Dermatology and pregnancy*
Dermatologia e gestação*

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Abstract: This study is a literature review on dermatology and pregnancy from 1962 to 2003, based on Medline database search. Intrahepatic cholestasis of pregnancy was not included because it is not a primary dermatosis; however, its secondary skin lesions must be differentiated from specific dermatoses of pregnancy. This overview comprises clinical features and prognosis of the physiologic skin changes that occur during pregnancy; dermatoses influenced by pregnancy and the specific dermatoses of pregnancy. A discussion on drugs and pregnancy is presented at the end of this review.
Keywords: Dermatology; Pregnancy; Pathology.

Resumo: Neste estudo conduz-se uma revisão bibliográfica da literatura sobre dermatologia e gravidez abrangendo o período de 1962 a 2003. O banco de dados do Medline foi consultado com referência ao mesmo período. Não se incluiu a colestase intra-hepática da gravidez por não ser ela uma dermatose primária; contudo deve ser feito o diagnóstico diferencial entre suas manifestações na pele e as dermatoses específicas da gravidez. Este apanhado engloba as características clínicas e o prognóstico das alterações fisiológicas da pele durante a gravidez, as dermatoses influenciadas pela gravidez e as dermatoses específicas da gravidez. Ao final apresenta-se uma discussão sobre drogas e gravidez
Palavras-chave: Dermatologia; Gravidez; Patologia.

PREGNANCY AND THE SKIN
INTRODUCTION

Pregnancy is a period throughout which women undergo significant changes. Virtually all body systems are affected, including the skin.
Most changes in the female body are due to hormonal and/or mechanical alterations. Hormonal changes are characterized by high levels of estrogen, progesterone, beta-hCG, prolactin, and a series of hormones and mediators that fully affect the functions of the body.
During pregnancy, there are changes in the metabolism of proteins, lipids, and carbohydrates; as well as in blood pressure, respiratory dynamics and appetite. There is an increase in cardiac output, blood volume, and hemodilution; glomerular flow; and presence of nausea and vomiting, gastroesophageal reflux and constipation. There are several immunological changes that allow women to bear the overload of gestating a child.¹

Intense immunological, endocrinological, metabolic and vascular alterations make pregnant women susceptible to physiological and pathological skin changes.
Pregnancy-related skin changes can be classified as physiological changes, specific dermatoses, and pregnancy-related dermatoses. Each change will be fully discussed, as well as the current use of specific drugs during pregnancy.
1 - Physiological changes in pregnancy

Based on the extent of the cutaneous involvement during pregnancy and the stigma experienced by the patients, there is no doubt that these changes are undervalued in pregnant women. The fact that many of these alterations are described as physiological does not minimize discomfort for the patients.

Pigmentary changes are extremely common and affect up to 90% of pregnant women. They appear very early during the pregnancy and are more noticeable in black women. Hyperpigmentation usually affects the whole body, and areas normally more pigmented become darker, such as the areolae, genitalia, perineum, axillae and inner thighs. Although hyperpigmentation tends to fade after delivery, the skin usually does not present the original color.

A greater number of melanocytes and higher susceptibility to hormonal stimulus are some of the causes of hyperpigmentation in these areas. Higher levels of the melanocyte stimulating hormone (MSH), estrogen, and progesterone have been associated with the etiology of hyperpigmentation. However, MSH serum level increases during late pregnancy and does not decline after delivery. Estrogen and progesterone levels seem to be more correlated to the clinical picture since they increase after the 8th gestational week and start to decrease as from the 30th week, and this pattern is compatible with progression of hyperpigmentation.

Melasma or chloasma affect up to 75% of pregnant women. It usually appears in the second trimester of the pregnancy, mostly in black women. During pregnancy it presents the usual pattern, particularly the centrofacial (63 percent), followed by the malar and the mandibular. Epidermal melasma, intensified by Wood’s lamp, is more common, when compared to the dermal type.

The etiology of melasma is multifactorial, and the following factors may contribute to its development: pregnancy, use of oral contraceptives, genetic and ethnic factors, exposure to sunlight, among others. Increased levels of estrogen, progesterone and MSH are possible etiological factors.

Melasma usually resolves within a year after delivery, but it may persist in up to 30% of patients, with some patch. It is more persistent in women who took oral contraceptives and in dermal melasma. Treatment includes sunscreen protection as well as to avoid excessive sunlight exposure. Formulas containing corticoids, hydroquinone and tretinoin can be used in the postpartum period.

The pigmentation of recent scars, ephelides and melanocytic nevi may be more intense throughout pregnancy. Nevi should be better evaluated since the role of hormones in melanomas is still under discussion. Other pigmentary skin changes such as linea nigra, darkening of the areolar area and hyperchromia of the vulva and anus tend to resolve after pregnancy.

Vascular changes are also common during pregnancy. Vascular spiders appear between the second and the fifth month of pregnancy, and are more common in white women (up to 67%). They are usually found in the draining areas of the superior vena cava, such as face, neck and upper limbs, and tend to enlarge throughout pregnancy. Elevated estrogen levels seem to be associated with their development. Vascular spiders usually disappear until the seventh postnatal week. There may be recurrence in subsequent pregnancies. No specific therapy is required.

Palmar erythema is also common in gestation. It occurs in the first trimester and is more common in white women. Clinically, it can affect the thenar and the hypothenar eminences or the whole palm, with presence of cyanosis and paleness. Palmar erythema disappears in the first week after delivery. It is also related to elevated levels of estrogens, in addition to increased blood volume. There is no correlation with liver disease in these cases.

Varicose veins affect more than 40% of pregnant women, and are more common in the legs and anal region. They usually appear as from the third month of pregnancy. Many factors are related to its etiology, such as family history, fragility of the elastic tissue and increased venous pressure because of the venous compression caused by the uterus. Varicose veins usually resolve in the postpartum period. They can be prevented by the use of compression stockings, elevating the legs while resting, or adopting the lateral decubitus positioning. Standing up for long periods of time should also be avoided.

Small cavernous hemangiomas can affect up to 5% of pregnant women, and they usually occur at the end of the first trimester. The treatment is surgical for persistent lesions, and, like the vascular changes above mentioned, they are also related to estrogen levels.

Cutis marmorata on the legs probably represents a vasomotor disorder secondary to changes in estrogen levels, and occurs in patients exposed to cold. It characteristically has an intermittent mottled cyanotic appearance. If it persists after delivery, secondary causes should be investigated.

Granuloma gravidarum or pyogenic granuloma of the pregnancy is a benign, gingival tumor, which cannot be histologically distinguished from pyogenic granuloma (lobular capillary hemangioma). It appears as an enanthema in the gingiva with a pedunculated or sessile lesion. They usually resolve at the end of pregnancy; therefore, they should not be inadvertently removed because this may cause frequent recur-
rences. Strict oral hygiene is one of the factors that may prevent or avoid formation of pyogenic granuloma of the pregnancy.4,6,7

Striae can be extremely uncomfortable for pregnant women. They are more commonly observed in white women and they appear in the opposite direction of lines of skin tension. They usually occur in the abdomen, breasts, arms and back.

The etiology of striae is still under discussion, but apparently they are related to distension of tissues and to adrenocortical and estrogenic activities. There is a significant association between striae formation and excessive weight of babies and their mothers. There are controversies about preventing the appearance of striae in pregnant women by means of massages made with oil. Even without complete resolution, striae can improve a great deal at the end of pregnancy when their color becomes lighter white nacreous. After delivery, they can also be treated with topical tretinoin.

Glandular activity is frankly altered due to pregnancy-related hormonal changes. The eccrine glands progressively enhance their activities, increasing the incidence of miliaria and dyshidrotic eczema in this period. Paradoxically, palmar sweating is decreased.

Apocrine glands have their activities reduced throughout pregnancy, with improvement of conditions such as hidradenitis suppurativa.

There is no consensus whether sebaceous gland activity is increased or maintained constant during pregnancy.8

Peripheral edema is a very common and long-lasting condition in pregnant women. Its etiology includes retention of sodium and water, in addition to circulatory changes caused by the pregnant uterus on the circulation of the inferior vena cana.2

Hirsutism is another common finding in pregnant women, mainly in those who already had too much hair before pregnancy. It is commonly observed early in the pregnancy, more pronounced in the face and arms. The etiology of hirsutism is probably hormonal and it occurs because of a reduced conversion of anagen into telogen hair. It usually disappears within six months after delivery and does not require specific therapy.

Telogen effluvium is also common and occurs between the first and fifth postpartum months, lasting several months. It is caused by the fast conversion of anagen into telogen hair, secondary to hormonal imbalance and delivery stress. Most patients present full recovery of hair within approximately one year.4,6

Nails are also affected and may become more fragile and brittle, with distal onycholysis and subungual keratosis.

As to mucosae, pregnancy gingivitis affects up to 100% of pregnant women, in several levels. It usually occurs in the first trimester, with increased severity until the ninth month. The interdental papillae are enlarged and present enanthema and are more intense in the lower incisor teeth. There may be ulceration. Its etiology includes elevated levels of progesterone, poor oral hygiene, local irritating factors and nutritional deficiencies. Treatment involves local care. Oral intake of vitamin C may be helpful.6

Up to 20% of pregnant women suffer from pruritus. Its onset usually occurs on the third month and it becomes more intense throughout pregnancy. It is more intense in the abdomen and some dermatoses, such as scabies, atopy or neurodermitis should be ruled out. Treatment is symptomatic after excluding other diagnoses.

Intrahepatic cholestasis of pregnancy is another condition that may cause pruritus and should be ruled out. It usually occurs on the third trimester and is secondary to difficulty in excreting biliary acids, with elevated alkaline phosphatase and slight increase in bilirubins. The clinical picture is characterized by intense pruritus, nausea, vomiting and jaundice. Fetal morbidity and mortality rates are increased. Treatment is difficult, and may include antihistamines and cholestyramine. Symptoms resolve immediately in the postpartum period.8

2 - Specific Dermatoses of Pregnancy

Specific dermatoses of pregnancy are eruptions that are triggered by gestation and occur only during this period. Its pathogenesis as well as its classification are still under discussion.

In 1982, Black & Holmes proposed a simplified classification: pemphigoid gestationis, polymorphic eruption of pregnancy, prurigo of pregnancy, and pruritic folliculitis of pregnancy. Some American authors are still reluctant to accept it and prefer terms like herpes gestationis (pemphigoid gestationis) and PUPPP (pruritic urticarial papules and plaques of pregnancy) for reasons that will be later discussed.9,10

a) Pemphigoid gestationis

It is a rare autoimmune bullous dermatosis that occur during pregnancy, particularly in the second and third trimesters and at the beginning of puerperium.

Its incidence varies from 1:50,000 to 1:60,000 pregnancies. There are reports in the literature on the association between hydatiform mole, choriocarcinoma and the use of oral contraceptives.

Tissue damage is caused by deposit of immune complexes in the basal membrane zone (BMZ), with posterior activation of complement and intense migration of eosinophils.
Clinically it may appear in the first or subsequent pregnancies. If it happens after a previous episode, it tends to occur earlier and more intensely. However, not all subsequent pregnancies are affected, which might be related to paternity change or higher HLA compatibility between the mother and the fetus.

Initially there are urticarial papules and plaques with intense pruritus. The urticarial lesions can be annular or polycyclic, with vesicles and blisters. The initial lesions are periumbilical in 81% of cases, followed by lesions in the trunk, limbs, palms and soles (Figure 1). The face and oral mucosa are usually spared. Blisters and vesicles burst leading to erosion and crust (Figure 2).

The lesions usually resolve within six weeks after delivery, but there are reports of patients who present new lesions in up to 10 years after pregnancy. During puerperium, recrudescence of pemphigoid gestationis is common, but the occurrence of new blisters three days after delivery should raise the suspicion of another diagnosis.

Following apparent resolution of the picture, there may be exacerbation during the menstrual period or with use of oral contraceptives.

At histopathological examination, we observe edema in the papillary dermis with inflammatory infiltrate of lymphocytes, eosinophils and some neutrophils. The blister produced is subepidermal and contains several eosinophils.

Direct immunofluorescence reveals linear deposits of C3 in the basal membrane. Deposits of IgG in the BMZ are found in 25% of the cases. Holubar, however, suggested that this reflects only lack of technical sensibility because IgG deposits were demonstrated in patients with negative immunofluorescence by immuneelectron microscopy.

Laboratory studies show increased levels of inflammatory markers and peripheral eosinophilia. No changes are observed in antinuclear antibodies and complement TESTS.

The etiology of pemphigoid gestationis seems to be auto-immune. In a study with 25 patients with pemphigoid gestationis, Holmes et al. found 61-80% of patients with antigen HLA-DR3, 52% with HLA-DR4 and 43-50% with both HLA forms. Women with this skin condition seem to be more susceptible to several autoimmune diseases, mainly Graves’ disease.

It was suggested that the disease could be triggered by a placental antigen that causes cross-reaction with skin antigens. This would explain the onset of the disease in the periumbilical region. The relation with hydatiform mole, use of oral contraceptives, menses, and other factors raises a strong possibility of hormonal influences in this condition.

Up to 75% of patients present IgG1 complement binding antibody in serum. The predominance of C3 in the basal membrane and the presence of eosinophils suggest that complement activation and eosinophil chemotaxis are extremely important in tissue damage. Complement activation is not the main factor in the pathogenesis of bullous pemphigoid.

The pemphigoid gestationis antigen is an 180kd transmembrane protein, codified by the long arm of chromosome 10. This differs from the 230kd intracellular protein of bullous pemphigoid, codified in chromosome 6. For these and other reasons, many authors still prefer to name it herpes gestationis, stressing the differences with pemphigoid bullous, although there is no viral etiology for the disease.

Up to 10% of newborns (NB) present lesions similar to those of their mothers, but they disappear with no sequelae. Even healthy NB may present com-
There is an increased trend for low birth weight and prematurity after pemphigoid gestationis episodes, but no morbidity or mortality has been confirmed to date.\(^{16,19,20}\)

Pemphigoid gestationis treatment should be initiated with oral antihistamines and topical steroids. If there is no response, prescribe oral steroids in doses of up to 1mg/kg/day, followed by slow dose reduction.\(^{21}\) In extreme cases, plasmapheresis can be an option.

c) Prurigo of pregnancy

It affects one in every 300 pregnancies and generally manifests between the 25\(^{th}\) and the 30\(^{th}\) gestational weeks. There are not fetal or maternal risks or predisposition to recurrence in subsequent pregnancies.\(^{8}\)

It is marked by small pruritic papulae that progress to the form of nodules on the extensor surfaces of the limbs (Figure 4).\(^{25}\) Occasionally the lesions are generalized. They usually disappear after delivery, but there are reports of cases lasting up to three months in the postpartum period.

Its exact etiology is not known, but it seems to be correlated with atopy. Histopathological examination shows acanthosis and parakeratosis, with perivascular lymphocyte infiltration in the dermis. Immunofluorescence does not add anything to the diagnosis in this case.

Treatment is symptomatic, with antihistamines and topical corticoids.

d) Pruritic folliculitis of pregnancy

This condition presents as erythematous, excoriated, papular or pustular follicular eruptions that appear between the fourth and ninth month of pregnancy and last for two to three weeks (Figure 5).\(^{23,26}\)

Its exact etiology is not known, even because it is a rare dermatosis. There is no immunohistopathological pattern established and histopathology shows unspecific inflammatory folliculitis. Apparently there are no major maternal or fetal complications and it responds well to benzoyl peroxide 10% and hydrocortisone 1% creams.

3 - Pregnancy-related dermatoses

There is no doubt that atopic dermatitis is one of the most common conditions found in dermatological practice. Based on the literature, its symptoms, may improve or worsen during gestation.\(^{5,27}\) The correlation with hormonal changes becomes evident as symptoms worsen during menstrual periods.

Some prospective studies carried out in London showed that atopic eczema accounted for 36% of dermatology appointments of pregnant women. Most of these patients (52%) revealed that there was aggrega-
tion during pregnancy. Actually, there are reports of first onset of atopic dermatitis during pregnancy of women who were predisposed to it.\textsuperscript{28}

Many dermatoses clinically manifest as pruritus, but it is key in atopic dermatitis. It is important to distinguish it from polymorphic eruption of pregnancy because this allows for more appropriate guidance as well as adequate treatment. Indirectly, atopic dermatitis is harmful for pregnant women since it affects their diet, sleep and emotional well-being.

The use of more potent topical corticosteroids should be spared to avoid striae.

Other allergic events that may be exacerbated in pregnant women are those of the urticaria/angioedema complex, and should be followed-up.\textsuperscript{27}

Systemic lupus erythematosus during pregnancy is still discussed. For some authors, its recurrence is more severe in pregnant women, with increased involvement of the skin (vasculitis) and articular areas. Systemic treatment with steroids and antimalarials should not be interrupted.\textsuperscript{8,11}

The antiphospholipid antibody syndrome is a severe condition related to lupus erythematosus. The lupus anticoagulant and the anticardiolipin antibodies should be assessed in these patients. Clinically, it manifests as thrombosis, fetal losses and thrombocytopenia. Pemphigus may manifest or worsen during pregnancy. In the first or second trimesters there are exacerbations with increased fetal morbidity and mortality. Clinically, the disease is not different from its regular presentation. Differential diagnosis from pemphigoid gestationis is important and can be made based on clinical findings and direct immunofluorescence. Therapy with steroids is effective during pregnancy, when cytotoxic drugs should be avoided.\textsuperscript{8}

The influence of pregnancy on malignant melanoma is controversial since the consequence of hormonal changes in its genesis has not been fully established. Overall, the prognosis of melanoma in pregnant women is directly related to tumor thickness, like in other patients. Metastases in the fetus have already been reported and it is recommended to avoid getting pregnant for at least two years after tumor resection.\textsuperscript{8} Treatment of this disease during pregnancy is obviously difficult once cytotoxic drugs should be avoided by pregnant women.

**DRUGS AND PREGNANCY**

When new drugs are under development, usually they are not tested in pregnant women. As a consequence, safety regarding the use of most drugs by pregnant women is not appropriately assessed. In general, it is recommended to prescribe a drug if the benefit compensates the risks to the fetus.

By and large, the Food and Drug Administration - FDA - classifies the drugs into six groups, as follows:\textsuperscript{29}

- X: contraindicated use during pregnancy;
- D: positive evidence of risk to the human fetus; however benefits may overcome the risks;
- C: risk cannot be excluded; studies in humans have not been carried out. Benefits can overcome risks;
- B: There are no risks to human fetuses, although there is a possible risk in animals;
- A: controlled studies did not report any risks.
- Undetermined: it was not classified by the

\textsuperscript{29} An Bras Dermatol. 2005;80(2):179-86.
FDA. In this case, other options may be used.

Teratogenesis is defined as dysgenesis of fetal organs, with structural or functional evidence.

Several drugs present proven teratogenic effect, such as methotrexate (limbs and CNS malformations), angiotensin converting enzyme inhibitors (renal changes), carbamazepine (neural tube defects), cyclophosphamide (CNS malformations), danazol (viralization of the female fetus), diethylstilbestrol (neoplasia of the vagina), hypoglycemic drugs, lithium, misoprostol, non-steroidal anti-inflammatory drugs (constriction of the ductus arteriosus), phenytoin (CNS changes), barbiturates, benzodiazepines, propylthiouracil and methimazole (fetal hypothyroidism), systemic retinoids (CNS, craniofacial and cardiovascular defects), tetracycline (tooth and bone alterations), thalidomide (defects in internal organs and shortening of the limbs), valproic acid (neural tube defects), warfarin (skeletal and CNS defects). As to topical use of corticosteroids, there are apparently no major risks involved. Among the topical medications frequently used in Dermatology, the following are safe: azelaic acid, ciclopirox, clindamycin, erythromycin, metronidazole, mupirocin, nystatin, permethrin and terbinafine, all classified as group B by the FDA. Benzoyl peroxide, bacitracin and hydroquinone can be used, although classified as group C by the FDA. Apparently no problems are observed regarding the use of topical retinoids, differently from its systemic use.

Therefore, it is extremely important that dermatologists know the drugs they prescribe to pregnant patients and the potential risks to the fetus. The drug that promotes the best benefit not increasing risks to the fetus should be chosen among the possible therapies.

**DISCUSSION**

Detailed history and physical examination are important for diagnosis and treatment of dermatoses of pregnancy. The physician should know the gestational age, parity, existence of possible twin pregnancy, previous history of pregnancy-related dermatoses, past clinical history and use of medications.

On physical examination, the dermatologist should evaluate the morphology and distribution of lesions. In pemphigoid gestationis, there are pruritic and urticarial lesions that progress to vesicles and blisters, initially affecting the periumbilical region and then the trunk and limbs, with resolution after delivery. The incidence of low-birth weight and premature babies seems to be increased. Polymorphic eruption of pregnancy manifests as urticarial and highly pruritic lesions, with onset on the abdominal striae and sparing the periumbilical region. It is associated with first pregnancy, twin pregnancy and excessive weight gain during pregnancy; it does not aggravate in the postpartum period and is not likely to recur in subsequent pregnancies. Pruritic folliculitis of pregnancy is characterized by erythematous, excoriated papulae or blisters with follicular distribution. Therefore each disease has its own clinical characteristics.

Laboratory studies should be directed by clinical findings. In most cases, skin biopsy is recommended, along with direct immunofluorescence when there is suspicion of pemphigoid gestations.

In the presence of dermatoses of pregnancy, the patient should be oriented about diagnosis, progression and prognosis of both mother and fetus, as well as about physiological changes and behavior of past diseases during pregnancy.
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