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PREGNANCY AND BORDERLINE PIGMENTED LESIONS OF THE SKIN

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Skin cancer melanoma or non-melanoma has an increasing incidence, without excluding the group of women of fertile age. In addition, skin cancer also bears a great burden on the quality of life of the patients and potentially also of their off-springs. The melanocyte derived lesions solely raised the question regarding the role of pregnancy in the nevi change and the potential risk for melanoma during pregnancy. There is substantial evidence that melanocytes present a response to the pregnancy hormones fluctuating levels. The keratinocyte cancers development seems to be associated to hormonal exposure as well. Although this non melanoma skin neoplasm represents a disease of old age, women complete their families later in life nowadays, thus the risk for keratinocyte cancers is elevated. Along with other risk behaviors such as tanning beds use during teenage increase the risk for pregnancy associated melanoma. Screening for skin cancer before, during and after pregnancy is a noninvasive maneuver, which can identify suspicious lesions. These lesions are usually excised leading to prevention of the undesired effects of a potential cancer during gestation.

Keywords: skin cancer, pregnancy, dermoscopy,. borderline melanocytic lesions melanoma, dermoscopy

INTRODUCTION

Pregnancy represents a period of modifications including growth and change in many organs, also including the largest organ: the skin [1].

Hormones, beta and alfa melanocyte-stimulating hormone, beta-endorphin and especially estrogen and progesterone, increase their levels during pregnancy and thus lead to various changes in the female body, skin included. It is of great importance to be able to recognize these physiological skin changes and to distinguish them from true skin disease [2].

Most women notice a generalized increment in the pigmentation of the skin during pregnancy and the change is more significant in women with darker skin types. Areas already pigmented have a tendency to become darker: the nipples, areolae, midline of the abdominal wall (linea nigra) and genital areas. This pigmentation usually fades after birth, but rarely to its previous color. The is a general observation in women regarding the increase in the size, number and activity of melanocytic nevi [2].

MELANOCYTIC NEVI AND PREGNANCY HORMONES

The pregnancy effect on nevi and malignant melanoma has encouraged much debate. Most clinical literature in this subject matter revolves around the skin hyperpigmentation and nevi darkening during pregnancy, followed by ulterior regression after birth. However, many of these reports are based on the patients' reports concerning size and color changes in nevi. Generally, the histologic comparison of nevus specimens from pregnant women and non-pregnant women have been unsuccessful to distinguish a significant difference in cytologic atypia. Nonetheless, one series concluded that there is an increasing trend including histopathological atypia in nevi from pregnant women [3]. A photographical, histological and clinical analysis of dysplastic nevus syndrome (DNS) using histopathology reports and clinical photographs documented macroscopic growth in nevi changes during pregnancy and also histopathological dysplasia. There were no such observations in pregnant patients without DNS [4-7].

Different theories and approaches were proposed to explain the interplay between hormones and changing nevi. The focal occurrence theory postulates that dysplasia of just one melanocyte may be the sole cause for the nevocytic alterations during gestation rather than a nest of melanocytes. This would further explain why the change is not always on clinical examination [4].

Epiluminescence microscopy techniques also known as dermoscopy (traditional or computerized) refined the evaluation process, allowing a much more objective and detailed analysis. This new imaging analysis revealed paramount changes such as disorganized architecture, increased vascularity or increased pigmentation (darker globules or thicker pigment network) in nevi of pregnant females [4].

Presently, the link between pregnancy and nevi remains uncovered. Its root traces back to the early 1950s, when the literature concluded that pregnancy associates an elevated risk for nevi malignant transformation [1,4]. Epidemiologic studies searching for tumor size and staging concluded the fact that there were no differences in survival rates of melanoma either in pregnant or non-pregnant women. Increased tumor thickness has been revealed in pregnant patients in some studies, but not always being statistically significant. Recently, pregnancy, more than one pregnancy and nevi changing during

recent gestation are linked to an elevated incidence of melanoma before 55 years old [8].

Clinical follow-up of nevi during pregnancy suggests there is a relationship between pregnancy and melanocytic responsiveness. In spite of this, no reports have successfully demonstrated an association between nevi and hormone responsiveness during pregnancy. The discovery of βeta estrogen receptor (β ER) and its presumptive role in estrogen signaling in the melanocytes promised to offer an explanation. In a study, nevus samples from pregnant women presented a variable response to estrogen. Typical nevi presented up-regulation of β ER; dysplastic nevi had a constant β ER activity. Down-regulation was recorded, surprisingly in congenital nevi [4].

The implications of an altered β ER expression during pregnancy represents a subject of interest. β ER from other estrogen-responsive tissues such as the uterus, mammary glands or even prostate inhibits cellular proliferation when stimulated by estrogen. α ER counteracts the effects of β ER. Subsequently, the predominant estrogen receptor in the tissue dictates whether cellular growth and proliferation or inhibition occurs [4]. The effects of β ER activity on melanoma cells and melanocytes, in the lack of presence of αER, are under investigation. However, there is increasing evidence that estrogen may have a protective role in women diagnosed with melanoma as they present a better prognosis than men, especially in early-stage melanoma [4].

Estrogen may play a protective and anti-invasive response in skin cancer cells, a mechanism that could block dermal and metastatic potential. Up-regulation of β ER could represent the body's intrinsic control mechanism with the role in preventing pro-oncogenic melanocytic progression in nevi when dealing with increased cellular atypia or in an estrogen elevated status such as pregnancy. Finally, the ERβ expression loss and its presumed inhibitory effects could promote melanoma transformation [4,9].

Mild histologic changes in melanocytic nevi could appear in pregnancy, but they do not correspond with a more threatening or malignant behavior. What is interesting, the histological characteristics were not different compared with male control groups (1).

Recent studies evaluating clinical (Figure 1, Figure 2) and dermoscopic changes in nevi (Figure 3, Figure 4, Figure 5) during pregnancy report either no change, or changes in size, pigment network, and/or vascular alterations that are reversible within approximately 12 months after delivery [4].

Dermoscopic changes during gestation include pigment lightening or darkening, pigment network reduced thickness and prominence, peripheral pigment globules, and increased vascularity (increased dotted or comma-shaped vascular structures (Table 1) [4,9]. All these modifications should be grouped into criteria.

There is insufficient evidence to distinguish a behavioral difference between dysplastic and normal melanocytic nevi during pregnancy, but closer patient follow-up in cases with dysplastic nevi is recommended. It is important to follow nevi changes during pregnancy with the help of the same criteria used in non-pregnant patients,

Figure 1. A 35 y.o. women in the 20th week of gestation presenting for many melaoncytic lesions on her back, which enlarged during pregnancy [Courtesy to dr. Virgina Chitu, Colentina Hospital, Bucharest]

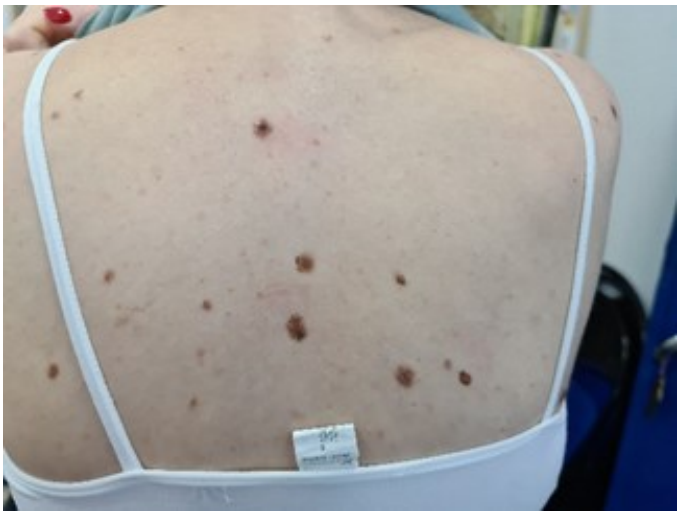
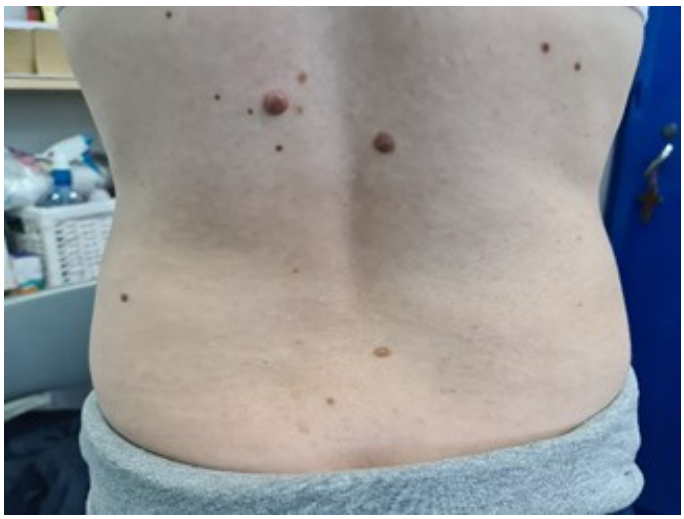


Figure 2. Papilomatous and common nevi during pregnancy [Courtesy to dr. Virgina Chitu, Colentina Hospital, Bucharest]



which includes pigment network assessment for asymmetry or atypia, blue-white veil, abnormal vascular structures, and appearance change or rapid growth. Lesions located on the abdomen and breasts, appear to be more susceptible to growth and also the peripheral pigment globules, secondary to skin stretching. Any lesion change disproportional to others should promptly raise caution. Suspicious lesions should undergo biopsy and subsequent treatment with excision if indicated. Severe atypia or swift changes of nevi should prompt for excision, while other atypical nevi may be excised post-partum [4,11].

MELANOMA AND PREGNANCY

Melanoma is a skin cancer responsible for 24-31% of all malignancies diagnosed during pregnancy, affecting one third of the women of childbearing age [4,11].

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Figure 3. Dermoscopy of melanocytic lesion showing symmetry, a mixt pattern bluish blotch centrally, pale dots and globules peripherally, suggestive of a combined nevus. The lesion was excised and the histopathology examination result was of an intradermic melanocytic nevus overlied by a blue nevus (Courtesy to dr. Virgina Chitu, Colentina Hospital, Bucharest)

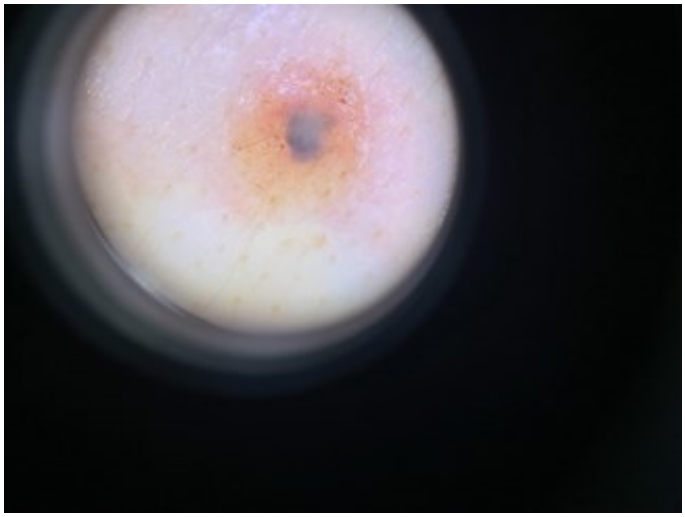
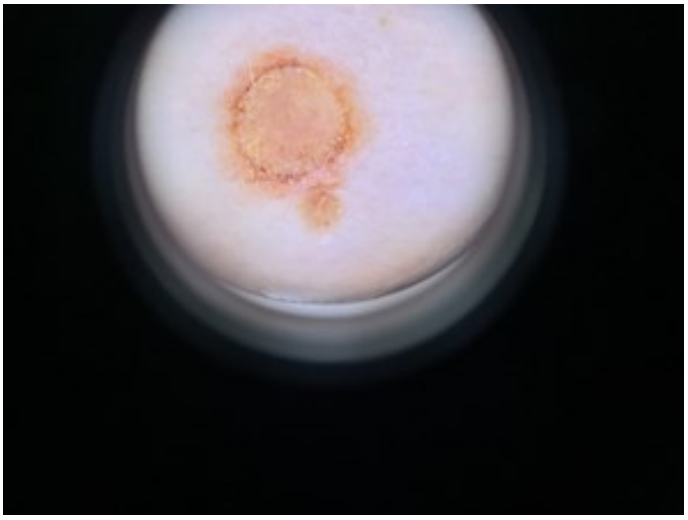


Figure 5. Dermoscopy of melanocytic combined lesion with a reticular pattern peripherally surrounding a papillomatous structure with light brown globules on its surface [Courtesy to dr. Virgina Chitu, Colentina Hospital, Bucharest]



While an advanced stage such as metastatic melanoma indicated a poor prognosis, the cutaneous affection could mean a potentially early diagnosis. Melanoma surveillance and early diagnosis start with patient self-examination and reporting, followed by a specialist evaluation [1].

Malignant melanoma (MM) represents the most common pregnancy-associated cancer. The incidence of melanoma in pregnancy ranges between 2.8 to 967 cases per 100,000 pregnancies [4,11].

Pregnancy-associated melanomas (PAMs) represent the melanoma tumors diagnosed during pregnancy and up to 1 year after birth. However, PAM remains a scarce phenomenon, making it hard to evaluate its due prognosis [4]. Mid -20th century reports demonstrate a diminished survival in PAM and a shorter disease-free interval, associated with a thicker MM index in pregnancy [10]. Presently there is no evidence suggesting that pregnancy-associated melanomas have a obscurer prognosis than other melanomas [12].

Figure 4. Dermoscopy of papilomatous round symmetric melanocytic lesion, with central blue-gray globules (Courtesy to dr. Virgina Chitu, Colentina Hospital, Bucharest)

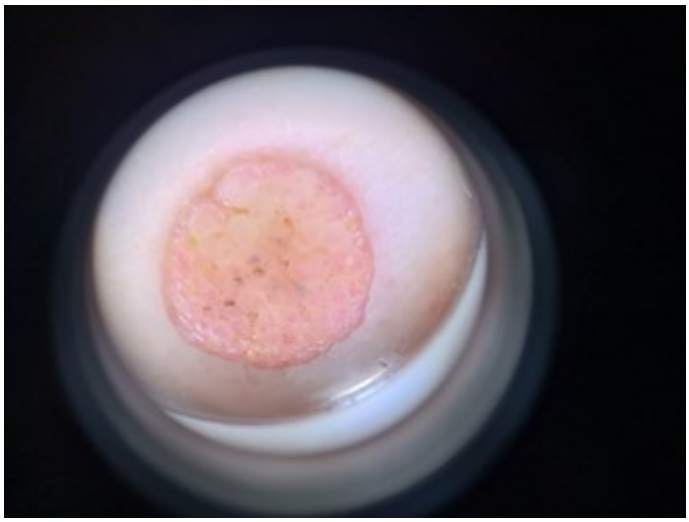


Table 1. Dermoscopic changes during gestation [10]

ermoscopic aspects	Percentage
Enlargement	55.6%
Pigmentation	
Hyperpigmentation	10.4%
Hypopigmentation	5.8%
Dermoscopic structures	
Network changes	23.2%
New dots/globules	12.4%
New vascular structures	3.2%
New streaks	1.7%
New structureless areas	1.0%

There are several studies pointing out that pregnancy has an adverse effect on melanoma prognosis. A British cohort study revealed no difference in Breslow thickness in pregnant groups compared to non-pregnant groups, the risk of death not being increased in lactating women [4,13].

On the other hand, the literature supports the notion that PAMs do not differ compared to non-pregnant MM in clinical or histopathologic characteristics, tumor depth, or overall maternal prognosis. Several studies suggest that there are actual similarities in the Breslow histologic subtypes, thickness or tumor location between pregnant and non-pregnant, age and stage-matching patients. As far as the histologic features are concerned, one group presented higher rates of peri-tumoral inflammation in the PAM group [13]. Some studies reveal that gestational hormones carry a negative role when it comes to melanoma [4,13]. The effect of fluctuating pregnancy

hormones levels in melanoma's development, progression, and overall patient survival remains controversial [13].

Nonetheless, recent research prompted that MM diagnosed during pregnancy is not poorly influenced by pregnancy-induced hormone levels. Actually, the b ER expression is known for its antitumor or pro-apoptotic effects, opposing the proliferative action of a ER. There has been demonstrated in vitro to have different expression in melanoma cell lines. Decreased bER expression has also been observed in increased Breslow thickness tumors and around lymphatic metastasis [13].

As far as other risk factors may be concerned, another group has revealed a decreased risk of MM in women with more than 15 years at menarche, irregular menstrual cycles, less than 48 years at menopause and also shorter ovulatory cycle, potentially suggesting a benefit in lower exposure to endogenous estrogen levels. In spite of this, the parity and ovulatory role in MM remains to be elucidated [13].

FETAL RISK

MM is the most common malignancy which has the ability to metastasize to the placenta and fetus [13]. Fetal involvement is always correlated with at least a microscopic invasion into the placenta [12,14]. Disease-free survival at 1 year of age for children is linked with a lack of metastatic involvement, being based on limited data. There are no evidence-based guidelines on monitoring an infant at risk, because metastatic MM to the fetus is a rarity [8]. Some authors suggest a gross and histologic examination of the placenta of women with known or suspected metastatic MM and also serial skin examinations, an abdominal ultrasound, and urine melanogen screening of infants [15].

CLINICAL MANAGEMENT

Before any surgical intervention, there is the evaluation of melanocytic lesions using total body photography and sequential digital dermoscopy in pregnant women [16,17]. Many studies concluded that this is the easiest and safest method for early detection of melanoma in pregnancy in high-risk patients [7,11].

The current standard of care refers to melanocytic lesions management in pregnant women similar to the one in non-pregnant women. Local anesthesia can be used with the minimum necessary amount of lidocaine 1% (pregnancy Category B) for shave, punch, or excisional biopsy, thus ensuring prompt diagnosis with no risks to mother or fetus. Once a histopathologic confirmation of MM is made, staging and prognosis, including establishing maternal and fetal risk involved in diagnostic procedures, as well as chemotherapy and immunotherapy [13,18,19].

KERATINOCYTE CANCERS

Keratinocyte cancers (KC), including basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), represent the leading invasive carcinoma [20,21].

Risk gender-specific patterns have not yet been studied enough, although behavioral gender patterns are traditionally thought to play a more significant role than biological differences. While sex-dependent steroids are known carcinogens involved in certain malignancies (e.g. breast, uterine, and prostate carcinoma), there are relatively few studies conducted on keratinocyte cancer [20].

A study found associations between both oral contraceptives (OC) and hormone replacement therapy (HRT) use and newly diagnosed SCC [9,20]. In addition, the use of OCs related to newly diagnosed BCC, and also both OC and HRT use were linked with aggressive BCC histology. No clear connections were revealed for endogenous estrogens related factors including timing of menarche, age of occurrence or type of menopause, and parity [20].

A large cohort study conducted in the United Kingdom found no link between use of OCs and "nonmelanoma skin cancer", presumed to be BCC and SCC summed. While this study presented the benefit of an enlarged sample size (n 529,875 cases), the study population was still young (aged between 25 and 39 years), therefore having had only 83 cases of KC [20].

Sex hormones increased physiologic exposure measured by the number of years ovulating, age at first pregnancy, and also the number of pregnancies, have been implied in certain cancers in women, although the effects on KC are not well documented. A single study reporting that an increased number of deliveries [10] was linked with a decreased incidence of BCC [13]. A meta-analysis found that older women at first pregnancy were at elevated risk of MM while having more than one child resulted in a diminished risk [13,20].

KC, BCC and SCC are the most common types of skin cancer, however their incidence is age dependent. Caucasian people of 65-79 years to more than 80 years present the highest increase in BCC and SCC incidence rates [22]. The incidence of KC in pregnancy is not known, but we consider it occurs with the same incidence as in non-pregnant women [13].

Delayed child-bearing age 30's and 40's may lead to an increasing incidence of KC in pregnancy [23]. As far as the tumoral behavior goes, studies indicate that BCC associated to pregnancy has an aggressive evolution, including metastasis during pregnancy. There is also a record of rapid growth over one month's time during twin pregnancy, in contrast with no significant growth in BCC during two prior singleton pregnancies [24].

DISCUSSION

Cancer in pregnancy is complex affliction carrying a huge impact on the quality of life of the mother and future child. Taking charge of these afflictions requires a multidisciplinary approach [7,24]. Evidence-based treatment of metastatic melanoma in pregnancy is challenging due to the lack of evidence [7,12]. Treatment of primary disease is not different for the pregnant patient [24]. We must stress that before treatment the role of screening is paramount, especially when it is a non-invasive procedure like dermoscopy [19]

Excisional biopsy permits histopathologic analysis and prognosis, and is has the ability to be potentially

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curative. This represents a fundamental step in obtaining information in order to further guide the disease management in context of pregnancy [24].

CONCLUSIONS

Borderline pigmented lesions of the skin such as atypical nevi, melanoma or KC may arise during pregnancy. The majority of preexisting nevi may enlarge and suffer changes dermoscopically. All this modification in melanocytic lesions seems to be due to their susceptibility to gestational hormones. Lesions like melanoma or KC, although rare, usually behaves much more aggressively. Clinicians should be aware of these lesions as a significant contributor to maternal morbidity and mortality.

The aspect of screening, management and follow up must be as well underlined. Traditional or digital dermoscopy in the hands of a trained specialist offers the chance of early detection and ensures a noninvasive way for diagnosing. Any suspicious lesions on dermoscopy should be excised and then performed a histopathology examination. In advanced stages such as metastatic melanoma multidisciplinary care is required.

Conflict of interest

The authors declare that there is no conflict of interest

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