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 mos later → liver metastases → died w/in 1 yr

3 MM & Mel 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
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 malig dx’d during preg
- Swedish study: MM was 24.5% of all malig dx’d during preg
- Norwegian registry cohort study: MM most freq malig dx’d during preg (160 of 516 or 31% of malig)

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 Inhibit Effect During Preg
   - Fetus expresses paternal alloAgs → 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?

2. Physiologic preg changes?
   - Cut hyperpig in preg & w/ exogenous hormones
   - 90% of preg women: hyperpigmentation (areolae, genital skin, linea nigra)

3. Old Wrong Info
   - “Pigmented nevi may enlarge & can 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 nevoid / melanocytic cells has been noted but the # of mitoses is not increased.”

4. Case Reports
   - Case reports & uncontrolled series (esp in 1950’s) of aggressive MM in preg 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 w/ a conversion of benign nevi to melanoma & apparently hasten the growth & dissemination of melanoma through hormonal stimulation…

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


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**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.”


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**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

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**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)


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**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, dermatofibros; 1 tick
• SI higher mean atypia scores in preg nevi Vs controls
  – (Evaluated cohesion, papetoed, mitoses, lentigious prolif, cytologic atypia, nucleoli 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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Melanocytic Nevi & Pregnancy

- 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 1mm & 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

Perroyer, Grin, Draccoll, Dry, Walsh, Goliner, Grant-Kels. JAAD 1997;36:378.

Dermoscopy Preg Changes: 2⁰ to Vessels, Expanding Skin, Less sun exposure

- Diameter & new dot formation on abd & breast
  - Returned to nl in 3-6 mos. No sig change in size
  - Changed linearly over time
  - Vascularization esp late in preg
  - Or of dots or globules
- Sun exposure during preg?

Spectrophotometric Intracutaneous Analysis (SIA) of Mel Nevi in Pregnancy

- SIAscropy 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 preg vs not preg
  - Twice as likely to demonstrate dysplastic features histologically during preg
- Conclude: Preg 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
• Preg pts w/ DNS need closer monitoring
• Bx of changing nevus in preg should not be delayed!
• What about myth # 3: Melanoma & Preg?
Jhaveri, Driscoll, Grant-Kels. Obstet Gynecol 2011;54:537

Dx of MM DURING Pregnancy

• 7 studies: preg Vs matched controlled non-preg re: 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 1,799 age matched non-preg controls
• Swedish National & Regional Registries 1958-99
  No diff in survival
  159 women w/ MM dx’ d during preg Vs 4,385 non-preg control

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

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

MM Risk: Pooled Analysis of 10 Case Controlled Studies

• No MM 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
    Vs nulliparous women
    Reduced oppor for sunbathing
• No reason to recommend deferral of subsequent preg in women w/ 1st MM dx’d during pregnancy

Mortality in Preg Assoc’d MM (PAMM)

• Lens 2004 data updated & expanded: pop. based cohort study (Swedish Ca & Multi-Generation Registers)
  – 6,857 women, 15 to 44 yo w/ dx of cut MM 1963 – 2009
  – 1,019 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 =
• 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 (pop based study, CA registries) Cancer 2005
• Included post preg study (w/in 5 yrs after childbirth) = postpartum MMs!!!
• Included study missing Breslow depth in 45% of cases & MMs at hi risk sites Stensheim, et al. Am Soc Clin Oncol 2009

Dermatology News (Skin & Allergy) 2015 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
• Retrospective single ctr tertiary care hosp based review
• < 50 yo: 41/462 women preg or preg w/in yr @ dx (19 dx preg)
• Preg or recently preg @ dx: 5 X’s more likely to die of MM, 7X’s increase in met & 9X’s increase of recurrence than those who were not!
• FLAWS: single tertiary ctr, very small # 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 Tellez, et al. JAAD 2016;74:731–738.

Critical Responses to this article Published in J Eur Acad Dermatol V

Proliferative Activity in 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
  – Stat sig higher survival rate in pts who had > 5 pregnancies
  – No difference in survival
  Women w/ pregnancies prior to dx of MM Vs controls

SUBSEQUENT Preg on MM Prognosis?
• 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 & Ncnes. J Can Aesthetic Dermatol 2010:3:22.
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 pregs:
   - 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)
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 & lymphoscintigraphy
   • Avoidance of lymphoscintigraphy before 30 wks gestation
   • Perform SLNB w/ only intraoperative dye injection, avoid radiolabeled technique
   • SLNB w/ radiocolloid alone (anaphylactic rxn to blue dye) (ok after 1st trimester)

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 when appropriate
    • CXR w/ shielding, ultrasonography
    • No CT scans w/ IV contrast
      – Radiation dose not sig enough to cause adverse affects in a developing embryo or fetus
      – Concern re: adverse rxn to dye
    • MRI avoidance during 1st trimester
      – Contrast agents gadolinium & manganese identified in placenta-bi barrier w/in minutes of injection
      – ? re: 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
    • Retrospective study: 34 depts derm & onc: 22 pts dx during preg 10 stage III, 12 stage IV MM
      - Prognosis not worse due to preg
        - 3 performed abortions; 1 miscarriage after MM surgery
        - Rx: 14 surgery, 4 chemo, 1 brain radiation
        - Mean gestational age = 36 wks; 0 fetuses & 1 placenta w/ mets
        - 17/18 newborns A&W; no neonatal mets or deformities; 1 died of SID
        - 2 yr maternal survival rates: 56% (III) & 17% (IV)
        - Rx conventional except during 1st trimester
12. **Outcome of fetus** in maternal Stage IV MM: Assoc w/ prematurity, low birth wt, higher rates of C-S


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Thanks for your attention!

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**Dermatology 5¢**

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**The Doctor is In**