

Skin cancer and pregnancy

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ABSTRACT

Skin cancer during pregnancy is common, with malignant melanoma being the most frequent and the most aggressive. Any pigmented skin lesion that suffers changes should be examined by a specialist and if considered high-risk, biopsy should be performed right away and not postponed as it is thought to be safe during pregnancy. Recent studies showed that it has the same outcome compared with the non-pregnant state, if diagnosed and treated as soon as possible. Diagnosis of skin cancer, including melanoma, does not necessarily require an early delivery or termination of pregnancy, if in the first trimester, except for pregnant patients with poor prognosis (advanced disease) that need more aggressive, systemic treatment. Management needs to be established in specialized centers with a multidisciplinary team. Monitoring should be performed by a team consisting of an obstetrician, a maternal-fetal medicine specialist, a neonatologist, and an oncologist.

Keywords: skin cancer, melanoma, pregnancy, malignancy, management, diagnosis

INTRODUCTION

Skin cancer can be subdivided in malignant melanoma (MM), non melanoma skin cancer (NMSC), with basal cell carcinoma (BCC) or squamous cell carcinoma (SCC) being the predominant (95%) forms of NMSC [1]. Actinic keratoses (AKs) are pre-malignant lesions that have the ability to develop into invasive SCC, are frequently diagnosed and represent a good dose meter for chronic sun exposure [2]. Mortality is low with 3-5 deaths/1000 cases [1]. They are clearly related to sun exposure and appear on exposed areas such as the face. Ultraviolet (UV) exposure is the main modifiable risk factor for NMSC and ongoing photoprotection would prevent the genetic and structural epidermal changes that lead to cancer [3]. Even though these lesions are not as common during pregnancy, chronic sun exposure should be avoided since childhood to minimize the risk.

Malignant melanoma (MM) is common in the young population given that one third of women affected are of fertile age [4]. Pregnant women are usually healthy individuals with fewer risk factors for cancer, but sun exposure is more relevant in this age group, so it is not surprising that malignant melanoma is the most common malignancy during pregnancy [5]. During the last decades there were growing concerns regarding the prognosis and possible increased incidence of melanoma during pregnancy caused by the immunosuppression implicated in the maternal-fetal tolerance that could possibly support tumor progression. Also, there was hypothesized that MM is a hormonal-induced tumor giving that the skin normally changes its pigmentation with the appearance of linea nigra, darkening of the periareolar skin or other areas with increased pigmentation (axillae, genitalia, perineum, anus, inner thighs, and the neck). Knowing that

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nowadays women delay their pregnancy and age is a risk factor, it should be expected that the incidence of MM in pregnancy will increase over time.

Contrary to common belief, MM is not associated with cumulative sun exposure, as with NMSC, but with intense, intermittent sun exposure and sunburns [6]. Keratinocytes usually undergo apoptosis after severe UV radiation which causes DNA damage, but melanocytes resist this radiation and mutate, possibly causing cancer. Some phenotypic features are also described as risk factors, such as red or blond hair, light eye color, presence of a large number of melanocytic nevi (> 50) and presence of atypical melanocytic nevi [7].

Many studies demonstrated that there are no worse outcomes or that pregnant women are not more susceptible to skin cancer (studies mainly involved MM) than non pregnant women [8], with the sole main implication of the delayed diagnosis and reluctance of adequate treatment during the gravid state.

METHODS

A systematic literature electronic search for reviews and guidelines was undertaken using PubMed and the official websites of Dermatology, Oncology and Obstetrics and Gynecology associations. Search words were "skin cancer", "melanoma", "pregnancy", "pregnancy-associated melanoma", "squamous cell carcinoma", "basal cell carcinoma". Publications were selected based on quality evaluation and year of publication. The sources used are mentioned in the References section.

CLINICAL EVALUATION AND DIAGNOSIS

BCC is the most diagnosed skin cancer overall. It is not usually found in women of fertile age, but with increasing sun exposure and rising popularity of tanning beds, the age of diagnosis is declining. It has a slow-growing, non-aggressive nature, but delayed treatment can result in significant disfigurement and morbidity through local invasion, with destruction of skin, bone, and cartilage. Metastasis is rare. Fair pigmentation and reduced UV protection have been shown to confer susceptibility to BCC. Clinical features vary with histologic subtype. It can be nodular or superficial as nonaggressive types or aggressive subtypes such as infiltrative, micronodular and mixed [9].

The less common form of cancer, SCC, has a higher ability to cause metastasis and is causing higher mortality. The most relevant risk factor is also chronic exposure to ultraviolet radiation (UV) [10]. These lesions can present in various ways: scaly-like, centrally ulcerated, or erythematous,

and with irregular borders that can easily bleed; they can develop from preexisting actinic keratoses. Pregnant women are not at increased risk, but any form of systemic immunosuppressive drugs elevate the risk and metastasis are more likely [11].

High melanocytic activity and hyperpigmentation can be physiologic during gestation: melasma, linea nigra, genital and areolar darkening. These conditions are caused by increased levels of estrogen, progesterone, beta- and alpha-melanocyte stimulating hormone and beta endorphins [12]. There can be subtle changes on melanocytic nevi located on breast and abdomen due to skin stretching, but it is important not to disregard any major alteration of melanocytic lesions as physiological during pregnancy. Delaying the diagnosis of melanoma during gestation because of a shared misconception of the patient and/or her physician that darkening and changing of a nevus is normal in pregnancy could be the main factor that could impact prognosis (survival and disease-free interval). Thus, a correct and prompt diagnosis is key in these cases, as for the non-pregnant patients.

A useful tool when evaluating pigmented lesions as potential lesions is the ABCDE mnemonic (asymmetry, irregular border, uneven color, diameter > 6 mm, evolving – change in size, shape, color) which should be well-known by all physicians, even if they are not dermatologists. This should at least raise the suspicion and refer the case to a specialist.

The noninvasive diagnostic tool that can be offered safely during gestation is dermoscopy and it improves diagnostic accuracy. It allows recognition of an early-stage disease when identifying the specific dermoscopic criteria [13]. If the suspicion for malignancy is high, an excisional biopsy with histopathological analysis should be performed promptly. Use of local anesthesia (lidocaine) is thought to be safe during gestation and the addition of epinephrine has also been endorsed as safe during pregnancy [14,15]. If a wide local excision is required, it is preferable to happen under local anesthesia, if possible. If it is to be performed under general anesthesia, the procedure should be coordinated with the obstetrician, anesthesiologist, and neonatologist.

Melanoma is an aggressive form of skin cancer and is the most aggressive form of cancer during pregnancy. Once the lesion has expanded beyond the boundary of the basement membrane and invades the dermis, it has the potential to metastasize. Regional metastasis usually occurs in the nearby skin, subcutaneous tissue or lymph nodes. Distant metastases in patients suffering from melanoma are usually found in the skin, lung, brain, liver, bone, and bowels. Metastasis to the lung is more frequent and often the first clinically site of internal metastasis [16].

Surgical treatment with margin control is the cornerstone of management for BCC and SCC. There is no clear cut-off for excision margins, but in practice, 4-5 mm for low-risk and 6-13 mm for high-risk SCC should be the aim [11] and for BCC, for low-risk (< 2 cm) – 3-4 mm and for high-risk BCC – 6-10 mm [9].

For melanoma, management strategies should be decided upon tumoral stage and gestational age. Stage of the disease is a main prognostic factor and a central step to further coordinate the therapeutic process, so every effort should be concentrated towards staging the disease, taking into consideration the pregnant state of the patient, but not delaying it by any means. One possible explanation of MM having a worse prognosis during pregnancy is the delayed diagnosis and management [17]. TNM staging system is used and this system describes four stages of melanoma based on the primary tumor, regional lymph nodes and metastasis classifications [16]. Stage I and II are considered local disease, while stage III and IV (with lymph nodes invasion or metastasis) are advanced disease.

Sentinel lymph node biopsy (SLNB) is technically safe after 14 weeks of pregnancy. It is mainly recommended for MM, as for SCC the relevance is still not clearly established. Most experts recommend using technetium 99m, considering that fetal exposure is minimal, and avoiding blue dye due to its anaphylaxis risk (<1%) and possible teratogenic effects on the unborn child [17]. The problem is that most cases require general anesthesia, facing the same challenges as lymphadenectomy. The second trimester is safest to perform the intervention and during the late third trimester, it should be preferably postponed after delivery [18]. For completing disease staging, ultrasound examination, chest X-ray with appropriate shielding and MRI imaging are safe during pregnancy. Gadolinium use should be limited for cases where benefits clearly outweigh possible risks. Recent data show that other imaging techniques (including CT scans) and nuclear medicine examinations using technetium 99m are acceptable, but iodine should be used only if truly necessary in order to get relevant additional information [18].

MANAGEMENT

Pregnancy-associated cancer is a difficult clinical situation to manage, having to take into consideration the well-being of both mother and fetus. This adds complexity to the treatment recommendations, but it is important to underline that there are still many treatment options available and considered safe during pregnancy, so delaying treatment out of fear of hurting the fetus is unacceptable.

This could have a drastic impact on the outcome and survival of the patient, given that melanoma, in particular, is a very aggressive cancer and time is very important during management. Also, it is worth mentioning that there is insufficient evidence available, and protocols are mainly based on retrospective studies or case presentations with limited follow-up. So ideally, these complex cases should be managed in specialized experienced centers and discussed in multidisciplinary meetings with medical oncologists, obstetricians, surgeons, and neonatologists.

Management of local disease for BCC, SCC, and stage I and II melanoma does not differ for pregnant women. Biopsies and wide local excision are considered safe. Sentinel lymph node biopsy can be performed, if necessary. The only mention is regarding radiotherapy, that should be postponed, if possible, until postpartum. If it is needed and the tumor site is far away from the uterus, it can be recommended, carefully taking into consideration the risks and benefits [19].

For advanced disease, mainly melanoma, stage III and IV, systemic chemotherapy should be considered, but not be administered in the first trimester, due to the higher risk of miscarriage and congenital malformations. Termination of pregnancy could be offered in patients who need chemotherapy administration in the first trimester. Patients with metastatic disease during the second or third trimester, interferon- α may be offered due to the lack of safety data of ipilimumab, vemurafenib, dabrafenib, trametinib and cobimetinib, during pregnancy [20].

TABLE 1. Treatment options for the pregnant patient with melanoma – adapted from NCCN guidelines and [21]

	First trimester	Second trimester	Third trimester
Stage 0, IA, IB	WLE+/-SLND	WLE+/-SLND	WLE+/-SLND
Stage IIA, IIB, IIC	WLE+/-SLND +/-Clinical trial or Observation	WLE+/-SLND +/-Clinical trial or Observation	WLE+/-SLND +/-Clinical trial or Observation +/- RT postpartum
Stage III	Surveillance	Surveillance or CLND or TLND +/- systemic treatment	Surveillance or CLND or TLND +/- systemic treatment
Stage IV	Elective termination of pregnancy and tailored treatment	Tailored treatment and induction of labor when fetus viable	Tailored treatment and induction of labor when fetus viable

WLE – wide local excision, SLND – sentinel lymph node biopsy, RT – radiotherapy, CLND – complete lymph node dissection, TLND – therapeutic lymph node dissection

A pregnant patient with cancer diagnosis should always be considered as high risk and regular fetal monitoring with ultrasound biometry and Doppler

assessment should be performed [13]. The placenta should always be carefully evaluated for micro-metastases in case of MM, melanoma being the most common neoplasm involving the fetus and the placenta [22].

CONCLUSIONS

Skin cancer is common during pregnancy, melanoma being the most common and the most aggressive

malignancy in pregnancy. Evaluation and treatment should not be delayed and staging should determine further steps. Most of the diagnostic tools can be performed safely. Any suspect lesion should be biopsied as soon as possible. While local disease has an accessible management with surgical resection being the mainstay of treatment, metastatic disease should have a multidisciplinary approach. Immunotherapy or target therapy are not recommended during pregnancy.

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REFERENCES

- Demers AA, Nugent Z, Mihalciou C, et al. Trends of nonmelanoma skin cancer from 1960 through 2000 in a Canadian population. *J Am Acad Dermatol.* 2005;53:320-328.
- Holmes C, Foley P, Freeman M, Chong AH. Solar keratosis: epidemiology, pathogenesis, presentation, and treatment. *Australas J Dermatol.* 2007;48:67-74.
- Barber K, Searles GE, Vender R, Teoh H, Ashkenas J; Canadian Non-melanoma Skin Cancer Guidelines Committee. Non-melanoma Skin Cancer in Canada. Chapter 2: Primary Prevention of Non-melanoma Skin Cancer. *J Cutan Med Surg.* 2015 May-Jun;19(3):216-26.
- Lens M, Bataille V. Melanoma in relation to reproductive and hormonal factors in women: current review on controversial issues. *Cancer Causes Control.* 2008; 19:437-442.
- Andersson TM, Johansson AL, Fredriksson I, Lambe M. Cancer during pregnancy and the postpartum period: A population-based study. *Cancer.* 2015 Jun 15;121(12):2072-7.
- Elwood JM, Gallagher RP, Hill GB, Pearson JC. Cutaneous melanoma in relation to intermittent and constant sun exposure – the Western Canada Melanoma Study. *Int J Cancer.* 1985 Apr 15;35(4):427-33.
- Swetter S, Geller AC. Melanoma: Clinical features and diagnosis. Available at: https://www.uptodate.com/contents/melanoma-clinical-features-and-diagnosis?search=melanoma&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1.
- Driscoll MS, M. K.-K. Pregnancy and melanoma. *J Am Acad Dermatol.* 2016;75(4):669-678.
- Zloty D, Guenther LC, Sapijaszko M, Barber K, Claveau J, Adamek T, Ashkenas J; Canadian Non-melanoma Skin Cancer Guidelines Committee. Non-melanoma Skin Cancer in Canada Chapter 4: Management of Basal Cell Carcinoma. *J Cutan Med Surg.* 2015 May-Jun;19(3):239-48.
- Madan V, Lear JT, Szeimies RM. Non-melanoma skin cancer. *Lancet.* 2010;375(9715):673-685.
- Sapijaszko M, Zloty D, Bourcier M, Poulin Y, Janiszewski P, Ashkenas J; Canadian Non-melanoma Skin Cancer Guidelines Committee. Non-melanoma Skin Cancer in Canada Chapter 5: Management of Squamous Cell Carcinoma. *J Cutan Med Surg.* 2015 May-Jun; 19(3):249-59.
- Tyler KH. Physiological skin changes during pregnancy. *Clin Obstet Gynecol.* 2015 Mar;58(1):119-24.
- Conforti C, Giuffrida R, Vezzoni R, Resende FSS, di Meo N, Zalaudek I. Dermoscopy and the experienced clinicians. *Int J Dermatol.* 2019 Jun 20.
- Kouba DJ, LoPiccolo MC, Alam M, Bordeaux JS, Cohen B, Hanke CW, et al. Guidelines for the use of local anesthesia in office-based dermatologic surgery. *J Am Acad Dermatol.* 2016 Jun;74(6):1201-19.
- Murase JE, Heller MM, Butler DC. Safety of dermatologic medications in pregnancy and lactation: Part I. Pregnancy. *J Am Acad Dermatol.* 2014 Mar;70(3):401.e1-14; quiz 415.
- Balch CM, Gershenwald JE, Soong SJ, Thompson JF, Atkins MB, Byrd DR, et al. Final version of 2009 AJCC melanoma staging and classification. *J Clin Oncol.* 2009 Dec 20;27(36):6199-206.
- Still R, Brennecke S. Melanoma in pregnancy. *Obstet Med.* 2017 Sep;10(3):107-112.
- Zelin E, Conforti C, Giuffrida R, Deinlein T, di Meo N, Zalaudek I. Melanoma in pregnancy: certainties unborn. *Melanoma Manag.* 2020 Jul 30;7(3):MMT48.
- Peccatori FA, Azim HA Jr, Orecchia R, Hoekstra HJ, Pavlidis N, Kesic V, Pentheroudakis G; ESMO Guidelines Working Group. Cancer, pregnancy, and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2013 Oct;24 Suppl 6:vi160-70.
- Zagouri F, Dimitrakakis C, Marinopoulos S, Tsigginou A, Dimopoulos MA. Cancer in pregnancy: disentangling treatment modalities. *ESMO Open.* 2016 May 4;1(3):e000016.
- Jhaveri MB, Driscoll MS, Grant-Kels JM. Melanoma in pregnancy. *Clin Obstet Gynecol.* 2011 Dec;54(4):537-45.
- Alexander A, Samlowski WE, Grossman D, Bruggers CS, Harris RM, Zone JJ, Noyes RD, Bowen GM, Leachman SA. Metastatic melanoma in pregnancy: risk of transplacental metastases in the infant. *J Clin Oncol.* 2003 Jun 1;21(11):2179-86.