

# 26 Pregnancy and melanoma (including hormone replacement therapy and oral contraceptives)

## 26.1 Naevi and pregnancy

Pregnancy increases melanocytic activity, causing hyperpigmentation as observed in the linea nigra, chloasma and areolar pigmentation. There is little evidence that significant changes in naevi occur during pregnancy.<sup>1–3</sup> It is therefore recommended that any naevus that changes during pregnancy and has other features suggestive of melanoma should be investigated. An excision biopsy can be performed safely using local anaesthetic during pregnancy with the obstetrician's and patient's consent.<sup>4</sup>

Evidence summary	Level	Reference
Naevi do not usually undergo significant changes during pregnancy	III–3	1–3

Recommendation	Grade
1. Any naevus that changes during pregnancy and/or has other features suggestive of melanoma be investigated	C

## 26.2 Melanoma and pregnancy

Melanoma is the most common malignancy in women of 25–29 years and internationally, it has been estimated that about 35% of women with melanoma are of child-bearing age.<sup>9</sup> Malignancy in pregnancy is reported in 1 in 1000 gestations, with malignant melanoma 8% of the total (1970s data).<sup>10</sup> Incidence of melanoma during pregnancy is estimated at 1 per 40,000 pregnancies<sup>11</sup> or 2.6 to 2.8 per 1000 pregnancies.<sup>9,12</sup>

Pregnancy does not increase the subsequent risk of having melanoma.<sup>13</sup> and there is no increased risk of melanoma developing during pregnancy.<sup>14</sup>

There is no significant difference in survival in pregnant patients diagnosed with melanoma or stage I disease.<sup>15–24</sup> The prognosis of pregnant women with melanoma is still dependent on tumour thickness and ulceration status.<sup>25</sup>

Pregnant women who present with regional or metastatic melanoma do not appear to have a worse prognosis.<sup>26,27</sup>

The effect of previous pregnancy on the prognosis of women subsequently diagnosed with melanoma is conflicting. One study showed previously pregnant women had a superior survival advantage (in particular those with stage I disease or women older than 50 years).<sup>28</sup> In another study there was a more favourable prognosis associated with five or more prior pregnancies.<sup>29</sup> Other studies showed no effect of prior pregnancy on the prognosis of melanoma in stage I disease.<sup>19,30,31</sup> But one study of stage II patients,<sup>30</sup> showed a significantly lower survival rate for pregnant patients and parous women who had experienced activation of the lesion in previous pregnancies.

There appears to be no effect of subsequent pregnancy on the prognosis of melanoma.<sup>15,19</sup>

Evidence summary	Level	Reference
There appears to be no relationship between pregnancy and risk of, or survival from melanoma	III-3	25

### Recommendation

	Grade
2. Melanoma in a pregnant woman be treated according to tumour thickness and ulceration, that is, as for a non-pregnant woman	<b>C</b>

## 26.3 Pregnancy after the diagnosis of melanoma

There are no standard, defined guidelines for patients who wish to become pregnant after the diagnosis and treatment of melanoma, but the consensus is to recommend that women avoid pregnancy for two to five years after the diagnosis of high-risk melanoma, whether or not the melanoma occurred during pregnancy,<sup>32</sup> as most recurrences are diagnosed within this period. Those with < 0.5mm thick melanoma have a 1–3% risk of recurrence within five years, while those with > 4mm thick melanoma have a risk of recurrence of up to 50% within two years. However, it is not completely predictable who will develop recurrent disease and each patient should be approached individually, with the patient ultimately making her own informed decision.<sup>33</sup>

### Recommendation

	Grade
3. Women of childbearing age who are within five years of primary treatment of a high risk melanoma should be fully informed of their prognosis when considering pregnancy	<b>C</b>

## 26.4 Treatment of melanoma during pregnancy

The treatment of primary melanoma does not differ because a woman is pregnant. The status of the sentinel node is one of the most important prognostic indicators for patients with clinically localised melanoma.<sup>34</sup> Lymphoscintigraphy is probably

safe in pregnant women<sup>5-8</sup> and they may be offered a SNB using technetium after careful counselling about the safety and efficacy of this procedure.<sup>35</sup> The use of the patent blue V dye does have a 1% risk of an allergic reaction. Its safety in pregnancy is unknown. Its use is therefore not recommended in SNB in pregnant women. The timing of the surgery is important: near term, the clinician would probably defer treatment until after delivery, but if the melanoma is diagnosed in the first or second trimester the decision is more difficult.

These patients and pregnant patients with metastatic melanoma should probably be treated in the setting of a comprehensive cancer centre.

Evidence summary	Level	Reference
Sentinel node biopsy is safe using technetium only in pregnant women.	III-3	5-8

### Recommendations

	Grade
4. Sentinel node biopsy can be performed using only technetium in pregnant women	<b>B</b>
5. Pregnant women with thicker melanomas and nodal metastases be treated in consultation with specialised centres	<b>C</b>

## 26.5 Melanoma and hormone replacement therapy and the oral contraceptive pill

There is no convincing evidence that either hormone replacement therapy (HRT) or the use of the oral contraceptive pill (OCP) affects the natural history of melanoma.<sup>32,36-53</sup>

Age at menarche, age at menopause, or duration of menstrual life does not affect melanoma risk.<sup>32,37-40,46</sup>

Evidence summary	Level	Reference
The use of HRT or OCP does not affect the natural history of melanoma	III-3	32, 37-53
Age at menarche, age at menopause, or duration of menstrual life does not affect melanoma risk	III-3	32, 37-40, 46

### Recommendation

	Grade
6. Hormone replacement therapy and oral contraceptives are not contraindicated in women who have had melanoma	<b>C</b>

## References

1. Grin CM, Rojas AI, Grant-Kels JM. Does pregnancy alter melanocytic nevi? *J Cutan Pathol* 2001; 28(8):389–392.
2. Katz VL, Farmer RM, Dotters D. Focus on primary care: from nevus to neoplasm: myths of melanoma in pregnancy. *Obstet Gynecol Surv* 2002; 57(2):112–119.
3. Gunduz K, Koltan S, Sahin MT, Filiz E. Analysis of melanocytic naevi by dermoscopy during pregnancy. *J Eur Acad Dermatol Venereol* 2003; 17(3):349–351.
4. MacKelfresh J, Chen SC, Monthrope YM. Pregnancy and changes in melanocytic nevi. *Obstet Gynecol* 2005; 106(4):857–860.
5. Keleher A, Wendt R, III, Delpassand E, Stachowiak AM, Kuerer HM. The safety of lymphatic mapping in pregnant breast cancer patients using Tc-99m sulfur colloid. *Breast J* 2004; 10(6):492–495.
6. Morita ET, Chang J, Leong SP. Principles and controversies in lymphoscintigraphy with emphasis on breast cancer. *Surg Clin North Am* 2000; 80(6):1721–1739.
7. Gentilini O, Cremonesi M, Trifiro G, Ferrari M, Baio SM, Caracciolo M et al. Safety of sentinel node biopsy in pregnant patients with breast cancer. *Ann Oncol* 2004; 15(9):1348–1351.
8. Mondil MM, Cuenca RE, Ollila DW, Stewart JH, Levine EA. Sentinel lymph node biopsy during pregnancy: initial clinical experience. *Ann Surg Oncol* 2007; 14(1):218–221.
9. Pavlidis NA. Coexistence of pregnancy and malignancy. *Oncologist* 2002; 7(4):279–287.
10. Potter JF, Schoeneman M. Metastasis of maternal cancer to the placenta and fetus. *Cancer* 1970; 25(2):380–388.
11. Stephenson HE, Jr., Terry CW, Lukens JN, Shively JA, Busby WE, Stoeckle HE et al. Immunologic factors in human melanoma “metastatic” to products of gestation (with exchange transfusion of infant to mother). *Surgery* 1971; 69(4):515–522.
12. Smith RS, Randall P. Melanoma during pregnancy. *Obstet Gynecol* 1969; 34(6):825–829.
13. Karagas MR, Zens MS, Stukel TA, Swerdlow AJ, Rosso S, Osterlind A et al. Pregnancy history and incidence of melanoma in women: a pooled analysis. *Cancer Causes Control* 2006; 17(1):11–19.
14. Houghton AN, Balch CM. Treatment for advanced melanoma. In: Balch CM, Houghton AN, Milton GW, et al, editors. *Cutaneous Melanoma*. Philadelphia: Lippincott, 1992.
15. Reintgen DS, McCarty KS, Jr., Vollmer R, Cox E, Seigler HF. Malignant melanoma and pregnancy. *Cancer* 1985; 55(6):1340–1344.
16. McManamny DS, Moss AL, Pocock PV, Briggs JC. Melanoma and pregnancy: a long-term follow-up. *Br J Obstet Gynaecol* 1989; 96(12):1419–1423.
17. Wong JH, Sterns EE, Kopald KH, Nizze JA, Morton DL. Prognostic significance of pregnancy in stage I melanoma. *Arch Surg* 1989; 124(10):1227–1230.
18. Slingluff CL, Jr., Reintgen DS, Vollmer RT, Seigler HF. Malignant melanoma arising during pregnancy. A study of 100 patients. *Ann Surg* 1990; 211(5):552–557.
19. MacKie RM, Bufalino R, Morabito A, Sutherland C, Cascinelli N. Lack of effect of pregnancy on outcome of melanoma. For The World Health Organization Melanoma Programme. *Lancet* 1991; 337(8742):653–655.
20. Lens MB, Rosdahl I, Ahlbom A, Farahmand BY, Synnerstad I, Boeryd B et al. Effect of pregnancy on survival in women with cutaneous malignant melanoma. *J Clin Oncol* 2004; 22(21):4369–4375.
21. Silipo V, De Simone P, Mariani G, Buccini P, Ferrari A, Catricala C. Malignant melanoma and pregnancy. *Melanoma Res* 2006; 16(6):497–500.
22. Daryanani D, Plukker JT, De Hullu JA, Kuiper H, Nap RE, Hoekstra HJ. Pregnancy and early-stage melanoma. *Cancer* 2003; 97(9):2248–2253.
23. Stukel TA, Demidenko E, Dykes J, Karagas MR. Two-stage methods for the analysis of pooled data. *Stat Med* 2001; 20(14):2115–2130.

24. O'Meara AT, Cress R, Xing G, Danielsen B, Smith LH. Malignant melanoma in pregnancy. A population-based evaluation. *Cancer* 2005; 103(6):1217–1226.
25. Balch CM, Soong SJ, Gershenwald JE, Thompson JF, Reintgen DS, Cascinelli N et al. Prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint Committee on Cancer melanoma staging system. *J Clin Oncol* 2001; 19(16):3622–3634.
26. Houghton AN, Flannery J, Viola MV. Malignant melanoma of the skin occurring during pregnancy. *Cancer* 1981; 48(2):407–410.
27. Holly EA. Melanoma and pregnancy. *Recent Results Cancer Res* 1986; 102:118–126.
28. Hersey P, Morgan G, Stone DE, McCarthy WH, Milton GW. Previous pregnancy as a protective factor against death from melanoma. *Lancet* 1977; 1(8009):451–452.
29. Bork K, Brauninger W. Prior pregnancy and melanoma survival. *Arch Dermatol* 1986; 122(10):1097.
30. Shiu MH, Schottenfeld D, Maclean B, FORTNER JG. Adverse effect of pregnancy on melanoma: a reappraisal. *Cancer* 1976; 37(1):181–187.
31. Lederman JS, Sober AJ. Effect of prior pregnancy on melanoma survival. *Arch Dermatol* 1985; 121(6):716.
32. Holly EA, Weiss NS, Liff JM. Cutaneous melanoma in relation to exogenous hormones and reproductive factors. *J Natl Cancer Inst* 1983; 70(5):827–831.
33. Schwartz JL, Mozurkewich EL, Johnson TM. Current management of patients with melanoma who are pregnant, want to get pregnant, or do not want to get pregnant. *Cancer* 2003; 97(9):2130–2133.
34. Gershenwald JE, Thompson W, Mansfield PF, Lee JE, Colome MI, Tseng CH et al. Multi-institutional melanoma lymphatic mapping experience: the prognostic value of sentinel lymph node status in 612 stage I or II melanoma patients. *J Clin Oncol* 1999; 17(3):976–983.
35. Schwartz GF, Giuliano AE, Veronesi U. Proceedings of the consensus conference on the role of sentinel lymph node biopsy in carcinoma of the breast April 19 to 22, 2001, Philadelphia, Pennsylvania. *Hum Pathol* 2002; 33(6):579–589.
36. Karagas MR, Stukel TA, Dykes J, Miglionico J, Greene MA, Carey M et al. A pooled analysis of 10 case-control studies of melanoma and oral contraceptive use. *Br J Cancer* 2002; 86(7):1085–1092.
37. Holman CD, Armstrong BK, Heenan PJ. Cutaneous malignant melanoma in women: exogenous sex hormones and reproductive factors. *Br J Cancer* 1984; 50(5):673–680.
38. Gallagher RP, Elwood JM, Hill GB, Coldman AJ, Threlfall WJ, Spinelli JJ. Reproductive factors, oral contraceptives and risk of malignant melanoma: Western Canada Melanoma Study. *Br J Cancer* 1985; 52(6):901–907.
39. Green A, Bain C. Hormonal factors and melanoma in women. *Med J Aust* 1985; 142(8):446–448.
40. Zanetti R, Franceschi S, Rosso S, Bidoli E, Colonna S. Cutaneous malignant melanoma in females: the role of hormonal and reproductive factors. *Int J Epidemiol* 1990; 19(3):522–526.
41. Beral V, Ramcharan S, Faris R. Malignant melanoma and oral contraceptive use among women in California. *Br J Cancer* 1977; 36(6):804–809.
42. Hannaford PC, Villard-Mackintosh L, Vessey MP, Kay CR. Oral contraceptives and malignant melanoma. *Br J Cancer* 1991; 63(3):430–433.
43. Adam SA, Sheaves JK, Wright NH, Mosser G, Harris RW, Vessey MP. A case-control study of the possible association between oral contraceptives and malignant melanoma. *Br J Cancer* 1981; 44(1):45–50.
44. Palmer JR, Rosenberg L, Strom BL, Harlap S, Zauber AG, Warshauer ME et al. Oral contraceptive use and risk of cutaneous malignant melanoma. *Cancer Causes Control* 1992; 3(6):547–554.
45. Le MG, Cabanes PA, Desvignes V, Chanteau MF, Mlika N, Avril MF. Oral contraceptive use and risk of cutaneous malignant melanoma in a case-control study of French women. *Cancer Causes Control* 1992; 3(3):199–205.

46. Osterlind A, Tucker MA, Stone BJ, Jensen OM. The Danish case-control study of cutaneous malignant melanoma. III. Hormonal and reproductive factors in women. *Int J Cancer* 1988; 42(6):821–824.
47. Helmrich SP, Rosenberg L, Kaufman DW, Miller DR, Schottenfeld D, Stolley PD et al. Lack of an elevated risk of malignant melanoma in relation to oral contraceptive use. *J Natl Cancer Inst* 1984; 72(3):617–620.
48. Bain C, Hennekens CH, Speizer FE, Rosner B, Willett W, Belanger C. Oral contraceptive use and malignant melanoma. *J Natl Cancer Inst* 1982; 68(4):537–539.
49. Holly EA, Cress RD, Ahn DK. Cutaneous melanoma in women. III. Reproductive factors and oral contraceptive use. *Am J Epidemiol* 1995; 141(10):943–950.
50. Westerdahl J, Olsson H, Masback A, Ingvar C, Jonsson N. Risk of malignant melanoma in relation to drug intake, alcohol, smoking and hormonal factors. *Br J Cancer* 1996; 73(9):1126–1131.
51. Beral V, Evans S, Shaw H, Milton G. Oral contraceptive use and malignant melanoma in Australia. *Br J Cancer* 1984; 50(5):681–685.
52. Holly EA, Cress RD, Ahn DK. Cutaneous melanoma in women: ovulatory life, menopause, and use of exogenous estrogens. *Cancer Epidemiol Biomarkers Prev* 1994; 3(8):661–668.
53. Persson I, Yuen J, Bergkvist L, Schairer C. Cancer incidence and mortality in women receiving estrogen and estrogen-progestin replacement therapy--long-term follow-up of a Swedish cohort. *Int J Cancer* 1996; 67(3):327–332.