CLINICAL PRACTICE

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The complex implications of dermatoses specifically associated with pregnancy

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Abstract: *Pregnancy-specific dermatoses are a heterogeneous group of inflammatory dermatoses associated exclusively with pregnancy. Although these dermatoses are rare, it raises problems in medical practice because of their appearance, being difficult to diagnose, treat and the possibility of the fetus being affected. Pemphigoid Gestationis (PG) is a rare, autoimmune, strongly pruritic, vesiculobullous dermatosis with a strong impact on the patient. Polymorphic Eruption of Pregnancy (PEP) is a benign, self-limited inflammatory skin disorder that usually affects first pregnancy in the third trimester or immediately in the postpartum period. Other dermatoses associated with pregnancy include: Intrahepatic Cholestasis of Pregnancy (ICP), Atopic Eruption of Pregnancy (AEP) and Pruritic Folliculitis of Pregnancy (PFP). We will extensively present PG and PEP, to draw attention to the importance of correct diagnosis and the implications of treatment during pregnancy.*

Keywords: *specific dermatoses in pregnancy, pemphigoid gestationis, polymorphic eruption of pregnancy*

INTRODUCTION

During pregnancy endogenous, immunological, metabolic and vascular complex changes can result in skin damage. The skin changes can be classified into: physiological skin changes, alteration of preexisting cutaneous conditions and specific dermatoses in pregnancy.

Pregnancy-specific dermatoses are a heterogeneous group of inflammatory dermatoses associated exclusively with pregnancy and/ or immediately after birth. Some are considered a significant risk to the fetus.

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These relatively rare conditions, often with variable clinical appearance, and the lack of definitive diagnostic tests have led to confusion in terms of proper diagnosis and management of pregnancy-specific dermatoses.

While many physicians are familiar with normal physiological changes during pregnancy, the knowledge of dermatoses in pregnancy, which is rarely encountered, is often minimal. This review is designed to highlight pregnancy-related

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dermatoses for easier diagnosis and management.

PEMPHIGOID GESTATIONIS (PG)

Pemphigoid gestationis (PG) is a rare, autoimmune, strongly pruritic, vesiculobullous dermatosis, with an incidence of 1: 50,000 to 60,000 pregnancies in USA [1]. The results of European studies suggest a global incidence of 0.5 cases per million people per year [2]. It occurs more frequently in the white race, which may reflect the association with specific HLA haplotypes. Most often, the disease occurs in the second or third trimester of pregnancy, but cases have also been reported in the first trimester and postpartum period [3].

The etiology of the disease is unknown. Nearly half of the cases develop during the first pregnancy. Women with a history of PG are considered to have a higher prevalence of autoimmune diseases, including Graves's disease, Hashimoto's thyroiditis, vitiligo, autoimmune thrombocytopenia, and pernicious anemia [4].

PG is associated with the following antigens: HLA-B8, HLA-DR3 and HLA-DR4 or combinations of HLA-DR3 and HLA-DR4 [5]. The presence of HLA-DR3/DR4 was highlighted in 45% of patients with PG compared with 3% of the general population, and all patients with a history of PG have anti-HLA antibodies [6].

The main antigen of PG is collagen XVII, present both in the skin and placenta, which is exposed to the maternal immune system through an abnormal expression of classical class II histocompatibility molecules in the placenta [7]. PG is exclusively a disease of pregnancy, so potential causes are focused on immunogenicity and potential cross reactivity between maternal-fetal transfer and placental tissue and skin [8]. PG onset in the first or second trimester may lead to negative outcomes, including premature delivery [9].

The diagnosis of PG relies on the clinical evaluation, histological findings, and direct immunofluorescence. Bullous changes are characterized by the formation of subepidermic blister, the bullae contain mostly eosinophils. Eosinophil infiltration is the most common histopathological finding [10].

The inflammatory cellular response of the upper dermis has numerous lymphoid cells, some neutrophils and eosinophilic leukocytes. Microscopic studies have confirmed that IgG is deposited along the basal membrane area, mainly in lucid lamina and located on the proximal anchor filament [11]. IgG class antibodies - the so-called herpes gestation factor (HG) - have an important effect on the genesis of this bullous dermatosis. These antibodies can be transmitted from mother to child, which can cause premature birth, low birth weight, bullous and papular lesions in the newborn; IgG antibodies can be detected by ELISA [12].

Laboratory tests are usually within normal limits. Peripheral eosinophilia may correlate with the severity of the disease, and changes in the level of immunoglobulins, erythrocyte sedimentation rates, acute phase reactants and antithyroid antibodies may occur [3].

A patient who suffered from PG at the previous pregnancy will also suffer from this disease in future pregnancies and the onset of PG will be earlier than in the previous pregnancy. Also, a patient with PG onset in the second trimester may experience remission, followed by exacerbation in the last 6 weeks of pregnancy. The mean duration of the disease at the end of the pregnancy is 4 weeks for bullous rashes and 14 weeks for the urticaria component. Neonatal PG is caused by the transfer of antibodies through the placenta, skin changes in these infants resolve spontaneously within a few weeks and rarely require treatment [13].

The clinical picture is characterized by pruritus, pain, disfigurement, papulovesicular polymorphic eruptions on the abdominal and distal extremities, including the palms, soles, chest and back. The lesions range from erythematous papules, edema papules, confluent vesicles and urticaria plaques through large and tight bullets [14].

Differential diagnosis should be made with: scarring pemphigoid, pruritic urticarial papules and pregnancy plaques, linear IgA dermatitis, multiform erythema, dermatitis herpetiforma, acute urticaria, allergic contact dermatitis, drug-induced bullous disorders,

pruritic pregnancy folliculitis, papular dermatitis of pregnancy, scab [15].

As for treatment, consideration should be given to the fact that PG disappears after birth, but treatment is necessary to minimize pruritus and to prevent vesicles and bullae rash. In mild cases of PG, oral antihistamines and topical corticosteroids will be used, while systemic corticosteroids (prednisone 0.5-1.0 mg/kg/day) will be used in severe cases. Due to prolonged corticosteroid therapy, both the mother and the newborn should be followed to rule out adrenal insufficiency [16]. Alternatives to corticosteroids include azathioprine, dapsone, intravenous immunoglobulin, pyridoxine, cyclosporine, plasmapheresis, minocycline/ nicotinamide, methotrexate and cyclophosphamide. Immunoapheresis is a useful therapeutic option in patients who do not respond to conventional therapy [6, 17].

The clinical course of PG can be altered by changes in estrogen and progesterone levels. Although PG normally recurs in subsequent pregnancies, 8% of cases may not have PG in subsequent pregnancies. 25% of patients may experience relapse when using oral contraceptives or during menstruation. Abortion and premature birth were frequently reported [18].

POLYMORPHIC ERUPTION OF PREGNANCY (PEP)

Polymorphic eruption of pregnancy (PEP), a specific dermatosis of pregnancy also known as pruritic urticarial papules and plaques of pregnancy (PUPPP), is a benign, self-limited inflammatory skin disorder that usually affects first pregnancy in the third trimester or immediately in the postpartum period [19]. The incidence of PPE was estimated to 1 in 160 pregnancies, with the mean age being 29 years [15, 20]. PEP is considered to be the most common dermatosis of the pregnancy [21].

PEP is predominantly present either at the first pregnancy in 70% of cases [15] or at pregnancies that were not performed earlier (for example, spontaneous abortion). The increased incidence of multiple pregnancies in women with PEP has been reported [22]. A specific multiple gestation study in PEP showed that 2.9% of 8000 twin pregnancies had a PEP diagnosis and 14.3% of the triple pregnancies were associated with PEP [23]. It has been shown in several studies that there is a predilection of pregnant women who have PEP to give birth to male children.

Pathogenesis is still unknown, the theory of distension suggests that overstressing of the abdominal wall causes subsequent damage to the connective tissue, triggering an inflammatory response [20, 24].

Infants born from mothers diagnosed with PEP usually do not experience complications or skin manifestations. Premature birth was reported before 37 weeks in 18.4% of PEP patients, compared with 5.8% of patients in the control group [25]. A possible increase in the incidence of cesarean section and premature labor in PEP has been suggested, but there is no clear evidence that it would occur in later pregnancies.

In over 79% of cases, onset occurs in the third trimester of pregnancy, with remission of symptoms after birth, between 1 and 4 weeks [26].

PEP shows papules and pruritic urticarial plaques during pregnancy. Clinical findings were categorized into three PEP subgroups: type I, mainly characterized by papules and urticarial plaques; type II, which included erythematous patches and nonurticarial papules (1-2 mm) or vesicles; and type III, a combination of the other two types. All three types often also have some obstructions with surrounding blanched halos [26]. In terms of distribution, 91% of patients were first found to be the abdominal area, the proximal thighs, and occasionally both [25, 27].

PEP atypical lesions, including vesicles, complicate the diagnosis and have been reported in up to 40% of cases. A retrospective study showed that initially classic clinical manifestations are present in 98% of cases, but 51% of them develop changes in the form of vesicles, target lesions and several eczematous plaques [24]. In less than 2% of PEP patients, it can affect palms and soles, with papulous or vesicular lesions similar to dyshidrotic eczema [25, 28].

PEP is a disorder with a broad clinical spectrum and diverse clinical features, but with absence of pathognomonic identifying features. To exclude other

conditions, laboratory and histopathological investigations will be performed, such as: complete blood cell counts, liver function testing, renal function testing, thyroid stimulating hormone level, urine level, and bile acid level. The differential diagnosis is made with: pemphigoid gestationis, contact dermatitis, toxic drug rash, viral sprain, pitiriasis rosea and urticaria.

Histopathologically, a superficial or deep perivascular dermatitis is found with lymphocytic vasculitis, eosinophils are often present, in some cases, acanthosis, hyperkeratosis and intraepidermal vesicles [29]. If the diagnosis is not conclusive, two biopsies should be performed, one from lesional skin for hematoxylin and eosin staining and one from perilesional skin for DIF. The histopathological examination confirms an inflammatory process underlying PEP and skin stretching has recently been suggested as a precipitation factor for "koebnerization" seen in vitiligo, psoriasis and lichen planus.

It was observed in PEP patients an increase in body weight of more than 15 kg and the infant weight at birth was on average 3.6 kg compared to 3.3 kg in the control group [30]. The prevalence of multiple pregnancies in PEP patients is 10 times higher than in the general population [31]. The skin from PEP lesions showed progesterone receptor immunoreactivity in the cytoplasmic keratinocyte suprabas, while non-lesional skin did not show [32].

Due to the fact that PEP is an autoimmune condition without significant maternal or fetal risk and without recurrence in future pregnancies, patients should not suffer from anxiety due to this condition. Interdisciplinary communication between dermatologist, obstetrician and neonatologist is essential in the management of severe cases of PPE.

Topical corticosteroids are the primary means of treatment for polymorphic eruption of pregnancy (PEP) [33]. The relief of symptoms may require high potency (Class I or II) topical steroids, such as fluocinonide (cream 0.05% / 0.1%, ointment 0.05%) or even systemic steroids (prednisolone 40-60 mg/day). Oral antihistamines can be effective. Symptomatic treatment therapy consists of cooling baths, frequent application of emollients, topical medications containing refrigerated menthol, lightweight cotton, first-generation sedative antihistamines (chlorpheniramine and diphenhydramine) and medically active topical corticosteroids [19, 34].

OTHER SPECIFIC DERMATOSES IN PREGNANCY

Intrahepatic Cholestasis of Pregnancy (ICP) also known as pruritus gravidarum, is a liver disorder characterized by severe pruritus and secondary skin lesions in the third trimester of pregnancy (25–30 weeks gestation). Pruritus typically starts on the palms and soles and later becomes generalized. Secondary lesions such as excoriations, scratch marks, and prurigo nodules might develop as a result of scratching [35]. The symptoms usually disappear 1-2 days after delivery, but is a high risk of recurrence of ICP in subsequent pregnancies (50–70%). ICP is correlated with fetal risks, the most common being premature birth (20–60%), intrapartal fetal distress (20–30%) and stillbirth (1-2%) [20, 36].

Atopic Eruption of Pregnancy (AEP) is a benign pruritic disease with eczematous or papular lesions occurring during pregnancy in patients with a predisposition or history of atopic dermatitis. Specific immunological changes in pregnancy are incriminated in the development of late onset [37]. Clinical manifestations include pruritus, prurigo lesions/ excoriations and eczematous skin lesions, the diagnosis being based on clinical features. Treatment is based on class III or IV topical corticosteroids; in severe cases, systemic or antihistamine corticosteroids may be administered [38, 39]. AEP is not associated with fetal risk factors, except for the child's uncertain risk of developing atopic dermatitis.

Pruritic Folliculitis of Pregnancy (PFP) manifests as small (3–5 mm), multiple, disseminated, erythematous, excoriated, follicular papules and sterile pustules [20]. PFP usually occurs in the 2nd or 3rd trimester of pregnancy (between the 4th and 9th gestation months). Etiology is unclear, has a good maternal prognosis, without recurrence in future pregnancies and without significant fetal harm. Differential diagnosis should be done with acne, bacterial folliculitis, or polymorphic eruption of

pregnancy. Treatment includes topical low-potency corticosteroids, topical benzoyl peroxide 10 %, and ultraviolet B phototherapy [40].

CONCLUSIONS

Most skin manifestations that occur during pregnancy are mild and resolve after birth. A special category is pregnancy-specific dermatoses, which, although rare, can pose great problems in terms of diagnosis, treatment and fetal harm. Good knowledge of these dermatoses is necessary for both gynecologist, dermatologist and family doctor. Proper diagnosis and management are essential for symptom relief and, in the case of fetal risk, adequate monitoring during pregnancy and monitoring of newborns after birth are of major importance. Increased attention should be paid to pregnant patients to understand the risks, adverse effects, and drug interactions of their medications in the treatment of pregnancy-specific dermatoses.

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