Melanoma & Melanocytic Nevi in Pregnancy
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Conflicts of Interest:
None

- Driscoll MS, Stein JA, Grant-Kels JM. Melanoma and pregnancy. UpToDate 2019.

• 41 yo woman pregnant after in vitro fertilization
- Complained to MD husband, PCP, & Ob of changing back “mole” X mos
- “Changes are physiologic” & “don’t worry”
- Derm PE: Numerous mel nevi & DN on trunk & exts
  - Mid upper back 1.5 cm irreg brown & white plaque
- Path: Melanoma 0.6 mm w/ regression
- Lesion widely excised w/ 1 cm margins. No SLNB done bc of MM depth & pt 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

- 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 preg!”
  - “If you are pregnant & you get MM, the preg should be terminated”
Why Should We Care?

- MM incidence higher for females than males during reproductive yrs.
  
  
  
- ~1/3 women dx'd w/ MM: childbearing age
  
  
- MM incidence in women doubles for every additional 10 yrs of life.
  
  Women delaying childbirth for career
  
  
- Swedish pop based cancer registry: MM = 31% of all malig dx'd during preg & most common malig in pregnancy
  
  Bloom & Polsky. The Melanoma Letter 2010;289 (1)

Basis for Myths?

- Mom doesn't mount immune response to fetus carrying paternal alloAg. T lymphocytes w/ impaired IL-2 & interferon gamma production.
  
  Th1 responses down regulated → T cell recognition of tumor Ag impacted?
  
  
- Pigmented nevi may enlarge & can become darker during pregnancy & nevi not previously noticed may become apparent.
  
  
- 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...

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 → No significant histologic changes compared to non-pregnant age matched women (controls)


- 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, dermatofibs; 1 tick
  
  "We would be reluctant to attribute prominent atypia in a melanocytic lesion to ‘pregnancy effect’.


- 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

Pennoyer, Grin, Driscoll, Dry, Walsh, Gelineau, Grant-Keis. JAAD 1997;36:371.
Dermoscopy Preg Changes:
2^t to Vessels, Expanding Skin, Less sun exposure
• ↑ Diameter & new dot formation on abd & breast
• Back & Abd nevi examined: TDS → ↑"mild"
  – 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?

Dysplastic Nevi in Pregnancy
• What happens to nevi of women w/ DNS when they are pregnant?
  – 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 vs non-pregnant
  – Twice as likely to demonstrate dysplastic features histologically during pregnancy
  – Conclude: Pregnancy assoc w/ increased rate of DN change in pts w/ DNS

Concentration 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. Clin 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
  1799 age matched non-preg controls
G Negueler et al. Cancer 2005;104:1271
• Swedish National & Regional Registries 1958-99
  No diff in survival
  159 women w/ MM dx’d during preg Vs
  4386 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 effect 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?
- Altto MM’s thicker in preg gp, there was a “preg-assoc’d prognostic advantage” increased survival in preg-assoc MM’s Vs non-preg-assoc MM’s


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 Vs nulliparous women
  - Reduced oppor for sunbathing
- No reason to recommend deferral of subsequent preg in women w/ 10 MM dx’d during pregnancy

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, 247 dx’d w/ MM during preg
  - Preg assoc: win 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 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, & stat analysis
- 56% increased mortality risk for preg assoc’d melanoma
- Excluded O’Meara study due to lack of confidence intervals (population 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 & melanomas at hi risk sites Sorsahl, et al. Am Soc Clin Oncol 2009

“Worse Melanoma Outcomes Found in Pregnant Women”

Dermatology News (Skin & Allergy) 2015 SF AAD
- Retrospective single ctr tertiary care hosp based review
- Women < 50 yo: 41/462 women preg or w/in a yr of preg @ dx (only 19 dx during preg)
  - Women preg or recently preg @ time of dx:
    - 5X’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 #’s of PAM gp, unclear staging, diff in length of FU unclear, authors report double the cases of advanced disease in the PAM gp later in the manuscript compared to earlier in paper profoundly affecting analysis, used logistic regression for outcomes rather than cox proportional hazards modeling, did not show confidence intervals, only19/462 women dx while pregnant!

Floranc, et al. JAAD 2016;74:85-93

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
  - Hx of PAM should NOT outweigh traditional factors, as advanced maternal age, in planning future pregnancies

Merkel, et al. JAAD 2016;74:88-93
Recent Study

- 155 pts pts diagnosed with MM during pregnancy
- Compared to non-pregnant matched controls (Breslow thickness, age, stage, ulceration status)
- CONCLUDE: No significant differences in disease free survival, overall survival or melanoma specific survival in PAM and non-PAM controls


Maternal Tumor

- Some MMs dx’d during preg greater Breslow depth
- Some studies show no sig diff in depth noted
- Retrospective review of 34 PAM Vs nonpreg age & disease matched controls: no sig diff in Breslow depth, ulceration, mitotic rate, stage of disease, anatomic location, histologic subtype. Clark level, regression, necrosis, vascular invasion.


Placental/Fetus Tumor

- MM most common ca to met to fetus but rare & only in widely met maternal disease
- Cases with placental MM mets from mom: 25% of fetuses affected
- Mom with advanced MM: alert path to multiply section placenta looking for small foci of MM


MM Dx Postpartum: Effect of PRIOR Pregnancies on Prognosis of MM

- 2 older controlled studies
- No difference in survival
- Stat sig higher survival rate in pts who had >5 pregnancies


MM Dx Postpartum: 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."


MM Dx prior to Pregnancy: Effect of SUBSEQUENT Pregnancy on Prognosis of MM

- 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."

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 & future 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)
   - If woman later in childbearing yrs: eval case by case

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 & amnt small // Some suggest avoid epi

8. Safety of SLNB in pregnancy: controversial
   - No contraindication to SLNB w/ dye & lymphoscintigraphy (less from second trimester)
   - Avoidance of lymphoscintigraphy before 30 wks gestation
   - SLNB w/ radiocolloid alone (anaphylactic risk to blue dye)
   - (after 1st trimester to avoid gen’l anesthesia)
   - Avoidance of lymphoscintigraphy before 30 wks gestation
   - CT scans but w/o IV contrast

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

10. Preg pts w/ hi risk MM → imaging studies:
    - CXR w/ shielding, ultrasonography, MRI w/ gadolinium
    - CT scans but w/o IV contrast
    - MRI but w/o gadolinium: avoidance during 1st trimester

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

   - Newer targeted treatments as BRAF inhibitors (vemurafenib, dabrafenib) & checkpoint inhibitors (anti-PD1 nivolumab; anti-CTLA Ipilimumab) may be teratogenic

   - FDA labeling recommends avoidance of pregnancy & lactation:
     - During BRAF inhibitor Rx & up to 2 weeks after last dose
     - During Ipi Rx & up to 3 mos after last dose
     - During Nivo Rx & up to 5 mos after last dose
12. Rx & Outcome of Met MM During Preg  

- Retrospective studies of 72 pregnant women dx’d with advance melanoma (stage III or IV)
- Surgery performed on almost all pts (excision, SLNB, CLND)
- Rare pt opted to terminate pregnancy
- ~18% premature deliveries (many induced)
- 8 pts had systemic Rx or radiation
- 1 placenta with mets; 1 fetus with mets (died)
- 94% pregnancies w/o complication; fetus A & W
- Maternal survival: 2 YR 56% (III) & 17% (IV); 5 YR ~61%
- Advanced disease in pregnant pt can be managed

13. Stage IV Melanoma: Impact on Baby

- MM dx’d at early stages → does not alter the evolution of gestation
- Pts w/ advanced stages of melanoma freq deliver   
  – prematurely (many induced)  
  – by C-S  
  – w/ lower neonatal weight  
  – higher neonatal morbidity & mortality


14. Exogenous Hormones Safety: OCT, HRT, ART cont’d

OCT: No apparent increased MM risk even for long durations so no need to w/hold use in pts w/ MM hx
  – 22 epidemiologic studies: no impact  
  – Pooled analysis: 10 case controlled studies (3796 pts who used OCP vs 9442 controls: no increased risk of MM  
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HRT: No apparent increased MM risk so no need to w/hold use in pts w/ MM hx
  – Women’s Health Initiative Trial analyzed 27,347 postmenopausal women: MM incidence no diff of those on HRT vs control gp  

Assisted Reproductive Technology

- 113,226 women needing ART Vs 53,859 who did not re: cancer incidence
  – ART women: statistically sig lower risk of all cancers  
  – EXCEPT non statistically sig lower risk for cut MM
  – Conclude no contraindication to ART related hormone use re MM risk


14. Exogenous Hormones Safety: CT, HRT, ART cont’d

CT: No apparent increased MM risk even for long durations so no need to w/hold use in pts w/ MM hx
  – 32 epidemiologic studies: no impact  
  – Pooled analysis: 10 case controlled studies (3796 pts who used OCP vs 9442 controls: no increased risk of MM  

Conclusion:

- No consistent pattern of assoc between IVF & MM among infertile women
-Potential increased MM risk in ever-parous pts Rx’d with IVF


14. Exogenous Hormones Safety: CT, HRT, ART cont’d

IVF & MM risk studies:
  – 5 showed no increased risk for MM among IVF users   
    compared to genl pop  
  – 2 showed an increase in MM in clomiphene users  
  – 4 showed an increase in MM among pts who were gravid or parous either before or after IVF

Conclusion:  
- No consistent pattern of assoc between IVF & MM among infertile women
- No significant increased MM risk in ever-parous pts Rx’d with IVF


Thanks for your attention!

Thanks to Caron Grin, Marcia Driscoll, Jennifer Stein, et al!!!