REVIEW ARTICLE

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Update on specific dermatoses of pregnancy

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INTRODUCTION

During pregnancy, changes in the immune, metabolic, endocrine, and vascular systems[1,2] can induce skin changes of three natures: (a) the physiological changes of pregnancy, (b) dermatoses and tumors influenced and/or aggravated by pregnancy, and (c) specific dermatoses of pregnancy (SDP)[3,4]. This review will address SDP, which constitutes a heterogeneous group of inflammatory dermatoses of unknown etiology, highly pruritic, and occurring during the immediate pregnancy-puerperal cycle[5]. Until 1982/1983, the nomenclature of these dermatoses was quite confusing. In 1982, Holmes et al. proposed a classification into four major groups: polymorphic eruption of pregnancy (PEP), pemphigoid gestationis (PG), pruritic folliculitis of pregnancy (PFP), and prurigo of pregnancy (PP)[6,7]. In 2006, Ambros-Rudolph et al. grouped PFP and PP into a group called atopic eruption of pregnancy (AEP). Furthermore, they included intrahepatic cholestasis of pregnancy (IHCP) in the SDP group[8]. AEP can be considered another specific dermatosis. However, several authors propose that PFP and PP continue to be contemplated until further studies are conducted to clarify this heterogeneous group of dermatoses[9-13]. Table 1 summarizes the SDP reviewed in this article.

Table 1. Specific dermatoses of pregnancy, according to the reclassification by Ambros-Rudolph et al.[8].

	Polymorphic eruption of pregnancy (PEP)	Pemphigoid gestationis (PG)	Atopic eruption of pregnancy (AEP)	Intrahepatic cholestasis of pregnancy (IHCP)
Frequency	Frequent	Rare	Frequent	Variable, according to geographic region and ethnic origin
Onset	Third trimester. Rare in the postpartum	Second/third trimester Rare in the postpartum	First/second trimester	Second/third trimester
Clinical feature	Urticarial papules with initial lesions in the striae, sparing the periumbilical region	Vesicobullous and urticarial lesions with periumbilical involvement	Eczematous lesions (AEP), monomorphic papules followed by pustules on the trunk (PFP), and papules and nodules on the extensor surfaces of the limbs and trunk (PP).	No primary skin lesion. Excoriations and/or prurigo due to scratching
Diagnosis	Clinical diagnosis Tests for differential diagnosis when necessary	DIF-deposit C3 BMZ IIF-anti-BMZ antibodies outlining the roof of the skin (salt-split technique)	Clinical diagnosis Elevated serum levels of IgE	Laboratory Increased bile acids, altered liver function, after ruling out other liver diseases
Fetal risk	No	Yes	No	Yes
Recurrence	No	Yes, including the use of oral contraceptives	Variable	Yes, including the use of oral contraceptives

DIF: direct immunofluorescence; IIF: indirect immunofluorescence; BMZ: basement membrane zone; PFP: pruritic folliculitis of pregnancy; PP: prurigo of pregnancy.

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POLYMORPHIC ERUPTION OF PREGNANCY

PEP has an unknown etiology. It is benign and self-limited, occurring at the end of pregnancy (between the 36th and 39th weeks) and, rarely, in the immediate puerperium[14]. The term PEP is preferred over previously used names, such as toxemic rash of pregnancy, erythema toxicum of pregnancy, erythema multiforme of pregnancy, and pruritic urticarial papules and plaques of pregnancy (PUPPP)[1,15], because this denomination encompasses all the clinical and morphological alterations involving this dermatosis[7,16,17].

It is considered the most frequent SDP[2], with an estimated incidence of 1:200 pregnancies, the vast majority occurring in primigravidae[2,7]. The suggested pathophysiology, although not yet elucidated[1], is related to an inflammatory process triggered by rapid abdominal distention, which may explain the association with excessive weight gain, twin pregnancy, and a large fetus for gestational age[4,8,18]. Recently, the authors have suggested that the immune mechanism of the upregulated Th2 cytokine profile, including IL-9 and IL-33, and the reaction against bacteria and fungi residing in the skin, may be involved[16]. A study of 517 *in vitro* fertilization (IVF) pregnancies and 1,253 spontaneous pregnancies concluded that PEP was statistically more frequent in pregnancies resulting from IVF than in spontaneous pregnancies. Also, it was suggested that prolonged treatment with progesterone might be related to a higher frequency of PEP[19].

The typical clinical feature begins with urticarial papules located along the abdominal striae, always sparing the periumbilical region, which is an essential differential diagnosis from PG[20,21]. The papules can converge, forming plaques and extending to the limbs, trunk, and buttocks, protecting the mucous membranes and face (Figure 1). They may exhibit small vesicles, target lesions, and polycyclic papules[14,22]. Generally, the condition persists for 4–6 weeks[4].

The diagnosis is clinical, with nonspecific histopathological examination and negative direct immunofluorescence (DIF) and indirect immunofluorescence (IIF)[10].

Therapy involves psychological support, clarification of doubts, and symptom treatment: use of comfortable cotton clothes, body moisturizers, and low or moderate-potency corticosteroid cream, in addition to topical antipruritics, such as water paste. Refractory cases can be treated with low-dose oral corticosteroids. There is a regression in weeks after delivery, and, in the authors' experience, a significant improvement is observed within a few hours after delivery[13,15,22]. PEP does not affect maternal and fetal prognosis, and there are no reports of recurrence in subsequent pregnancies[4].

PEMPHIGOID GESTATIONIS

Bunel recognized PG in 1811, and Milton reported it in 1872, naming it *Herpes gestationis*[1]. It is a rare, pruritic autoimmune bullous disease with clinical and pathological features similar to bullous pemphigoid (BP). Its incidence varies from around 1:50,000 to 1:60,000 pregnancies, and it is more common in multiparous women[23,24].

Autoantibodies of the IgG class form the skin lesions. These antibodies are formed against the NC16a domain of BP 180 transmembrane antigen, currently known as collagen XVII, located in the skin basement membrane zone (BMZ) and chorionic amniotic epithelia[21,24]. PG is associated with the abnormal expression of MHCII antigens HLA-B8, DR3, and DR4[24].

PG manifests commonly in the second and third trimesters of pregnancy (between 21 and 28 weeks) and, rarely, postpartum[20,21,24,25]. It usually recurs in future pregnancies, starting earlier and with a more severe presentation[7,24,25]. Also, it can relapse with menstruation and during the use of oral contraceptives[18,23-26]. The literature has reported PG associated with trophoblastic tumors such as hydatidiform mole and

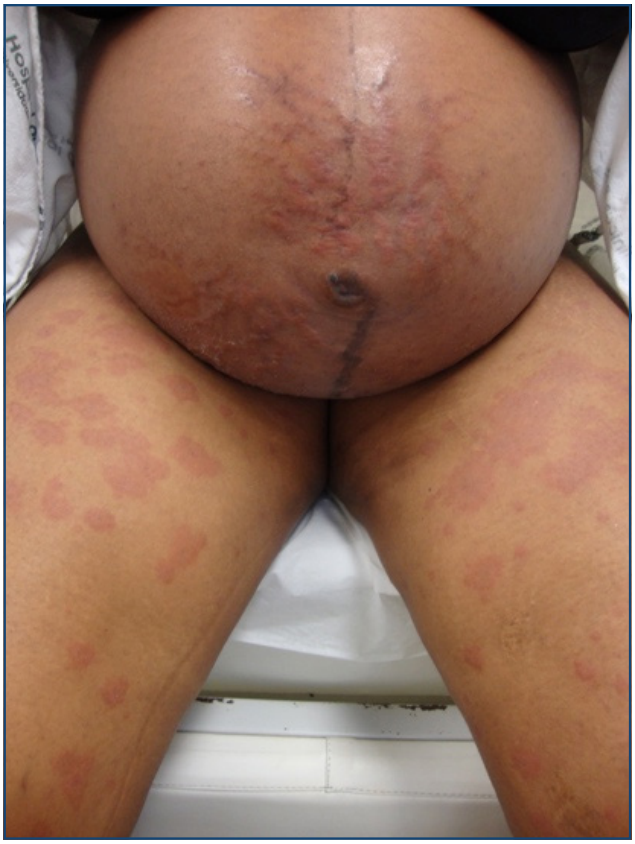

Figure 1. Polymorphic eruption of pregnancy with erythematous-urticarial papules accompanying the striae (forming fibrous cords) and sometimes going beyond the striae and forming plaques in the abdominal region, always sparing the periumbilical region. Confluent papules form plaques in the region of the thighs. Source: High Risk Prenatal Service (PNAR) at the Clinical Hospital at the Federal University of Minas Gerais.

choriocarcinoma[7,24]. The risks for the fetus are prematurity, low birth weight, and, rarely, a bullous eruption due to transplacental passage of maternal antibodies (<10%), with rapid and spontaneous resolution in most cases[14,21,24,26].

Clinically, there is an initial phase in which erythematous and urticarial papules and plaques predominate, followed by vesicles and blisters. Itching is intense and can be disabling[23]. In 90% of the cases, the lesions are initially located in the periumbilical region and spread to the abdomen and limbs[20,21,23,24]. The oral mucosa is rarely affected (15–20%)[26]. The primary differential diagnosis is PEP, where immunofluorescence studies are negative and generally spare the periumbilical region[20,21]. PG can be associated with other autoimmune diseases[23].

Histopathological examination of the initial lesions shows papillary edema with lymphocyte infiltration and a variable number of eosinophils in the dermis[24,25]. The histopathological pattern of a recent, intact blister is that of a subepidermal cleavage without acantholysis[26]. DIF of perilesional skin biopsies reveals linear deposition of C3 in approximately 30% of cases of IgG along the BMZ[20,21,24-26]. IIF in patient serum can be positive in most cases, and immunoblotting studies show that 90% of serum from patients with PG recognizes collagen XVII[21,24]. Detection of the NC16A domain of collagen XVII by ELISA has a sensitivity and specificity of 96%[21,26]. It is directly related to disease activity and helps differentiate PG from other pruritic dermatoses of pregnancy, including PEP[21]. It should also be differentiated from other bullous dermatoses, drug reactions, and erythema multiforme[27].

Mild cases with localized lesions are treated with low- to medium-potency topical corticosteroids and local skin care[23-26]. For patients with severe disease, therapy is based on systemic corticosteroid therapy[23,24]. The only criterion proposed in the literature to differentiate between mild and severe forms is the affected body surface area (< or>10%). There may be a worsening in the immediate postpartum period that may require an increase in medication dose. The drug should be discontinued 2 weeks after delivery withdrawing in 3–6 months, depending on the severity and progression of lesions[24,26]. The involvement of the multidisciplinary team is encouraged in approaching the diagnosis and management of this condition[14].

ATOPIC ERUPTION OF PREGNANCY

AEP, a term proposed by Ambros-Rudolph et al. in 2006[8], encompasses clinical conditions of atopic dermatitis that exacerbate or appear during pregnancy[4]. This dermatosis is often idiopathic, and its pathogenesis has not been fully understood. Its clinical manifestations have an earlier onset (first and second trimester of pregnancy) than the other SDP[4]. However, patients without an atopic history are more likely to have a later onset of the disease[11].

Ambros-Rudolph et al. described two clinical presentations: the eczematous type (E-type) with a classic distribution of lesions, including eczematous eruption on the face, neck, pre-sternal region, and flexors, and the prurigo type (P-type) with the presence of small, pruritic, erythematous papules, often clustered, disseminated predominantly on extensor surfaces of extremities and trunk[8]. IgE measurement has not been systematically studied in pregnancy, and its role as a diagnostic criterion is unclear[4].

There are controversies about including PFP and PP in AEP. Some authors consider them to be separate entities[9-13,15]. PFP, described in 1981 by Zoberman and Famer, constitutes an erythematous papular, monomorphic eruption found in the second and third trimesters of pregnancy[28] with spontaneous regression after delivery[12]. A prospective study found 0.03% of cases consistent with PFP in 3,192 pregnant women followed up[14,29]. PP, formerly known as Besnier's prurigo gestationis and early pregnancy prurigo, begins around the 25th to 30th weeks of gestation as pruritic and erythematous papules and nodules in the extensor regions of the extremities and trunk[30].

Regardless of the clinical manifestation and classification, the treatment of this group of SDP is symptomatic[12]. They regress after delivery and do not affect maternal-fetal health[30].

INTRAHEPATIC CHOLESTASIS OF PREGNANCY

IHCP, described by Kehrer in 1907 as recurrent jaundice of pregnancy[1], has several names: cholestasis of pregnancy, prurigo gravidarum, and pruritus of pregnancy[13,15]. It is the only SDP that initially presents with pruritus without primary cutaneous lesions. Its prevalence ranges between 0.3 and 5.6% of pregnancies, depending on geographic and ethnic factors. A large study in Australia found a prevalence of 0.7%[14,31]. The family history is positive in 50% of the cases, and it is more frequent in twin pregnancies[1]. It occurs at the beginning of the second or third trimester of pregnancy, but there are reports of early onset, around the 8th week of pregnancy. IHCP may recur in subsequent pregnancies in 70% of cases and with the use of oral contraceptives[14,18,32].

IHCP pathogenesis is multifactorial and not fully understood. It is believed that genetic, hormonal, immunological,

and environmental factors may contribute and that the estrogen-bile acid axis plays a dominant role. Also, extracellular matrix and oxygen supply deregulation, organelle dysfunction, and epigenetic alterations may occur[33].

Clinically, it is characterized by intense, persistent, and generalized skin itching, which almost always gets worse at night and, at first, can be located only on the palmar and plantar region. Excoriations, erosions, and small papules are often secondary to scratching (Figure 2)[14]. Jaundice occurs in less than 20% of cases, and choluria and acholic stools may occur in 50% of cases, usually 2–4 weeks after the onset of pruritus[1].

There is no consensus on diagnostic criteria: some entities use persistent pruritus that disappears after delivery with bile acid concentration >10 µmol/L[33]. Liver enzymes, such as ALT, AST, and ALP, may be slightly elevated. Other causes of liver dysfunction must be ruled out[34].

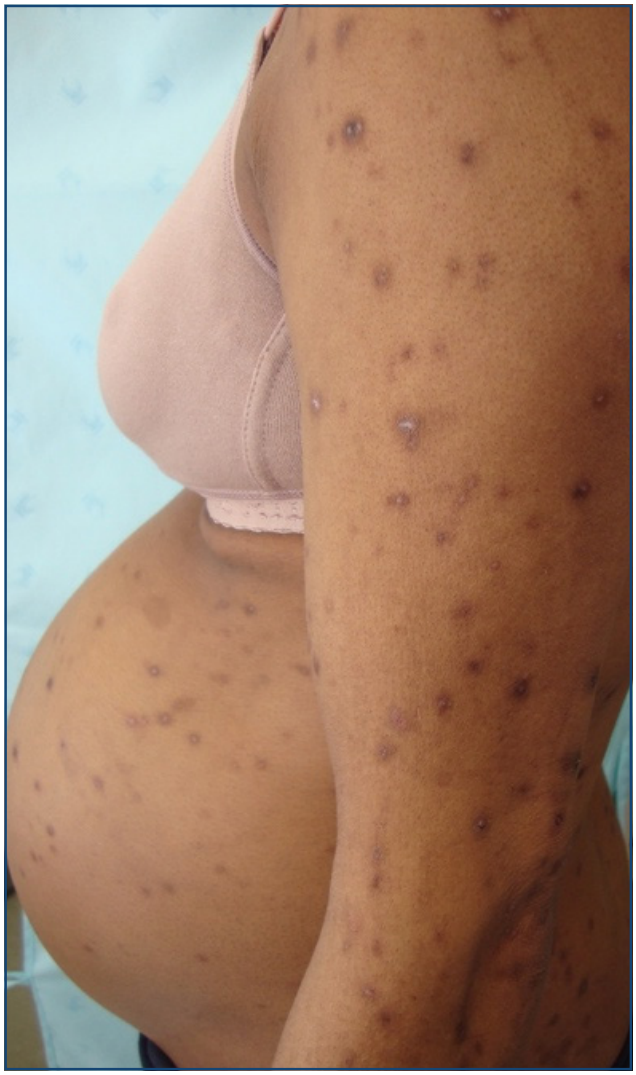

Figure 2. Pregnant woman with severe intrahepatic cholestasis of pregnancy, starting in the second trimester: excoriations, erosions, and residual hyperchromia throughout the integument secondary to scratching. Source: High Risk Prenatal Service (PNAR) at the Clinical Hospital at the Federal University of Minas Gerais.

The treatment of choice is ursodeoxycholic acid (UDCA) at 10–15 mg/kg/day to control itching and reduce bile acid levels[32]. Although UDCA is also used to improve fetal outcomes, there is controversy about its effect[33,34]. Emollients, topical antipruritic agents, and antihistamines are ineffective. In cases of prolonged cholestasis, administration of vitamin K may be necessary[35]. Pruritus usually resolves within 48 hours after delivery, and laboratory tests resolve within 2–4 weeks[30].

Maternal prognosis is usually favorable, and fetal risks are prematurity, perinatal mortality, and fetal distress. In a meta-analysis, Ovadia et al. provided evidence that IHCP is associated with a significantly increased risk of stillbirth for women with total serum bile acids of 100 µmol/L or higher. This study reinforces the inclusion of serum bile acid measurement in the diagnostic criteria for IHCP and recommends its wide use and monitoring during pregnancy[36].

The advances in the last 10 years regarding pathogenesis can bring potential targets for our drugs[33]. Intensive maternal and fetal monitoring is recommended, in addition to follow-up by an experienced multidisciplinary team to help decide the exact and safest moment for delivery[35].

FINAL CONSIDERATIONS

In SDP, the diagnosis is mainly based on clinical findings. Aside from PG and IHCP, no laboratory method is sufficient to differentiate these dermatoses, making clinical observation essential and leaving laboratory analysis for the differential diagnosis. Thus, the itching symptom should never be neglected, especially after the second and third trimesters of pregnancy. It affects the quality of life of the pregnant woman and can be a sign of several diseases.

Future elucidations of the etiology and pathophysiology of SDP will possibly bring new therapeutic modalities. Monitoring by a multidisciplinary team involving obstetricians, dermatologists, and other health professionals is encouraged in approaching the diagnosis and management of these conditions. The ultimate goal is optimal quality prenatal care for the pregnant woman and the fetus, with clinical monitoring and risk-benefit assessment on an individual basis.

AUTHORS' CONTRIBUTIONS

MLRC: Conceptualization, Writing – original draft. **GMM**: Conceptualization, Writing – original draft. **HVL:** Conceptualization, Writing – original draft.

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