Malignant melanoma and pregnancy: second thoughts∗,∗∗

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Summary Malignant melanoma (MM) was considered a hormone-sensitive tumour, and pregnancy was thought to increase its risk and cause faster progression and earlier metastasis. Several controlled studies demonstrated similar survival rates between pregnant and non-pregnant patients and concluded that early reports of advanced MM of pregnancy were probably due to late diagnosis. We retrieved information from our database between 1997 and 2006 on all patients diagnosed as having MM during and up to 6 months after pregnancy (n = 11) and compared them to age-matched, non-pregnant, MM patients (n = 65, controls) treated by us during that period. The mean Breslow thickness was 4.28 mm for the pregnant patients and 1.69 mm for the controls (p = 0.15). The sentinel nodes were metastatic in five pregnant patients compared to four controls (p < 0.0001). Two patients in the pregnancy group and one control died of MM (p = 0.0532). Our results indicate a negative effect of pregnancy on the course of MM.

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Malignant melanoma (MM) during pregnancy is rare, appearing in 0.14 to 2.8 in 1000 births and accounting for 8% of all malignancies during pregnancy.1,2 Pregnancy was considered for many years to have an adverse effect on the course of MM; several reports in the 1950s suggested that pregnancy increased the risk of developing melanoma and caused the disease to advance more rapidly and metastasise earlier, especially in patients with a history of melanoma.3,4 The rationale behind these findings was that...
MM is a hormone-dependent tumour that occurs more frequently in women than in men, especially during childbearing years, and is extremely rare prior to puberty. Moreover, melanoma, or increased pigmentation, is common during pregnancy and among women using oral contraceptives. The belief was that similar changes take place in pigmented nevi, causing more malignant transformations. Furthermore, early laboratory findings showed that melanocytes have the ability to bind oestrogen (E2) and progesterone, supportive of these claims.

Several controlled trials were carried out for the World Health Organization (WHO) and shed new light on the issue. About 400 pregnant MM patients were compared to 1800 matched, non-pregnant, MM patients. Two studies demonstrated thicker melanoma tumours in the pregnant group compared to controls, but related this finding to later diagnosis of the tumour in pregnant women. No trial showed a difference in survival between the groups.

More recent investigations on large groups of patients (about 450 women who were pregnant or who were shortly after pregnancy compared to 3000 non-pregnant women) also demonstrated no difference in survival between the groups.

In vitro studies added inconclusive data, with two trials finding neither E2 nor progesterone receptors on several melanoma cell lines, while other trials found hormone down-regulating cell activity. Another investigation demonstrated an influence of hormones on nuclear morphology.

Following two recent cases of MM in pregnant women seen fairly close in time, we began to question the lack of any association between the condition and the pathology. We searched our own institutional database and retrieved the files of 11 MM patients during or shortly after pregnancy, and compared them to an age-matched group of non-pregnant MM women.

Patients and methods

The study was approved by our institutional Helsinki Committee. We retrospectively reviewed the institutional database between 1997 and 2006 and retrieved information on all the patients who had been diagnosed of having MM during pregnancy or shortly afterwards. Information on age, marital status, medical history, the anatomic location and the tumour staging of the melanoma was available for each patient as was pregnancy status at diagnosis, history of fertility hormonal therapy, and oncological follow-up. Data on age-matched, non-pregnant, MM women treated at our institute during the same period of time were also available and retrieved as well.

Treatment had included wide excision of the primary tumour area and sentinel lymph node biopsy (SNLB) when indicated. SNLB for MM was introduced into our institution in 1997. Inclusion criteria for SNLB were MM with a Breslow thickness of 1 mm or deeper and no clinical evidence of enlarged regional lymph nodes or metastatic disease. Mapping of the sentinel lymph node (SLN) was performed by lymphoscintigraphy using radio-guided surgery and intra-operative patent blue dye injection. Pregnant MM patients had only intra-operative patent blue dye injection, with no radioactive material injection. All women in whom metastasis was found in the SLN underwent formal lymph node dissection.

Statistical methods

Comparison between pregnant women with MM and non-pregnant MM controls was by the chi-square test for categorical variables (nodes, location, survival) and the non-parametric Mann–Whitney test for age and the Breslow staging. The SAS for Windows version 9.1 was used for all statistical analysis. Significance was set at \( P < 0.05 \).

Results

Eleven women who had been diagnosed as having MM during pregnancy or up to 6 months after pregnancy were available for analysis. We compared them to 65 age-matched, non-pregnant, MM patients who served as controls. All the patients in this study were Caucasian, except for one African patient who was in the pregnant group. The mean ± standard deviation (SD) age at the time of diagnosis was 34 ± 3.7 years for the pregnancy group and 34 ± 7.7 years for the control group. Ten patients in the pregnancy group (91%) had primary melanoma and one (9%) had recurrent melanoma during pregnancy. MM was diagnosed during pregnancy in six patients (54.5%), with an average of 26 gestational weeks (range: 11–36 weeks, median 28 weeks). The diagnosis of MM was made after delivery in the remaining five patients (45.5%), with an average of 3.8 months post-delivery (range: 2–6 months). Three women (27.2%) had undergone fertility hormonal treatments prior to conception (Table 1).

The mean Breslow thickness was 4.28 ± 4.48 mm in the pregnancy group, and two patients had ulceration of the tumour on pathological examination. The mean Breslow thickness was 1.69 ± 1.13 mm in the control group (\( p = 0.15 \)).

Eight women in the pregnancy group were treated with combined wide local excision and SLNB and the other three with only wide excision during or shortly after pregnancy. Two of these patients had a Breslow of 0.5 mm, and a third patient had recurrent melanoma in the cheek area. All 65 patients in the control group underwent SLNB.

The SLNs were metastatic in five of the 11 patients in the pregnancy group (45.5%) and in only four of the 65 (6.1%) patients in the control group (\( p < 0.0001 \) (Table 2). These nine patients underwent radical dissection of the involved lymph node basin. Two patients died of the disease in the pregnancy group (18.1%), compared to one patient (1.5%) in the control group (\( p = 0.0532 \) (Table 2).

The anatomic location of the melanoma differed between the groups. Most of the tumours were located in the upper limb in the pregnancy group (six of 11 patients, 55%), while the most common site in the control group was the lower limb (22 of 65 patients, 34%).

Discussion

Early reports in the 1950s on MM during pregnancy suggested that there was a greater risk of developing the disease and a more aggressive manifestation in these women compared...
to non-pregnant women. Pack and Scharnagel\(^3\) reported 10 patients with melanoma during pregnancy, of whom five died within 30 months of diagnosis, suggesting unusual rapidity and earlier metastatic spread associated with pregnancy. George and Fortner\(^4\) noted that the disease was more advanced among 115 patients with MM during pregnancy compared to a non-pregnant, age-matched, control group, although there was no difference in the 5-year survival rate between the two groups. These early findings seemed logical, and so the consensus was that MM was a hormone-sensitive tumour that occurs more in women and mostly during their fertile years.\(^5\) Mackie et al.\(^13\) also reported thicker tumours in a group of 92 patients with MM during pregnancy, and a greater frequency of tumours in truncal regions. Again, there was no change in DFI or survival between the pregnancy and non-pregnancy groups.\(^13\) According to all these authors, the thicker tumours of pregnant MM patients could be attributed to later diagnosis, since patients consider changes in pregnancy (2009), doi:10.1016/j.bjps.2009.05.050

### Table 1  Summary of our reported patients with pregnancy-related melanoma

<table>
<thead>
<tr>
<th>Age at diagnosis, (y)</th>
<th>Pregnancy status at diagnosis</th>
<th>Site of melanoma</th>
<th>Staging of melanoma</th>
<th>SLNB</th>
<th>Lymph node dissection</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>37</td>
<td>Clitoris</td>
<td>Bres. (-11.8) mm</td>
<td>+</td>
<td>+</td>
<td>Disseminated Disease</td>
</tr>
<tr>
<td>2</td>
<td>41</td>
<td>Back</td>
<td>Bres. (-2) mm</td>
<td>+</td>
<td>-</td>
<td>No Recurrence</td>
</tr>
<tr>
<td>3</td>
<td>26</td>
<td>Back</td>
<td>Bres. (-2.1) mm</td>
<td>+</td>
<td>-</td>
<td>Disseminated Disease</td>
</tr>
<tr>
<td>4</td>
<td>44</td>
<td>Upper Limb</td>
<td>Bres. (-6.6) mm</td>
<td>+</td>
<td>+</td>
<td>Disseminated Disease</td>
</tr>
<tr>
<td>5</td>
<td>29</td>
<td>Upper Limb</td>
<td>Bres. (-1.5) mm</td>
<td>+</td>
<td>-</td>
<td>No Recurrence</td>
</tr>
<tr>
<td>6</td>
<td>34</td>
<td>Back</td>
<td>Bres. (-6.8) mm</td>
<td>+</td>
<td>+</td>
<td>No Recurrence</td>
</tr>
<tr>
<td>7</td>
<td>33</td>
<td>Back</td>
<td>Bres. (-1) mm</td>
<td>+</td>
<td>-</td>
<td>No Recurrence</td>
</tr>
<tr>
<td>8</td>
<td>30</td>
<td>Upper limb</td>
<td>Bres (-0.5) mm</td>
<td>-</td>
<td>-</td>
<td>No Recurrence</td>
</tr>
<tr>
<td>9</td>
<td>34</td>
<td>Cheek</td>
<td>Bres. (-2.2) mm</td>
<td>-</td>
<td>+</td>
<td>Recurrence</td>
</tr>
<tr>
<td>10</td>
<td>29</td>
<td>Arm</td>
<td>Bres. (-12) mm</td>
<td>+</td>
<td>+</td>
<td>Disseminated Disease</td>
</tr>
<tr>
<td>11</td>
<td>35</td>
<td>Hand</td>
<td>Bres. (-0.5) mm</td>
<td>-</td>
<td>-</td>
<td>No Recurrence</td>
</tr>
</tbody>
</table>

SLNB, sentinel lymph node biopsy; Bres, Breslow thickness.

Table 2  Comparison of tumour thickness, metastatic lymph nodes and mortality between pregnancy-related melanoma group and the non-pregnancy-related melanoma (control) group

<table>
<thead>
<tr>
<th></th>
<th>Pregnancy ((n = 11))</th>
<th>Control ((n = 65))</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor thickness (Breslow)</td>
<td>4.28 mm</td>
<td>1.69 mm</td>
<td>0.15</td>
</tr>
<tr>
<td>Metastatic lymph nodes</td>
<td>5 patients (45.5%)</td>
<td>4 patients (6.1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mortality</td>
<td>2 patients (18.1%)</td>
<td>1 patient (1.5%)</td>
<td>0.0532</td>
</tr>
</tbody>
</table>

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other studies, found no difference in survival between the two groups, with a slight trend towards better survival in the pregnant group. Those authors suggested that their findings could be related to hormonal changes, immunological inhibitory effect of pregnancy or late diagnosis. A recent retrospective trial by Daryanani et al. found 46 pregnant MM patients to 368 non-pregnant MM patients and reported no difference in tumour thickness or in survival between the groups. The largest and latest trial on this issue, by O’Meara et al., compared 412 pregnant and up to 1 year post-pregnancy MM patients to 2451 non-pregnant MM controls. This large trial also failed to show any difference in tumour thickness or survival between the groups (Table 3).

In spite of such convincing and consistent evidence that emerged from all these trials, our growing impression was that pregnancy-related MMs were more aggressive than the non-pregnancy-related ones and so we decided to check our files to see if there was any factual basis for this line of thought. Similar to some of the former trials, we also found the pregnancy group to have more advanced disease than the control group. The mean Breslow thickness for the pregnancy group was higher than the thickness for the control group (2.82 mm vs. 1.69 mm, respectively), although the difference did not reach a level of significance, probably due to the small trial group. There was a significantly higher percentage of positive nodes in the pregnancy group, and a greater mortality rate (of borderline significance) among these women compared to the controls. These findings are in contrast to the WHO-supported trials and the latest published trials. Although our results could be attributed to a delay in diagnosis and to our small study group, the aggressiveness of the pregnancy-related tumours, as demonstrated by patient number 9 (Table 1), must be taken into account: she had recurrent MM only 2 months after undergoing wide excision and SLNB. Patient number 10 in Table 1 is a 29-year-old African woman diagnosed as having a metastatised 12-mm MM of her left arm. MM is rare in black populations and is usually diagnosed in later stages than in non-black populations.31,32 A similar advanced-stage melanoma of a pregnant African-American woman was reported by Hu et al.33

Since clinical trials have not reached conclusive results, further investigation at the cellular level is all the more important. Several in vitro studies that have been published in recent years seem, however, only to add to the confusion. Duncan et al. used advanced monoclonal antibody staining techniques and reported finding no E2 or progesterone receptors in 14 pregnancy-related MM. Other in vitro studies showed a variation of hormonal factors. Morvillo et al. recently reported a lack of E2 or progesterone receptors, but they did demonstrate the presence of androgen receptors on two human melanoma cell lines. They showed that testosterone, E2 and progesterone significantly stimulated cell proliferation in those cells. Kanda and Watanabe, however, found that melanoma cell lines with hormone receptors were down-regulated by 17 beta-oestradiol, progesterone and testosterone, and that other cell lines lacking these receptors were not influenced by the hormones. Yet another in vitro study showed testosterone (DHT) and E2 to change nuclear morphology in melanoma cells,22 while Miller et al. noted that there were limited E2 receptors in MM (two out of 69 melanoma specimens). Finally, luteinising hormone-releasing hormone (LHRH) receptors were demonstrated in a BLM melanoma cell line that showed inhibited proliferation and reduced metastatic activity in response to an LHRH agonist.

Another question that had been addressed in several trials is the risk of recurrent MM in subsequent pregnancies. Mackie et al. compared pregnant MM patients to women with MM who had never been pregnant, were between pregnancies or had completed all planned pregnancies. They found no difference in survival between the latter three groups. Reintgen et al. compared 43 women who became pregnant within 5 years of being diagnosed as having stage 1 melanoma to a cohort of 2938 non-pregnant melanoma patients and found no effect of subsequent pregnancy on recurrence or survival. Since most recurrences of stage 1 melanoma occur within the first 2 years after excision,13,15 several authors recommend delaying the next pregnancy for 2–3 years after treatment.5,6,13,15,20 Survival seems to be mostly related to the stage of melanoma at diagnosis and whether there is ulceration.11,12 Based on these considerations, recommendations for

### Table 3

Summary of the published literature on melanoma and pregnancy

<table>
<thead>
<tr>
<th>First author</th>
<th>Melanoma and pregnancy (n)</th>
<th>Melanoma and no pregnancy (control) (n)</th>
<th>Breslow study group</th>
<th>Breslow control group</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reintgen11</td>
<td>58</td>
<td>585</td>
<td>1.9 ± 0.39 mm</td>
<td>1.51 ± 0.78 mm</td>
<td>No diff.</td>
</tr>
<tr>
<td>Slingluff12</td>
<td>100</td>
<td>86</td>
<td>2.17 mm</td>
<td>1.52 mm (P = 0.052)</td>
<td>No diff.</td>
</tr>
<tr>
<td>MacKie13</td>
<td>92</td>
<td>296</td>
<td>2.38 mm</td>
<td>1.71 mm (P = 0.002)</td>
<td>No diff.</td>
</tr>
<tr>
<td>Wong14</td>
<td>66</td>
<td>619</td>
<td>No diff.</td>
<td>No diff.</td>
<td>74% trial, 87% control (NS)</td>
</tr>
<tr>
<td>McManamy15</td>
<td>23</td>
<td>243</td>
<td>No diff.</td>
<td>No diff.</td>
<td>74% trial, 87% control (NS)</td>
</tr>
<tr>
<td>Travers16</td>
<td>45</td>
<td>420</td>
<td>2.28 mm</td>
<td>1.22 mm</td>
<td>No diff.</td>
</tr>
<tr>
<td>Darayanani17</td>
<td>46</td>
<td>368</td>
<td>1.7 mm</td>
<td>2.0 mm (NS)</td>
<td>No diff.</td>
</tr>
<tr>
<td>O’Meara18</td>
<td>412</td>
<td>2451</td>
<td>Localised disease, Preg. −0.77 mm</td>
<td>0.81 mm (NS)</td>
<td>No diff.</td>
</tr>
</tbody>
</table>

NS, not significant; Diff., difference; Preg., pregnancy group; y post., year postpartum.
treatment are similar to those of non-pregnant patients. Excisional biopsy under local anaesthesia poses little risk to either mother or foetus, and sentinel node biopsy using dye and lymphoscintigraphy is generally not contraindicated during pregnancy. Lloyd et al. of the St. George Healthcare NHS Trust Melanoma Unit, London, recommend the avoidance of lymphoscintigraphy before 30 weeks of gestation, and usually to postpone SLNB until delivery. We chose to avoid lymphoscintigraphy during pregnancy and to perform the SLNB with only intra-operative dye injection.

Several other aspects of the melanoma—hormone issue have also been addressed by a number of authors. One is hormone replacement therapy (HRT), which does not seem to be a risk factor for melanoma, and MacKie et al. reported that the use of HRT after treatment for stage 1 melanoma does not have adverse effects on patient outcome. Another is the use of oral contraceptives, which also seems to have no effect on the incidence of MM. The effect of high-dose hormones, such as in the case of protocols for in vitro fertilisation or intrauterine insemination, on the incidence of melanoma has not yet been addressed in the literature.

The long-held belief that MM is a hormone-sensitive tumour and one that is affected by pregnancy was later rejected for not having any scientific basis. Our current results indicate that there is a significant relation between pregnancy, more advanced disease stage and greater mortality. We have shown that MM does seem to be influenced by pregnancy in certain cases, in contradiction to the findings of controlled trials that concluded that there is no greater risk of MM during pregnancy and that thicker tumours in pregnant women are most likely related to later diagnosis stemming from the woman’s expectation of changes to occur in her pigmentation during pregnancy, the lack of awareness of an existing lesion or delay of medical attention due to fear. Only two of the controlled trials in the literature were prospective, and the data that emerged from in vitro studies were inconclusive. While the lack of effect of HRT and contraceptive pills on the course of MM has been established, the effect of increasingly popular hormonal fertility treatments on MM is unknown and warrants investigation.

Study limitations

We recognise that a series of only 11 MM patients diagnosed during pregnancy or shortly after delivery precludes our arriving at firm conclusions about a direct link between MM and pregnancy. We can, however, hope to raise the level of awareness of MM in pregnancy for the sake of early detection and prompt treatment: new suspected lesions or changing moles should be evaluated with an excisional biopsy under local anaesthesia and SLNB should be performed when MM is discovered. We endorse the recommendation that a subsequent pregnancy should be delayed for at least 2 years after treatment.

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Conflict of interest

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