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Physiologic changes of pregnancy: A review of the literature☆☆☆

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ABSTRACT

Throughout pregnancy, the body undergoes a variety of physiologic changes. The cutaneous findings can be most noticeable and often worrisome to both physicians and patients. Obstetricians and dermatologists must be able to differentiate between changes that are benign and those that may be pathologic. Most physicians recognize benign changes that are commonly described in literature such as hyperpigmentation, melasma, striae gravidarum, and telogen effluvium; however, they may be unaware of changes that tend to be less frequently discussed. This comprehensive review provides a broad overview of the physiologic cutaneous changes that occur during pregnancy as described in the literature over the past 10 years.

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Introduction

Pregnancy induces a variety of hormonal, immunologic, and metabolic changes that exert significant effects on a woman's body. Altered levels of circulating hormones, increased intravascular volume, and

compression from the enlarging uterus underlie the complex physiological adaptations that are essential for the development of the fetus. These factors also contribute to the variety of cutaneous changes that may concern patients and physicians. Obstetricians and dermatologists must be able to differentiate normal physiologic findings from pathologic lesions and rashes. A misdiagnosis of benign changes can lead to unnecessary stress and intervention.

We provide a comprehensive review of the physiologic changes of the skin that occur during pregnancy as characterized in the literature over the past 10 years. The pathologic dermatoses of pregnancy will

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not be covered in this review because we will focus on the characterization and clinical presentation of benign physiologic changes in pigmentation, nevi, mucosa, connective tissue, hair, nails, and breasts as well as vasculature and glands as they relate to dermatologic findings.

Methods

A comprehensive search of the literature was performed to identify all articles that described changes in *pregnancy or gestation* combined with the search terms *dermatol-, skin, cutaneous, integumentary system, pigmentation, nevus, mucosa, gingiva, oral, vulva, vagina, gland, acne, pruritus, hair, or nail*. The search produced 7338 articles in total, which were filtered to include only studies that were performed on humans and those written in English.

Only manuscripts that were published between July 1, 2007 and July 1, 2017 were included. A total of 972 manuscripts were reviewed to exclude those unrelated to the topic. Manuscripts that described pathologic changes or treatment interventions were included only if physiologic changes were also described. At the end of this selection, 25 manuscripts were considered eligible for inclusion in this review as either review articles, studies, or clinical case reports. Studies were assessed and findings were categorized according to type of change to provide a comprehensive review of all relevant cutaneous physiological changes that occur throughout gestation.

Pigmentation

The most commonly reported skin change during pregnancy is hyperpigmentation, which develops in some form in 85% to 90% of pregnant women, typically during the second half of the pregnancy (Bieber et al., 2017; Fernandes and Amaral, 2015; Geraghty and Pomeranz, 2011; Rathore et al., 2011; Tyler, 2015; Van Onselen, 2012). The exact mechanism of hyperpigmentation of the skin is not well understood; however, it is commonly attributed to a combination of hormonal factors, genetic predisposition, and ultraviolet exposure (Bieber et al., 2017; Geraghty and Pomeranz, 2011). Melanocytes may be more sensitive to the elevated levels of α - and β -melanocyte-stimulating hormone, estrogen, progesterone, and β -endorphins. These hormones likely stimulate the production of melanin, which underlie the hyperpigmentation that is seen clinically (Bieber et al., 2016). Upregulation of tyrosinase by human placental lipids may further potentiate melanin synthesis (Bieber et al., 2017; Tyler, 2015).

Although generalized hyperpigmentation can occur, more commonly affected are those areas that are already physiologically darker such as the areolas (termed secondary areolas [Bieber et al., 2017]), nipples, genitalia, axillae, periumbilical area, and inner thighs. Intertriginous areas and skin folds may also darken. Patients can develop new acanthosis nigricans or have exacerbation of preexisting lesions. Linea nigra describes the darkening of the linea alba, which is a line that runs along the midline of the lower abdomen and suprapubic area. Darkening here is seen most commonly from the umbilicus to the pubic symphysis (Bieber et al., 2017; Geraghty and Pomeranz, 2011; Tyler, 2015; Van Onselen, 2012).

Pigmentary lines of demarcation (Fig. 1), which are known as Voigt or Futch lines, are rare phenomena that are characterized by abrupt, linear boundaries between areas of lighter and darker skin. They tend to follow the distribution of the peripheral cutaneous nerves (Bieber et al., 2017; Ponnappula and Boberg, 2010; Rathore et al., 2011; Tyler, 2015). Melasma (Fig. 2), also called the mask of pregnancy, reportedly occurs in up to 70% of gravid women and typically in patients with darker skin (Bieber et al., 2017; Farage and Maibach, 2011; Farage et al., 2009; Fernandes and Amaral, 2015; Geraghty and Pomeranz, 2011; Rathore et al., 2011; Soutou and Aractingi, 2015; Turcic et al., 2009; Tyler, 2015; Van Onselen, 2012).

Nevi

Historically, melanocytic nevi were thought to darken during pregnancy; however, studies have revealed that this phenomenon is uncommon during pregnancy and requires further research (Bieber et al., 2016). Although color changes are uncommon, nevi are likely to undergo some widening in diameter when they are located in areas that are affected by skin stretching and particularly the chest and abdomen (Akturk et al., 2007; Bieber et al., 2016; Goldberg and Maloney, 2013). Several reports describe the transient dermoscopic changes in nevi such as new dot formation, thickening of the pigment network, darkening of globules, and increasing numbers of vessels, which are not necessarily suggestive of melanoma (Akturk et al., 2007; Bieber et al., 2016; Goldberg and Maloney, 2013).

Histologic changes in nevi that are consistent with increased rates of mitotic activity have also been described. These include increased numbers of dermal mitoses and what have been termed "superficial micronodules of pregnancy," which are rounded clusters of large epithelioid melanocytes with prominent nucleoli, abundant pale eosinophilic cytoplasm, and occasional fine melanosomes. The significance of these remains unclear because they are also found in patients who are not pregnant (Bieber et al., 2016; Chan et al., 2010). Although physiologic changes of nevi do occur, any changes in their clinical appearance that elicit concern for malignancy warrant an immediate biopsy, which can be performed safely with the use of lidocaine regardless of the location or trimester of pregnancy (Goldberg and Maloney, 2013).

Vasculature

Increased venous hydrostatic pressure can result in a nonpitting edema, which most commonly affects the lower extremities but involvement of the face and hands has also been described (Rathore et al., 2011; Soutou and Aractingi, 2015; Van Onselen, 2012). This benign edema can be relieved by bed rest, leg elevation, compression stockings, or sleeping in the left lateral decubitus position (Ponnappula and Boberg, 2010). Persistent edema, particularly of the face and hands, can be a sign of preeclampsia and warrants further examination.

Varicosities can arise throughout the body and most commonly involve the saphenous vein (Fernandes and Amaral, 2015; Ponnappula and Boberg, 2010; Rathore et al., 2011; Soutou and Aractingi, 2015; Tyler, 2015). The gravid uterus may compress the femoral and pelvic vessels, thereby increasing venous pressure and contributing to the development of varicose veins. Venous dilation typically returns to baseline in the postpartum period and is unrelated to the number pregnancies (Engelhorn et al., 2010).

Elevated levels of estrogen during gestation can increase the number and appearance of telangiectasias including spider angiomas (Fig. 3) and unilateral nevoid telangiectasias (Fernandes and Amaral, 2015; Geraghty and Pomeranz, 2011; Ponnappula and Boberg, 2010; Rathore et al., 2011). These can be particularly noticeable in patients with lighter skin. They appear in areas that are drained by the superior vena cava, which include the face, neck, upper chest, and arms. Preexisting hemangiomas, subcutaneous hemangioendotheliomas, glomangiomas, petechiae, and purpura may worsen or new lesions may develop (Fernandes and Amaral, 2015; Geraghty and Pomeranz, 2011).

Pyogenic granuloma of pregnancy (Fig. 4), also termed granuloma gravidarum or pregnancy tumor, is a benign hyperplasia of capillaries that presents as a rapidly growing, lobulated or pedunculated lesion with a color that ranges from pink to red to purple. This painless lesion occurs in 0.5% to 5% of pregnant women and may bleed but usually regresses spontaneously after childbirth (Van Onselen, 2012; Ramos et al., 2016; Silva de Araujo Figueiredo et al., 2017; Tyler, 2015).

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