Melanoma & Nevi in Pregnancy
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RELEVANT RELATIONSHIPS
W/ INDUSTRY:
None

Driscoll, Martires, Bieber, Pomeranz, Grant-Kels, Stein. Melanoma & pregnancy. CME review Part II. JAAD – in press

The Message of Melanocytes During Pregnancy …
• 41 yo woman married to a prominent MD
• Pregnant after in vitro fertilization
• Complained to her husband, PCP, & Ob of a changing back “mole” for many mos
• She was told by all her physicians: changes were “physiologic” & “not to worry”
• No Dermatology referral or bx done

Physical exam:
– 8 mo preg woman
– Many melanocytic nevi & dysplastic melanocytic nevi on trunk & exts
– Mid upper back
1.5 cm irreg brown & white plaque

Pathology:
Melanoma 0.6 mm w/ regression
Lesion widely excised w/ 1 cm margins. No SLNB done bc of MM depth & pt's preg.
Delivered healthy baby girl 3 wks later
CAT scan of lung: positive for a nodule
–Wedge resected: metastatic melanoma
–All surgical margins were involved
6 months later → liver metastases → died w/in 1 yr

3 Melanoma & Melanocytic Nevi Myths in Pregnancy

• Myth 1: Do not worry about melanocytic nevi that change during pregnancy!
• Myth 2: Do not worry if melanocytic nevi that are bx’d during pregnancy demonstrate cytologic atypia!
• Myth 3: Preg has a neg impact on MM prognosis!
  –”If you have had a MM do not get pregnant”
  –”If you are pregnant & you get MM, the preg should be terminated”

Why Care?

• MM incidence higher for females than males during reproductive yrs
• WHY?

Jaime Regan Rea

• Spent her HS lunch hrs tanning in a nearby salon to be “tan & popular”
• Self proclaimed tanning bed addict
• Dx’d w/ MM at 20yo
• Died 3 wks before her 30th birthday

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**MM in Preg Women on the Rise**

- 2.8-8.5 cases of MM per / 100,000 preg women
- MM incidence in women doubles for every additional 10 yrs of life. Women delaying childbirth for careers
  - Women 20-30 yo = 5% of all women dx’d w/ MM
  - Women 30-39 yo = 11% & women 40-49 yo = 19%
- MM: at least 8% of all malignant dx’d during preg
  Pavlidis. Oncologist 2002;7:279
- Swedish study: MM was 24.5% of all malignant dx’d during preg
  Mathiasson, Berg. Lakartidningen 1989;86:2845
- Norwegian registry cohort study: MM most frequent malign dx’d during preg (160 of 516 or 31% of malign) Stensheim, et al. J Clin Oncol 2009;27:45

**Why Should I Especially Care about Melanoma in Women?**

- Peak incidence of MM in 4th & 5th decades → rising incidence of MM during preg
  - Working women delay pregnancy
- 35% of women w/ MM are child bearing age @ Dx
- Melanoma represents 8% of all malignancies diagnosed during pregnancy
- MM represents 58% of cancers metastatic to fetus &/or placenta!!!

**Basis for Myths: 1. Immunologic Inhib Effect During Pregnancy**

- Fetus expresses paternal alloAg → maternal immune system recognizes paternal fetal Ags as foreign
- Why doesn’t Mom mount immune response against these Ags?
- Adaptive immunity preserved
- Innate immunity down regulated
- B lymphocyte function & Ab production WNL
- T lymphocytes w/ impaired IL-2 & interferon gamma production. Th1 responses down regulated
- **T cell recognition of tumor Ag impacted?**

**Basis for Myths: 2. Physiologic preg changes?**

- Cut hyperpig in preg & w/ exogenous hormones
- 90% of preg women: hyperpigmentation (areolae, genital skin, linea nigra)
  2^o to increased MSH in pregnancy

**Basis for Myths: 3. Old Wrong Info**

- “Pigmented nevi may enlarge & become darker during pregnancy & nevi not previously noticed may become apparent.”
  – self reported by pt; none documented or bx’d
- “Histologically nevi may have larger melanocytes, an increase in melanization, & more fully developed dendritic processes. An atypical appearance of some nevus / melanocytic cells has been noted but the # of mitoses is not increased.”
  Ainsworth, et al. Human Malignant Melanoma 1979

**Basis for Myths: 4. Case Reports**

- Case reports & uncontrolled series (esp in 1950’s) of aggressive MM in pregnant pts → poor survival
  – 10 dx’d during preg → 5 died w/in 30 mos
  – 11 pts reported changes in nevi during preg & subsequently dx’d w/ MM in postpartum period → 3 w/ widespread mets, 2 died w/in 3 yrs
  – 10 dx’d w/ MM who shortly thereafter became preg → 7 w/ mets @ dx , all 7 died w/in 20 mos
Basis for Myths
– “…clearly demonstrated that pubescence & pregnancy are associated with a conversion of benign nevi to melanoma & apparently hasten the growth & dissemination of melanoma through hormonal stimulation…”

• Conclude: “The prognosis of pregnant women with melanomas is bad & few cures are obtained”


Basis for Myths
• “The young woman who has had a MM should be advised of the grave risk of pregnancy in that it may produce recrudescence of her tumor & appreciably shorten her life span.”

• “This risk …justify surgical sterilization in those women who are amenable to terminating their child bearing career.”


Basis for Myths: 5. Hx link between hormones & MM?
• Older studies reporting assoc between exogenous hormones & occurrence of MM
• Early case reports implied hormonal milieu of preg could cause MM to met
• Presence of receptors for estrogen & prog in some MMs w/ biochemical assays (neg w/ monoclonal Abs)
• Increased MM growth rate in mice after admin of estrogen
  Gordon, et al. 1948; Lopez, et al. 1978

6. Many of the older (& even newer) studies FLAWED …
• Melanoma & Pregnancy Studies (esp. prior to 1983):
  –Incomplete histology data (esp re: thickness)
  –No control gp (non-preg women w/ MM)
  –Confounding prognostic factors not considered: site, age, depth, ulceration, etc.
  –Small population sample or case studies
  –FU relatively short


Melanocytic Nevi & Pregnancy
• 389 preg pts examined & interviewed
• 10.5% reported change, most during 1st trimester
  –Increased pigmentation 25%, pruritus 25%, occ pain 20%, new lesions 10%, hair growth 7%, crust 2%
• 26 bx’d (20 w/ changes in pigment, 6 cosmetic) → 22 mel nevi; 3 tags; 1 simple lentigo
  –No significant histologic changes compared to non-pregnant age matched women (controls)


Melanocytic Nevi & Pregnancy
• 128 nevi randomly bx’d from 86 preg white pts
  –Control gp: non-preg 16-39 yo. (path file)
• 1/3 self reported change (enlargement or change in color) in nevi during preg: majority = tags, dermatofibrs; 1 tick
• SI higher mean atypia scores in preg nevi Vs controls
  –(Evaluated cohesion, pagetoid, mitoses, lentiginous prlf, cytologic atypia, nuclear prominence, maturation, demarcation of lat margins, pigment dispersion)
• Preg gp bx’d in summer; control all yr long. Role?
• “We would be reluctant to attribute prominent atypia in a melanocytic lesion to ‘pregnancy effect’. ”

Melanocytic Nevi & Pregnancy

- 16 Pred IDN in preg Vs age & site matched non preg IDN
- Sup micronodules of preg (SMOP)= rounded clusters of 3-20 large epithelioid melanocytes w/ prominent nucleoli, abundant pale eos cytopl & occ fine melanosomes

<table>
<thead>
<tr>
<th></th>
<th>Preg</th>
<th>Control</th>
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<tbody>
<tr>
<td>SMOP</td>
<td>81.3%</td>
<td>26.7%</td>
</tr>
<tr>
<td>Mitoses</td>
<td>62.5%</td>
<td>13.3%</td>
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<tr>
<td>Mitotic rate</td>
<td>1.44/mm²</td>
<td>0.20/mm²</td>
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<tr>
<td>Ki-67</td>
<td>3%</td>
<td>1%</td>
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Prospective study: Do nl nevi change during preg?
- 129 nevi on back of 22 preg F followed w/ photos & PE
- 8 (6.2%) changed in diameter from 1st to 3rd trimester:
  4 increased by 1 mm & 4 decreased by 1 mm →
  Mean change in size = 0
- 6 lesions removed for cosmetic or comfort &
  3 removed b/c of concern: DN, halo nevus, lymphangioma.
  Only halo nevus changed during preg (smaller)

Conclude: Pregnancy is not associated w/ any sig change in size of mel nevi
Pennoyer, Grin, Driscoll, Dry, Walsh, Gelineau, Grant-Kels. JAAD 1997;36:378.

Spectrophotometric Intracutaneous Analysis (SIA) of Mel Nevi in Pregnancy

- SIAscopy augments dermoscopy by using lt across visible & infrared spectrum to penetrate more deeply. Images analyzed by computer program
  - visible & infrared lt creates subsurface map of chromophores including Hgb, melanin, collagen

No statistical diff in nevi of preg Vs non-preg

Dysplastic Nevi in Pregnancy

- What happens to nevi of women w/ DNS when they are preg?
  - 17 women w/ DNS followed prospectively during 22 pregnancies (photo and PE)
  - Clinical nevus change (color, size, etc.) 3.9 times higher when DNS pts pregnant vs not pregnant
  - Twice as likely to demonstrate dysplastic features histologically during pregnancy

Conclude: Pregnancy assoc w/ increased rate of DN change in pts w/ DNS
Conclusion re: Myth 1 & 2
Melanocytic Nevi & Pregnancy

• Historical belief: **Nevi** typically darken & enlarge during pregnancy (physiologic)
  – NEVER PROVEN!!!
  – Enlarge only where skin expands: Abd & Breasts
• Bx of **changing nevus** in preg should **not** be delayed!

What about myth # 3: Melanoma & Preg?

Anatomic Site of MM in Preg Women

• Norwegian Pop based cohort study
• MM most common malig dx’d during preg & lactation
• MM was only ca in which preg **appeared** to slightly increase risk of death
  – Preg women had MM in anatomic sites assoc w/ poorer prognosis (head, neck, trunk)
  – Adjusted for this diff → hazard ratio reduced
  – **Conclude that preg did not adversely affect MM prognosis**


MM Risk: Pooled Analysis of 10 Case Controlled Studies

• 5,590 women
• **No NM risk assoc’d w/ pregnancy**
• **Preg did not impact MM survival**
  • # of live births & age at 1st birth:
    – Higher parity & earlier age at 1st birth = sig lower MM risk
  • Women w/ 5 or more live births → lower MM risk
  • Reduced oppor for sunbathing
  • **No reason to recommend deferral of subsequent preg in women w/ 1st MM dx’d during pregnancy**


Dx of MM DURING Pregnancy


• 7 studies: preg Vs matched controlled non-preg
  • survival rates in women dx’d w/ localized MM
  **No sig diff in survival rates**
• CA Cancer Registry 1991-1999: **No diff in survival**
  303 women w/ pregnancy assoc MM Vs 1799 age matched non-preg controls
  O’Meara et al. Cancer 2005:103:1217
• Swedish National & Regional Registries 1958-99
  **No diff in survival**
  159 women w/ MM dx’d during preg Vs 4385 non-preg control

Thickness of MM Dx’d DURING Pregnancy?

• 4 case controlled studies demonstrated significantly **increased thickness of preg assoc’d MM**
  – Delay in dx b/c changes in nevi considered physiologic?
  – Altho MMs thicker in preg gp, there was a **“preg-assoc’d prognostic advantage”** increased survival in preg-assoc MMs Vs non-preg-assoc MMs

Mortality in Women w/ Preg Assoc’d Melanoma (PAMM)

• Lens 2004 data updated & expanded: pop. based cohort study (Swedish Ca & Multi-Generation Registers)
  – 6857 women, 15 to 44 yo w/ dx of cut MM 1963 – 2009
  – 1019 cases classified as PAMM
  – Preg assoc: w/in 9 mos before or 2 yrs after or during preg
• Cause-specific mortality did not differ between PAMM & MM not dx’d near childbirth → no neg impact
• **No evidence of adverse prognostic influence of preg or a recent birth → counsel & monitor**
Heterogeneous Data Confusing!

- Cochrane, MEDLINE, PUBMED, etc database review → 14 studies met inclusion criteria → included only 4 studies that reported hazard ratios & confidence intervals
- Few studies, vary in design, def of PAM, & statistical analysis
- 56% increased mortality risk for preg assoc’d melanoma
- Excluded O’Meara study due to lack of confidence intervals
- Included post preg study (w/in 5 yrs after childbirth)-postpartum MMs!! Moller, et al. Eur J Cancer 2013;49:368-93
- Included study missing Breslow depth in 45% of cases & melanomas at hi risk sites Stensheim, et al. Am Soc Clin Oncol 2009

Critical Responses to this article Published in JEADV

Heterogeneous Data Confusing!
Dermatology News (Skin & Allergy) 4/8/15: SF AAD
“Worse melanoma outcomes found in preg women”:
- “Preg increases risk of poor outcomes in MM according to review of MM cases @ Cleveland Clinic.” Natasha Mesinkovska lecture at AAD
- Retrospective single ctr tertiary care hospital based review
- Women < 50 yo: 41/462 women preg or w/in a yr of preg @ dx (19 dx preg)
- Women preg or recently preg @ time of dx: 5 X’s more likely to die of MM, 7X increase in met & 9X increase of recurrence than those who were not
- FLAWS: single tertiary ctr, very small #'s of PAM gp, unclear staging, diff in length of FU unclear, used logistic regression for outcomes rather than cox proportional hazards modeling, did not show confidence intervals

Proliferative Activity in Preg Assoc Melanoma (PAM)
• PAM = MM during preg or w/in 12 mos postpartum
• PAM vs non PAM: Assessed tumor stage & prolif activity – mitotic rate & immunohistochem markers of prolif: phosphohistone H3 (pHH3) & Ki-67
• Results: Higher % of in situ’s noted in PAM gp
No statistical diff in tumor stage, Breslow depth, or prolif activity markers
• Conclude: Preg has no sig impact on MM progression
• Hx of PAM should NOT outweigh traditional factors, as advanced maternal age, in planning future pregnancies
Merkel, et al. JAAD 2016;74:88-93

Effect of PRIOR Pregnancies on Prognosis of MM
2 controlled studies
  – No difference in survival
  Women preg 1 or 2X before MM dx Vs nulliparous controls
  – No difference in survival
  Women w/ pregnancies prior to dx of MM Vs controls

Effect of SUBSEQUENT Pregnancy on Prognosis of MM
3 controlled studies.
• No significant difference in survival
Women who became preg after dx’d w/ MM Vs Women who did not have subsequent preg
• “There is no compelling evidence that pregnancy adversely affects outcome in MM pts who have clinically localized disease. Continuing to recommend a delay in childbearing for these pts is not supported by published medical literature.” Brady & Noce. J Clin Aesthetic Dermatol 2010;3:22.

Effect of PRIOR Pregnancies on Prognosis of MM
2 controlled studies
  – No different in survival
  Women preg 1 or 2X before MM dx Vs nulliparous controls
  – No different in survival
  Women w/ pregnancies prior to dx of MM Vs controls
Conclusions re: MM & Preg

- Multiple controlled studies of women w/ localized MM dx’d during preg have NOT revealed an effect on survival.
- Preg before or after a dx of localized MM has NOT been shown to influence survival.

Recommendations for the Pregnant Patient:

1. Management of nevi during preg:
   - Identical to those for non-preg pt. Do NOT assume changes are hormonally driven & physiologic. Bx should NOT be delayed!

2. Pts w/ DNS should be photo’d & FU’d each trimester

3. Localized MM in preg women: prognostic factors no diff than for non-preg woman

4. Women w/ previous MM & subsequent preg:
   - If MM is early & thin no need to delay preg.
   - If MM is hi risk for recurrence defer preg for 2-3 yrs (majority of recurrences) schwartz, et al. Cancer 2003;97:2130

5. Pregnancies prior to dx of localized MM no impact on prognosis

6. Once MM dx’d, Rx is same but avoidance of gen’l anesthesia recommended if possible

7. Excision w/ “caine” (category B) + epi (category C: uterine art spasm):
   - dilution & amt small // Some suggest avoid epi

8. Safety of SLNB in pregnancy: controversial
   - No contraindication to SLNB w/ dye & lymphoscintography
   - Avoidance of lymphoscintography before 30 wks gestation
   - SLNB w/ radiocolloid alone (anaphylactic rxn to blue dye)
   - Perform SLNB w/ only intraoperative dye injection, avoid radiolabeled technique
   - Postpone SLNB until after delivery. Anesthesia risk to developing brain & fetus. Delay likely no impact on OS

9. CLND when necessary
   - Has been performed w/o harm to Mom or fetus

10. Preg pts w/ hi risk MM → imaging studies can be done (CXR w/ shielding, ultrasonography, MRI)
    - No CT scans w/ IV contrast
    - Radiation dose not sig enough to cause adverse affects in a developing embryo or fetus
    - Concern re: adverse rnx to dye
    - MRI avoidance during 1st trimester
    - Contrast agents gadolinium & manganese identified in placenta-bi barrier w/ n minutes of injection
    - sp: fetus safety 2nd to heat in mom’s body from magnetic fields & radio frequencies

11. Rx for Stage I & II: same for non preg pts
    - Rx for Stage III & IV: individualized
    - Chemo in 18 (2 w/ MM) pts in 2nd & 3rd trimester no fetal abn

12. Rx & Outcome of Met MM During Preg
    - Retrospective study of 34 depts of derm & onc: 22 pts → 10 w/ stage III, 12 w/ stage IV MM dx’d during preg
    - 3 performed abortions; 1 miscarriage after MM surgery
    - Rx: 14 surgery, 4 chemo, 1 brain radiation
    - Mean gestational age = 36 wks
    - No neonatal mets or deformities; 1 placenta w/ mets
    - 17/18 newborns A&W, 1 died of sudden infant death
    - 2 yr maternal survival rates: 56% (III) & 17% (IV)
    - Rx conventional except during 1st trimester
    - Prognosis not worsened due to pregnancy
Women’s Dermatology Society Journal

- Open Access
- Fee to publish, no subscription
- 40% of profits go to WDS
- Same publisher as JAAD
- Rapid turnaround

http://www.ijwdonline.org

Thanks for your attention!

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