Moles, Melanoma & Maternity

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Conflict of interests

- Nothing to declare
Incidence

- Most common malignancy in pregnancy
- Incidence:
  - 2.8-5 / 100,000 pregnancies in Europe
  - 50 / 100,000 pregnancies in NSW
- 25% of melanomas in 25-29 year age group are pregnancy associated

Incidence malignancy per 100,000 pregnancies

Elbye 2013
Cutaneous Melanoma During Pregnancy: Is the Controversy Over?
• Survey with scenarios
• 290 questionnaires returned (89%)
• 50% discordance in management
Does pregnancy increase the risk of melanoma?

• Probably no
• Parity reduces risk (probably behaviour-related)
• Incidence of pregnancy-associated melanoma is increasing proportionate to increasing maternal age
Melanoma

- Does pregnancy influence the prognosis of melanoma?
Risk of death HR 1.56, 95% CI 1.23–1.99
Byrom et al

- **Problems**
  - Excluded studies with no hazard ratio
    - Including those with largest sample size
    - Pool small number of studies (4/14 eligible studies)
    - Weighting of studies
  - Heterogeneity in definition of pregnancy-associated
    - 3x studies during pregnancy
    - 1x study during or 12 months post-partum
  - Heterogeneity of outcome
    - delivery from melanoma
    - death from melanoma (disease-specific and overall survival)
  - Not all studies controlled for breslow
    - Stensheim
    - Moller
**Authors** | **Effect estimate (95% CI)** | **Weight (%)**
--- | --- | ---
MacKie R *et al.* | 1.30 (0.54, 3.15) | 6.15
Stensheim H. *et al.* | 1.45 (0.96, 2.21) | 27.51
Johansson A.L.V. *et al.* | 1.09 (0.83, 1.42) | 66.34
**New overall** | 1.19 (0.96, 1.48) | 100

**Figure 1** Non-significant increase in the risk of mortality associated with pregnancy-associated melanomas.
Table I. Summary of controlled studies on melanoma diagnosed during pregnancy

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of pregnant patients</th>
<th>No. of controls</th>
<th>Duration of follow-up</th>
<th>Did pregnancy influence survival?</th>
<th>Did pregnancy result in a shorter DFI?</th>
<th>Stage of disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reintgen et al(^{17})</td>
<td>58</td>
<td>585 not pregnant at time of dx or within 5 y</td>
<td>5 y</td>
<td>No</td>
<td>Yes (P = .04)</td>
<td>I</td>
</tr>
<tr>
<td>Slingluff et al(^{18})</td>
<td>88 (continuation of patient base used by Reintgen et al(^{17}))</td>
<td>79 not pregnant at time of dx</td>
<td>6 y</td>
<td>No</td>
<td>Yes</td>
<td>I</td>
</tr>
<tr>
<td>McManamny et al(^{19})</td>
<td>23</td>
<td>243 not pregnant at the time of dx or afterwards</td>
<td>2 months to 20 y</td>
<td>No</td>
<td>No</td>
<td>I</td>
</tr>
<tr>
<td>Wong et al(^{20})</td>
<td>66</td>
<td>619 not pregnant at time of dx; 66 matched for Breslow depth, anatomic location of primary, lesion, and histopathologic subtype</td>
<td>N/A</td>
<td>No</td>
<td>Actuarial DFI curves not calculated; no mean DFI was longer for pregnant patients (37.7 months) vs controls (27.3 months)—statistical analysis not done</td>
<td>I</td>
</tr>
<tr>
<td>MacKie et al(^{11})</td>
<td>92 (group 2)</td>
<td>143 not pregnant at time of dx (group 3); 68 patients subsequently became pregnant (group 4); 85 patients who were pregnant before dx (group 1)</td>
<td>N/A</td>
<td>No (when groups 1-4 compared)</td>
<td>No</td>
<td>I</td>
</tr>
<tr>
<td>Daryanani et al(^{22})</td>
<td>46</td>
<td>368 not pregnant at time of dx and matched for age and sex</td>
<td>109 months (median)</td>
<td>No</td>
<td>No (10-year survival curve)</td>
<td>I and II</td>
</tr>
<tr>
<td>Lens et al(^{24})</td>
<td>185</td>
<td>5348 not pregnant at time of dx</td>
<td>11.6 y (median)</td>
<td>No</td>
<td>N/A</td>
<td>All</td>
</tr>
<tr>
<td>O’Meara et al(^{26})</td>
<td>145</td>
<td>2451 not pregnant at time of dx</td>
<td>N/A</td>
<td>No; HR, 0.79 (P = .570)</td>
<td>N/A</td>
<td>All</td>
</tr>
<tr>
<td>Stensheim et al(^{27})</td>
<td>160</td>
<td>4460 not pregnant at time of dx or after dx</td>
<td>11.9 y (median)</td>
<td>No; HR, 1.45 (95% CI, 0.96-2.21)</td>
<td>N/A</td>
<td>All</td>
</tr>
<tr>
<td>Johansson et al(^{16})</td>
<td>247</td>
<td>5838 not pregnant at time of dx or &gt;2 y postpartum at dx</td>
<td>Up to 10 y</td>
<td>No; HR, 0.79 (95% CI, 0.44-1.41)</td>
<td>N/A</td>
<td>All</td>
</tr>
<tr>
<td>Tellez et al(^{23})</td>
<td>19</td>
<td>421 not pregnant within 1 year of dx</td>
<td>91 months</td>
<td>Yes (analysis included 1-year postpartum); OR = 5.10 (P = .03)</td>
<td>N/A</td>
<td>All (including 35% in situ)</td>
</tr>
</tbody>
</table>

CI, Confidence interval; DFI, disease-free interval; dx, diagnosis; HR, hazard ratio; N/A, not available; OR, odds ratio; y, year.
Additional prognosis studies

• Lemaitre 2016
  – 40 patients choroidal melanoma in pregnancy
  – Single institution France
  – No difference in prognosis

• Merkel 2016
  – 50 patients; 122 controls
  – Single institution US
  – No difference in Breslow; higher percentage of melanoma in situ on pregnant group

• Jones 2017
  – 156 pregnancies in cohort 2025 patients
  – Single institution US
  – No difference in disease free survival, overall survival or melanoma-specific survival
  – No difference in Breslow

• Tellez et al. JAAD 2016
  – 41 pregnancies; 441 controls
  – Single institution US
  – a 9-fold increase in recurrence (P<.001), 7-fold increase in metastasis (P = .03) and 5-fold increase in mortality (P = .06)
Melanoma Prognosis in pregnancy

Arguments for worse
- Hormonal change
- Relative immunosuppression
- Increased lymphangiogenesis

Against
- Delayed diagnosis
- Delayed treatment
- Sub-optimal treatment
Are hormones relevant?

• Molecular pathways not well understood
• Physiological hyperpigmentation of certain sites
• Some dysplastic naevi and melanomas have oestrogen receptor beta receptors
• Melanocyte stimulating hormone higher in pregnancy
• Clinical relevance unclear
Article Highlights

- Systemic immunity in metastatic melanoma (cancer) mimics the systemic immune response of early pregnancy.
- Sex hormones promote/suppress different T cell responses during pregnancy and in melanoma.
- Metastatic melanoma and early pregnancy promote a systemic state of Th2 dominant chronic inflammation.
- Near parturition, hormones play a role in the return to cytotoxicity (Th1) of maternal immunity and the promotion of labor.
- Understanding the mechanism that causes immunity to switch from Th2 to Th1 in pregnancy may help researchers better understand how to break tolerance and improve patient outcomes in advanced cancers.

Figure 2. Effects of sex hormones during early pregnancy to promote implantation and fetal tolerance and the proposed role in initiation of cancer. CRH = corticotropin-releasing hormone; E2 = estradiol; hCG = human chorionic gonadotropin; IFN-γ = interferon gamma; Treg = regulatory T; uNK = uterine natural killer; VEGFR = vascular endothelial growth factor receptor.

Mayo clinic proceedings 2014

‘No specific evidence suggesting that the immunosuppressed state may lead to melanoma development or progression’ Driscoll JAAD 2016
Does pregnancy influence the prognosis of melanoma?

- Pregnancy and prognosis - other malignancies
  - Breast carcinoma: worse prognosis HR death 1.84 (Moller)
  - Haematological malignancy: no effect (Albright 16)
  - Cervical carcinoma: no effect (Albright 16)
  - Thyroid carcinoma: no effect (Albright 16)
  - Colon carcinoma: no effect (Albright 16)
Reasons for delayed diagnosis

• Symptoms of malignancy similar to symptoms pregnancy
  – Nausea, fatigue etc
• Mother does not prioritise own health
• Clinicians avoid investigation due to concerns results inaccurate or tests harmful
Breslow

- 10 studies examining Breslow (Driscoll JAAD 2016)
  - 3 showed increased Breslow in pregnant group
    - Median 0.75mm vs 0.60mm (p=0.002)
      - Bannister-Tyrrell 2015
    - 1.49mm (before pregnancy); 2.38mm (during pregnancy); 1.96mm (after pregnancy) and 1.48mm (in between pregnancies)
      - Mackie 1991
    - Mean 2.28mm vs 1.22mm (p<0.007)
      - Travers et al 1996
Melanoma Prognosis in pregnancy?

Arguments for worse

• Hormonal change
• Relative immunosuppression
• Increased lymphangiogenesis

Against

• Delayed diagnosis
• Delayed treatment
• Sub-optimal treatment

Diagnose!
Does pregnancy affect treatment of melanoma?

• Treatment of early stage disease is unchanged
  
  • Delayed treatment not indicated
  • Local anaesthetic safe
  • Excision biopsy with normal margins and histopathologic examination
Sentinel node biopsy in pregnancy

• No evidence based guidelines
• Refer specialist centre
• Sentinel node remains most powerful prognostic marker
• Definitive excision should not be delayed
• Consider impact on management

• Radiation risk to foetus is minimal
  - Sentinel node
    • Reported >50 pregnancies
    • Limited to lymphoscintigraphy without SPECT/CT
    • Technitium 99m exposure to foetus is low (<2mGy)
    • Blue dye recommended against due to possible anaphylactic reactions
    • ? Avoid in first trimester
Does pregnancy affect staging of melanoma?

- Does pregnancy affect staging of melanoma?
  - Imaging
    - Indivualise depending on gestation, mother’s wishes and symptoms
    - Consider impact on management
    - Refer specialist centre
Melanoma

• Does pregnancy affect treatment of advanced melanoma?
  – Balance treatment mother vs harm baby
  – Depends extent of disease, gestational age, treatment options
  – Refer specialised multidisciplinary centre in conjunction teratology service

– Stage III disease
  • Therapeutic lymph node clearance – surgery generally safe

– Stage IV disease
  • Targeted therapies (BRAF & MEK inhibitors)
    – More data for single agent BRAF
    – No foetal anomalies
  • Immunotherapies (PD-1 & CTLA4)
    – No reports that I’m aware of
    – High incidence of endocrinopathies
    – PD1/PD-L1 interactions appear to play a key role in maintaining fetal tolerance
    – Placenta has strong and ubiquitous PD-L1 expression
    – PD1 – animal studies: high incidence abortion; no increased birth defects
    – Ipilimumab category C – of the CTLA4 axis in fetal immune tolerance (Johnson et al 2017)
Melanoma

• Outcomes for baby
  – Most common impact is iatrogenic prematurity, especially for stage IV disease

– Transplacental spread
  • Most common malignancy to metastasize to placenta & foetus (31% of placental metastases
  • Extremely rare
    – Placental involvement does not mean foetal involvement

• Prognosis
  – Poor
  – Infant and maternal death in most

• Management
  – Macroscopic & histological examination placenta
  – Clinical examination baby
  – Some have suggested liver ultrasound and urine melanin analysis of infant
Anxiety, recurrence & second primary

Preconception counselling

- Case by case
- Depends age mother, thickness melanoma, wishes mother
- Appropriate education & counselling
- Various time-frames have been suggested in literature, but are arbitrary
  - Eg 2 years for stage II (based on time to recurrence) (Mackie 1991)
  - Eg 5 years for thick melanoma (Tierney 2013)
Hormone therapy post melanoma

• Contraception & HRT
  – OCP or HRT
  – No evidence affects risk or prognosis
Part 2

Melanocytic naevi
Melanocytic naevi in pregnancy

• Do moles change in pregnancy?

• What is an acceptable change?

• What is the difference between physiological change & melanoma?
Moles in pregnancy

• Self-reported changes in naevi are common
  – 10-30% percent of women

• Studies don’t support frequency of change
  – Most self-reported changes are probably other not melanocytic naevi (eg skin tags)
Few studies

- **Akturk 2006 (Turkey)**
  - 56 women / 97 naevi
  - 1 or 2 naevi chosen per person
  - Exclusion: dysplastic naevus syndrome
  - 1 & 3 trimester
  - Clinical & dermoscopic examination and measurement size

- **Gundez 2012 (Turkey)**
  - 21 women / 21 naevi
  - 1 naevus per person, face or back
  - 1 & 3 trimester; 6 months postpartum for changing lesions
  - Clinical & dermoscopic photography

- **Pennoyer 1997 (USA)**
  - 22 women / 129 naevi
  - All naevi on their backs
  - Exclusion: dysplastic naevus syndrome
  - 1 & 3 trimester
  - Clinical photography and measurement size

- **Zampino 2006 (Italy)**
  - 47 women / 86 naevi
  - 1-3 naevi per person; back only
  - 1 & 3 trimester; 6 months postpartum
  - Dermoscopic photography

- **Rubegni 2007 (Italy)**
  - 35 women & 35 controls / 204 naevi
  - All flat naevi >4mm diameter excluding acral naevi, naevi on abdomen and breasts, lesions with clinical or dermoscopic atypia
  - Exclusion: sun exposure in month before enrolment
  - 1 trimester, 3 trimester, 12 months post-partum
  - Digital dermoscopy

- **Strumia 2002 (Italy)**
  - 12 women / 56 naevi
  - 2 & 3 trimester
  - Clinical & dermoscopy

- **Tatu 2012 (Romania)**
  - 420 women
  - 1642 naevi (4 per patient?)
  - During pregnancy and post-partum
  - Comparison distended/non-distended areas and sun-exposed/non sun-exposed areas
  - Type of analysis: hyperpigmentation. Methods not detailed

- **Wyon 2007 (Sweden)**
  - 34 primigravidae, 21 nulliparous controls
  - Maximum 25 naevi per patient
  - 15 on back and 10 on legs
  - Examined <11 weeks & 37 weeks gestation
  - Spectrophotometric analysis
Case

Right lower back
Naevi are dynamic

16% of naevi changed over 12 months, EVEN IN MEN
Moles are dynamic

Non-pregnant male

Pre & post-partum female
Melanocytic naevi in pregnancy

• Size
  – 6% change size - increase and decrease (Pennoyer 97)
  – 3% increase in diameter (Tatu 11)
    • 14% abdominal & breast
  – Increase size in sites prone to expansion (Strumia 02)
  – No change in size (Zampino 06)
  – Increase in size 2.1%, decrease in size 1.3% (Wyon 07)
  – Mean increase in diameter 20% (Akturk 06)
    • Abdominal lesions more likely to increase
    • And greater mean increase
Enlargement on stretched area

Pre-natal

Post-partum
Enlargement on stretched area

Histology - benign
Melanocytic naevi in pregnancy

• Pigmentation
  – 59% naevi on abdomen hypopigmented in pregnancy and 40.9% increase in pigment 6 months post-partum (Tatu 12)
  – 31% non-distended areas hyperpigmented (Tatu 12)
  – Lightening of colour (Zampino 06)
  – Increases & decreases in epidermal & dermal pigmentation (Wyon 07)

Wyon 07:

<table>
<thead>
<tr>
<th></th>
<th>Increase epidermal pigmentation</th>
<th>Decrease epidermal pigmentation</th>
<th>Increase dermal pigmentation</th>
<th>Decrease dermal pigmentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant</td>
<td>0.2%</td>
<td>3.7%</td>
<td>4.7%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Not pregnant control</td>
<td>0.0%</td>
<td>1.8%</td>
<td>4.9%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>
Lightening on stretched area

Third trimester

Post partum
Melanocytic naevi in pregnancy
Dermoscopy studies

• **Vascularity**
  – Increased dotted and comma-like vessels - reversible (Zampino 06)

• **Pigment network**
  – Pseudonetwork more prominent in 3rd trimester (Gundez 03)
  – Darkening network – reversible (Rubegni 07)
  – Broadening network (Tatu 11)

• **Globules**
  – Increased peripheral brown globules (Strumia 02)
  – New dot formation, especially front of body (Akturk 06)
  – Increased globules - reversible (Rubegni 07)
  – New dots & globules (Tatu 11)

• **Architecture**
  – Changes in symmetry – reversible (Zampino 06)
  – Disorder – Irreversible (Rubegni 07)

• **Total dermoscopy score**
  – Increase – reversible (Zampino 06, Akturk 06)
Increased/changed peripheral dot pattern
Increased/changed peripheral dot pattern

Histology - Dysplastic compound melanocytic naevus
Melanocytic naevi in pregnancy

Histology

- Increased dermal mitoses
- Increased SMOP (superficial micronodules of pregnancy)
- Increased Ki-67 proliferation index
- Normal architecture and cytology
- No atypical mitoses

Melanocytic nevi in pregnancy: histologic features and Ki-67 proliferation index.
Chan, May; Chan, Maren; Tahan, Steven

DOI: 10.1111/j.1600-0560.2009.01491.x
Conclusion – naevi in pregnancy

• ‘Normal’ changes in naevi are still to be categorised
  – Increased size on abdomen & breasts only (6%)
  – Hypopigmentation on stretched areas
  – Increased peripheral dots & globules on dermoscopy
  – Increased mitoses on histology

• Changing naevi during pregnancy should be investigated
Pregnancy and your skin
(and your sister’s too)

Pregnancy can affect your skin in many ways. At Melanoma Institute Australia, we are researching how pregnancy affects moles (melanocytic naevi).

The study involves free review by a specialist Dermatologist and photographs of all your moles (you keep a copy). We need to see you twice during the pregnancy, and once 6 months after your baby is born.

To accurately determine the effect of pregnancy on moles, we need you to bring your sister. She gets a free skin check and mole photography too.

To be included, you need:
- To be less than 26 weeks pregnant
- To have a full biological sister
- To have less than 100 moles on your body (or less than 12 per arm)
- To attend 3 appointments (1 hour each) at the Institute in North Sydney

If you would like to participate, please contact us on 02 9911 7277 or pregnancymolesstudy@melanoma.org.au for more information.
Breastfeeding & prescribing

- Relative infant dose (RID)
  - Infant dose mg/kg/day divided by maternal dose
  - Most drugs with RID <10% are safe
  - Most drugs have RID of <1%
- Infant plasma levels also affected by
  - oral bioavailability, liver metabolism in infant
- Consider the safety of the drug in infancy
  - Eg antibiotics commonly given to babies OK
  - What are the potential Aes?
  - Age & weight of the child
  - Alternatives
    - Breast-milk only contains IgA
    - Lactocytes actively block transfer IgG
- Choose drug with published data, short half-life, high protein binding, low oral bioavailability, high molecular weight.
- Breastfeeding should not be discontinued to take a medication
- When there is no evidence, go back to first principles
Acknowledgements

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Mothersafe