Indeed, including the study of that of Johansson et al. As the rate is considerably different, details regarding the 8 deaths of Tellez et al (20% of 41 patients) should be provided, and cannot be used to reach major conclusions.

In summary, increased awareness of the skin of pregnant women is appropriate as changes in pigmented lesions are likely not physiologic and may be significant. It is our opinion that the results of this single study, given the concerns highlighted, should not overturn the current body of literature that suggests there is no impact on prognosis for the patient with PAMM.

Kathryn J. Martire, MD, Miriam Kitz Pomeranz, MD, Jennifer A. Stein, MD, Ph.D., Jane M. Grant-Kels, MD, and Marcia S. Driscoll, MD, PharmD

Ronald O. Perelman Department of Dermatology, New York University School of Medicine; Department of Dermatology, University of Maryland School of Medicine, Baltimore; and Department of Dermatology, University of Connecticut, Farmington

Dr Stein was supported by the Irwin I. Lubove Fellowship in Dermatology.

Dr Pomeranz has served on the scientific advisory board for Procter and Gamble and as an author for UpToDate. Drs Martire, Driscoll, Stein, and Grant-Kels have no conflicts of interest to declare.

Fig 1. Meta-analysis of studies on melanoma survival during pregnancy. Pooled effect estimate of melanoma death in pregnancy-associated melanomas: increased risk of melanoma death in pregnant group. CI, Confidence interval.
Does pregnancy influence melanoma prognosis?
A meta-analysis

Athanassios Kyrgidis\textsuperscript{a}, Aimilios Lallas\textsuperscript{a}, Elvira Moscarella\textsuperscript{a}, Caterina Longo\textsuperscript{a}, Roberto Alfano\textsuperscript{b} and Giuseppe Argenziano\textsuperscript{c}

The literature has not been able to conclude whether pregnancy influences the prognosis of melanoma. The aim of this study was to explore the prognosis of melanoma diagnosed during pregnancy or post partum [pregnancy-associated melanoma (PAM)] compared with melanoma in female patients who were not pregnant. We systematically searched for studies of female patients with melanoma that reported outcomes related to survival. Fifteen eligible studies were found. Overall, PAM was associated with a 17% higher mortality compared with melanoma diagnosed in female patients who were not pregnant (hazard ratio = 1.17, 95% confidence interval: 1.03–1.33, \(P = 0.02\)). The heterogeneity associated with this test was moderate (\(P = 0.07; I^2 = 38\)). PAM was also associated with a 50% higher recurrence rate compared with melanoma not associated with pregnancy (hazard ratio = 1.50, 95% confidence interval: 1.19–1.90, \(P < 0.001\)). The heterogeneity associated with this test was low (\(P = 0.69; I^2 = 0\)). A limitation of this meta-analysis is the definition of PAM, which is not unanimous among the studies included. Our results indicate that PAM is associated with a worse prognosis than melanoma not related to pregnancy, both in terms of overall survival and disease-free survival. On the basis of our data, we anticipate that the survival difference we report here will be further amplified with the addition of future well-carried out studies. We suggest that detection of PAM requires particular awareness by healthcare professionals. *Melanoma Res* 27:289–299 Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

Melanoma Research 2017, 27:289–299

Keywords: disease-free survival, disease-specific survival, melanoma, meta-analysis, overall survival, pregnancy, systematic review

\textsuperscript{a}Skin Cancer Unit, Arcaspale Santa Maria Nuova IRCCS, Reggio Emilia, \textsuperscript{b}Department of Anesthesiology, Surgery and Emergency and \textsuperscript{c}Dermatology Unit, Second University of Naples, Naples, Italy

Correspondence to Athanassios Kyrgidis, MD, DDS, MSc, PhD, 18 Iasonidou Street, Panormio Theissaloniki 562 36, Greece
Tel: +30 6947 566727; fax: +30 2310 549701; e-mails: skyrgid@gmail.com, kyrgidis@auth.gr

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- Included 15 studies
- PAM was associated with a 17% higher mortality compared with melanoma diagnosed in non-PAM
- PAM was also associated with a 50% higher recurrence rate compared with non-PAM
- Limitation: PAM was not consistently defined across studies
Is Pregnancy-Associated Melanoma Associated with Adverse Outcomes?

Maris S Jones, MD, Jiheey Lee, PhD, Stacey L Stern, MS, Mark B Faries, MD, FACS

**BACKGROUND:** Melanoma is the most common malignancy encountered during pregnancy. Conflicting data have led to ongoing confusion regarding pregnancy-associated melanoma (PAM) in the media and among the public. The objective of this study was to better characterize both the clinical presentation of PAM and its prognostic implications.

**STUDY DESIGN:** Female patients of reproductive age, with stage 0 to IV cutaneous melanoma, were identified from our prospectively maintained database. Clinical and histopathologic factors were analyzed with appropriate statistical methods. Univariable and then multivariable analysis were used on matched data to compare disease-free survival (DFS), overall survival (OS), and melanoma-specific survival (MSS) for stage 0–III PAMs vs non-PAMs. Kaplan-Meier survival curves were then plotted for OS and MSS and compared using the log-rank test.

**RESULTS:** The clinical presentation of melanoma was similar for PAM and non-PAM patients. There was no significant difference in recurrence between the 2 groups; for PAM patients, 38.5% of patients had recurrence, as compared with 36.6% of non-PAM patients (p = 0.641). For PAM patients, median follow-up was 14.6 years (range 0 to 42.6 years) and 11.1 years (0 to 48.5 years) for the non-PAM patients. No significant differences in DFS, MSS, or OS were identified on univariable or multivariable analysis for PAM vs non-PAM patients in stage 0/I/II and stage III cutaneous melanoma, respectively (p = 0.880 DFS, p = 0.219 OS, and p = 0.670 MSS).

**CONCLUSIONS:** We observed no difference in DFS, OS, or MSS between the 2 groups. Pregnant patients should be screened for melanoma in a similar manner to nonpregnant patients and should be counseled that their survival is not adversely affected by their pregnancy. (J Am Coll Surg 2017;225:149–158. © 2017 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

- Single institution study of 2,025 female patients with Stage 0/I/II/III melanoma
- PAM was defined by a positive answer to the question “Did melanoma develop during pregnancy?”
- PAM in this cohort was 7.7% (156 patients)
- Found no difference in DFS, OS, or MSS between the 2 groups
Do melanomas diagnosed during pregnancy have a worse prognosis than those in non-pregnant patients?

Maybe, which is complicated by different definitions of pregnancy-associated melanoma.
Why does it seem like pregnancy associated melanoma is worse?

• Lag time in diagnosis in pregnant women and potentially in new mothers

• True and unrelated
  – Melanoma is increasingly common, including in patients of childbearing age

• Actual pregnancy-induced biological change
Melanomas considered to be potentially hormone-responsive, because:

- Pregnancy is associated with increase pigmentation (linea alba, melasma, ? nevi)
- There is evidence of receptors for estrogen and progesterone in some melanomas
- Increased growth rate was observed of some melanomas in mice after administration of estrogen

Driscoll and Grant-Kels, JAAD 2007
Pregnancy and immunosuppression

• Likely increased immune tolerance for foreign antigens during pregnancy (this may include cancer antigens)
  – Increased T-regulatory cells during pregnancy

• However, little evidence to suggest that melanoma formation or progression is aided by immunosuppression of pregnancy

Driscoll et al., JAAD 2016
How does pregnancy impact nevi?

• Do they change in size?
  – Contribution of stretching?
• Is there a change in pigmentation?
• Are there histopathologic changes?
Changes in the moles of pregnant women are frequently attributed to pregnancy, but recent studies suggest that pregnancy does not induce significant physiologic changes in nevi. It is common for nevi on the breasts and abdomen to grow with normal skin expansion, but studies that have examined melanocytic nevi on the backs or lower extremities have found no significant changes in size during pregnancy. Several studies have also investigated the belief that moles darken during pregnancy and have found insufficient evidence to support this idea. Dermoscopically, transient changes have been identified, but none are suggestive of melanoma. Results vary in terms of histologic changes seen in samples taken from pregnant women, but all authors agree that any histopathologic features consistent with melanoma should be viewed as melanoma and not attributed to pregnancy. Biopsy specimens should be obtained promptly from any changing mole that would raise concern for malignancy in a nonpregnant patient. Such procedures can be performed safely during pregnancy. (J Am Acad Dermatol 2016;75:661-6.)

Key words: biopsy; dermoscopy; histopathology; melanoma; mole; nevi; pregnancy.

Table I. Summary of studies of changes in nevus size during pregnancy

<table>
<thead>
<tr>
<th>Study</th>
<th>Findings during pregnancy</th>
<th>Locations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akturk et al\textsuperscript{13}</td>
<td>Diameter increases</td>
<td>Changes most significant on abdomen and breasts</td>
</tr>
<tr>
<td>Strumia et al\textsuperscript{14}</td>
<td>Some changes in size</td>
<td>Only appreciable on abdomen and breasts</td>
</tr>
<tr>
<td>Pennoyer et al\textsuperscript{15}</td>
<td>No significant change in size</td>
<td>Back</td>
</tr>
<tr>
<td>Zampino et al\textsuperscript{16}</td>
<td>No significant change in size</td>
<td>Back</td>
</tr>
<tr>
<td>Grin et al\textsuperscript{7}</td>
<td>No significant change in size</td>
<td>Back</td>
</tr>
</tbody>
</table>

Summary of studies in pregnant patients without dysplastic nevus syndrome
Dysplastic nevi may change during pregnancy

17 patients followed through 22 pregnancies
Rate of clinical change of nevi was 3.9x higher in pregnancy compared to non-pregnancy
Change also observed in patients that were biopsied during pregnancy
A Histopathologic Evaluation of Nevocellular Nevi in Pregnancy

Elliott Foucar, MD; Teresa J. Beatley, MD; Douglas W. Laube, MD; Jean Rosai, MD

128 patients examined in 3 groups: pregnant female, non-pregnant female, male

Mild degree of histopathology atypia associated with pregnancy, NOT felt to be clinically significant when making the diagnosis of melanoma in this setting. The present histopathologic study of nevocellular nevi obtained from pregnant women and from age-matched control women and men was designed to determine if diagnostically significant histopathologic atypia is a common occurrence in pregnancy.

SUBJECTS, MATERIALS, AND METHODS

Pregnant white patients visiting the obstetrics clinic at the University of Iowa Hospitals and Clinics, Iowa City, were approached between June and August 1982 with a brief explanation of this study; approximately 25% of patients agreed to participate. We followed the guidelines established by our hospital's Human Experimentation Committee, and each patient signed an informed consent. The patients' nevi were evaluated during a cutaneous examination performed in the obstetrics clinic by one of the authors (T.J.B.). Nevi with atypical clinical features were searched for, but when none were present, the patient

Fig 4.—Nevi from pregnant women and two control groups segregated by range of atypia. Most nevi from each group are in lowest atypia range. Nevi from control female population have smallest percent of cases in highest atypia range.

Foucar et al., JAMA Derm 1985
Melanocytic nevi in pregnancy: histologic features and Ki-67 proliferation index

Background: Changes in the clinical appearance of benign dermal nevi during pregnancy may be concerning for malignant transformation. Because the hormonal milieu of pregnancy has not proven to alter their basal behavior, histologic characterization is needed to prevent over-diagnosis and unnecessary treatment.

Methods: Dermal nevi excised from pregnant women (n = 16) were compared with nevi from locations- and aged-matched control patients (n = 15). Histologic features and Ki-67 proliferation index were evaluated.

Results: Nevi in pregnancy were more likely to have dermal mitotic figures (22.3% vs. 13.3%, p = 0.028) and higher mitotic rates (1.44 vs. 0.20 mitoses/mm², p = 0.002) than control nevi. A distinctive histologic entity, termed superficial microintraducts of pregnancy (SMOPs), was observed more frequently in the nevi of pregnancy (14.3% vs. 26.7%, p = 0.046), and showed slowed immunoreactivity for HMB45. There was a trend toward higher Ki-67 proliferation index in the nevi of pregnancy (3.0% vs. 1.0%, p = 0.073). Prominent melanocytic nevi were seen only in controls. There was no significant difference in pigment or inflammation changes between groups.

Conclusions: Dermal nevi removed during pregnancy share characteristic histologic features including increased dermal mitoses, superficial microintraducts of pregnancy (SMOPs), and trend toward increased Ki-67 proliferation index.


Chan et al., JCP 2010

Table 2. Summary of histologic and immunohistochemical findings

<table>
<thead>
<tr>
<th></th>
<th>Mitoses present (# cases, %)</th>
<th>Mitotic rate (per mm²)</th>
<th>SMOPs present (# cases, %)</th>
<th>Ki-67 (%)</th>
<th>Prominent MNC (# cases, %)</th>
<th>Pigment (0–3)</th>
<th>IRRITATION changes (# cases, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant (n = 15)</td>
<td>10 (62.5)</td>
<td>1.44 (±0.35)</td>
<td>13 (81.3)</td>
<td>3.6 (±3.2)</td>
<td>0 (0)</td>
<td>1.4 (±0.9)</td>
<td>12 (75.0)</td>
</tr>
<tr>
<td>Control (n = 15)</td>
<td>2 (13.3)</td>
<td>0.20 (±0.06)</td>
<td>4 (26.7)</td>
<td>1.0 (±1.7)</td>
<td>5 (33.3)</td>
<td>1.1 (±0.8)</td>
<td>10 (66.7)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.028</td>
<td>0.0027</td>
<td>0.046</td>
<td>0.073</td>
<td>0.021</td>
<td>0.34</td>
<td>0.78</td>
</tr>
</tbody>
</table>

SMOPs, superficial microintraducts of pregnancy; MNC, multinucleated cells; p-value in boldface indicates statistically significant.
Sex steroids regulate skin pigmentation through nonclassical membrane-bound receptors

Christopher A Natale¹, Elizabeth K Duperret¹, Junqian Zhang¹, Rochelle Sadeghi¹, Ankit Dahal¹, Kevin Tyler O’Brien², Rose Cookson³, Jeffrey D Winkler³, Todd W Ridky⁴

¹Department of Dermatology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, United States; ²Department of Chemistry, University of Pennsylvania, Philadelphia, United States

Abstract The association between pregnancy and altered cutaneous pigmentation has been documented for over two millennia, suggesting that sex hormones play a role in regulating epidermal melanocyte (MC) homeostasis. Here we show that physiologic estrogen (17β-estradiol) and progesterone reciprocally regulate melanin synthesis. This is intriguing given that we also show that normal primary human MCs lack classical estrogen or progesterone receptors (ER or PR). Utilizing both genetic and pharmacologic approaches, we establish that sex steroid effects on human pigment synthesis are mediated by the membrane-bound, steroid hormone receptors G protein-coupled estrogen receptor (GPER), and progesterin and adipoG receptor 2 (PAGR7). Activity of these receptors was activated or inhibited by synthetic estrogen or progesterone analogs that do not bind to ER or PR. As safe and effective treatment options for skin pigmentation disorders are limited, these specific GPER and PAGR7 ligands may represent a novel class of therapeutics.

DOI: 10.7554/eLife.15184.001

Potential mechanism for hormone-induced pigmeny changes

Figure 4. Topical GPER agonists increase pigmentation in vivo. (A) Mouse ear skin treated for 3 weeks with vehicle only on the left ear, and 2% (w/v) G-1 on the right ear. (B) Melanin assay on whole ear tissue that was treated with either vehicle or 2% G-1 for 3 weeks. (C) Fontana-Masson (melanin) staining of tissue sections from ears treated with either vehicle or 2% G-1, quantification of staining on right. (D) Schematic model of estrogen and progesterone signaling in melanocytes. n=3 biologic replicates for each experiment. Error bars denote +/- s.d.; *p<0.05, scale bar = 20 µm.

DOI: 10.7554/eLife.15184.014

The following figure supplement is available for figure 4.
How does pregnancy impact nevi?

• Do they change in size? No
  – Contribution of stretching?

• Is there a change in pigmentation? In some cases

• Are there histopathologic changes? Yes, although not clinically significant
Is it okay for patients with a history of melanoma to try for a (or another) pregnancy?

• For stage I and IIA melanoma patients: Yes

• High risk melanoma (Stage IIB, IIC, III): Yes, but favor waiting 3-5 years
  – This allows for enough time for risk of recurrence to decrease (2-3 years), plus allows time for additional imaging surveillance outside of pregnancy
Is it okay for patients with a history of melanoma to use oral contraceptives?

- Yes, but prefer progesterone only pills if possible

- If not progesterone only, then the lowest dose estrogen possible in a combination oral contraceptive is recommended
What is appropriate dermatologic care for pregnant patients with history of melanoma?

• Continue pre-pregnancy schedule for clinical examinations
• A pigmented lesion showing significant change during pregnancy should be biopsied
• Biopsies can be safely (and painlessly) performed during pregnancy
• Use your clinical judgement
Penn Multidisciplinary Melanoma Program

Medical Dermatology
- Michael Ming
- Rose Elenitsas
- Brian Capell

Dermatopathology
- Rose Elenitsas
- David Elder
- George Xu

Medical Genetics
- Kate Nathanson

Medical Oncology
- Lynn Schuchter
- Ravi Amaravadi
- Tara Gangadhar

Surgical Oncology
- Giorgos Karakousis

Derm Surgery
- Chris Miller
- Joseph Sobanko
- Thuzar Shin
- Jeremy Etzkorn
Thank you!

emily.chu@uphs.upenn.edu