

Dermatoses of pregnancy

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SUMMARY

The dermatoses of pregnancy represent a heterogeneous group of pruritic inflammatory skin diseases related to pregnancy and/or the postpartum period. Whereas some dermatoses are distressing only to the mother because of severe pruritus, others are associated with fetal risks including fetal distress, prematurity, and stillbirth. Early diagnosis and prompt treatment are essential for improving maternal and fetal prognosis. This review discusses the various pregnancy dermatoses in detail and offers an algorithmic approach to their diagnosis and management.

Introduction

Pregnancy is associated with complex endocrinological, immunological, metabolic, and vascular changes that may influence the skin in various ways. In addition to physiological skin changes and changes in the course of preexisting skin diseases, specific dermatoses of pregnancy may develop. These represent a heterogeneous group of inflammatory skin diseases related to pregnancy and/or the postpartum period. The leading symptom is severe pruritus. Over decades, attempts have been made to establish a reasonable classification (1, 2), but the rarity of these diseases, their variable clinical morphology, and the lack of unequivocal diagnostic tests has led to confusing terminologies. Based on the results of a retrospective two-center study on more than 500 pregnant patients, a new classification of these specific dermatoses of pregnancy has recently been proposed (3) that includes the following diseases: pemphigoid gestationis, polymorphic eruption of pregnancy, intrahepatic cholestasis of pregnancy, and atopic eruption

of pregnancy (Table 1). Atopic eruption of pregnancy encompasses the entities formerly described as prurigo of pregnancy and pruritic folliculitis of pregnancy. Although the severe pruritus associated with polymorphic and atopic eruption of pregnancy is distressing only for the mother, pemphigoid gestationis may be associated with small-for-date babies, and intrahepatic cholestasis of pregnancy poses an increased risk for fetal distress, prematurity, and stillbirth (4, 5). Because specific diagnostic tests are only available for some diseases and a pregnant patient with pruritus needs information on her condition as well as the possibly associated fetal risks preferentially at the first visit, before test results are available, exact knowledge of the clinical presentation of these diseases is essential. This review discusses the various pregnancy dermatoses in detail with special emphasis on epidemiology, clinical features, diagnostic tests, maternal and fetal prognosis, therapy, and management.

KEY WORDS

pruritus, pregnancy dermatoses, pemphigoid gestationis, polymorphic eruption of pregnancy, intrahepatic cholestasis of pregnancy, atopic eruption of pregnancy

Pemphigoid gestationis

Pemphigoid gestationis (PG, also known as herpes gestationis) is a rare autoimmune bullous disorder that presents mainly in late pregnancy or the immediate postpartum period. Its incidence is estimated to be 1 in 50,000 to 60,000 pregnancies and the disease shows a correlation with the haplotypes HLA-DR3 and DR4 (6). There is also an increased risk of developing other autoimmune diseases, in particular Grave's disease. PG tends to recur in subsequent pregnancies, with earlier onset and increasing severity. Very rarely (5%) a pregnancy may be passed over ("skip pregnancies").

Pathogenetically, circulating complement-fixing IgG antibodies of the subclass IgG1 (formerly known as "herpes gestationis factor") bind to a 180-kDa protein, BP-180 or bullous pemphigoid antigen 2, in the hemidesmosomes of the basal membrane zone (BMZ), leading to tissue damage and blister formation (7). Of interest, the primary site of autoimmunity seems not to be the skin, but the placenta, because antibodies bind not only to the BMZ of the epidermis, but also to that of chorionic and amniotic epithelia, both equally of ectodermal origin. Aberrant expression of MHC class II molecules on the chorionic villi suggests an allogenic immune reaction to a placental matrix antigen, thought to be of paternal origin.

Clinical features

PG presents with intense pruritus that may occasionally precede the appearance of skin lesions. Initially, erythematous urticarial papules and plaques develop typically on the abdomen, but may spread to the entire skin surface. The umbilical region is almost always involved. In this "pre-bullous" stage, differentiation between PG and polymorphic eruption of pregnancy is almost impossible, both clinically and histopathologically. Diagnosis becomes clear when lesions progress to tense blisters that resemble those in bullous pemphigoid. Facial and mucous membranes are usually spared (6).

Diagnostic tests

Histopathological findings from lesional skin depend on the stage and severity of the disease. Whereas the pre-bullous stage is characterized by edema of the upper and middle dermis accompanied by a predominantly perivascular inflammatory infiltrate, composed of lymphocytes, histiocytes, and a variable number of eosinophils, the bullous stage reveals subepidermal blistering that, ultrastructurally, may be located to the lamina lucida of the BMZ (6).

Direct immunofluorescence of perilesional skin, the gold standard in the diagnosis of PG, shows linear C3 deposition along the BMZ in 100% of cases and additional IgG deposi-

tion in 30%. Depending on the technique used, circulating IgG antibodies in the patient's serum may be detected by indirect immunofluorescence in 30 to 100% of cases, binding to the roof of the artificial cleft on salt-split skin. Antibody levels may also be monitored using modern ELISA and immunoblot techniques, and show a good correlation with disease activity (6, 7).

Prognosis

The natural course of PG is characterized by exacerbations and remissions during pregnancy, with frequent improvement in late pregnancy followed by a flare-up at the time of delivery (75% of patients). After delivery, the lesions usually resolve within weeks to months but may recur with menstruation and hormonal contraception. Rarely, severe courses with persistence of skin lesions over several years may occur. Fetal prognosis is generally good; there is an increase in small-for-date babies but not in prematurity or stillbirths (4). Due to a passive transfer of antibodies from the mother to the fetus, 10% of newborns develop mild skin lesions that resolve spontaneously within days to weeks (6).

Therapy and management

Treatment depends on the stage and severity of the disease and aims to control pruritus and to prevent blister formation. Only in cases of mild pre-blistering, topical corticosteroids with or without oral antihistamines may be sufficient (6). All other cases require systemic corticosteroids (prednisolone, usually started at a dose of 0.5–1 mg/kg/day) that are considered safe in pregnancy (8, 9). When the disease improves, the dose can usually be reduced, but should be increased in time to prevent the flare-up common at delivery. Cases unresponsive to systemic corticosteroid treatment may benefit from immunoadsorption (10). After delivery, if necessary, the full range of immunosuppressive treatment may be administered.

Polymorphic eruption of pregnancy

Polymorphic eruption of pregnancy (PEP), also known as pruritic urticarial papules and plaques of pregnancy (PUPPP), toxic erythema of pregnancy, toxemic rash of pregnancy, late-onset prurigo of pregnancy) is a benign, self-limited pruritic inflammatory disorder that usually affects primigravidae in the last weeks of pregnancy or immediately postpartum (15%; 11). Its incidence is about 1:160 pregnancies and the condition is associated with excessive maternal weight gain and multiple pregnancies (11, 12).

The pathogenesis of PEP remains unclear. The main theories proposed to date focus on abdominal distension,

Table 1. Classification of the dermatoses of pregnancy (3).

Classification	Synonym(s)
Pemphigoid gestationis (PG)*	Herpes gestationis [†]
Polymorphic eruption of pregnancy (PEP)*	Pruritic urticarial papules and plaques of pregnancy [†] Toxic erythema of pregnancy Toxemic rash of pregnancy Late onset prurigo of pregnancy
Intrahepatic cholestasis of pregnancy (ICP)	Obstetric cholestasis Cholestasis of pregnancy [†] Jaundice of pregnancy Pruritus/Prurigo gravidarum
Atopic eruption of pregnancy (AEP)	Prurigo of pregnancy* [†] Prurigo gestationis Early onset prurigo of pregnancy Pruritic folliculitis of pregnancy* Eczema in pregnancy

Previous classifications by Holmes & Black* (1) and Shornick[†] (2).

hormonal, and immunological factors (13). The fact that PEP starts within striae distensae at the time of greatest abdominal distension favors connective tissue damage due to overstretching as playing a central role. It has been suggested that previously inert structures develop an antigenic character, thus triggering the inflammatory process. Hormonal and immunological changes have not definitively been shown; nor has an association with increased birth weight or male sex of the newborn been confirmed (4, 11). (Figure 1.)

Clinical features

PEP typically starts on the abdomen, within striae distensae, with severely pruritic urticarial papules that coalesce into plaques, spreading to the buttocks and proximal thighs. Often the eruption remains located to these sites but can quickly generalize in severe cases. Unlike in PG, a characteristic finding is the sparing of the umbilical region. Later on, the clinical picture becomes polymorphous, as vesicles (but never bullae), widespread non-urticated erythema, and targetoid and eczematous lesions appear in more than half of patients. The rash usually resolves within 4 to 6 weeks (11).

Diagnostic tests

Histopathology is non-specific and varies with the stage of disease. Next to a superficial to mid-dermal perivascular lymphohistiocytic infiltrate intermingled with eosinophils, early biopsies show a prominent dermal edema, and later biopsies reveal frequent epidermal changes including spongiosis, and hyper- and parakeratosis. Direct and indirect immunofluorescence investigations are essentially negative in PEP.

Prognosis

Maternal and fetal prognosis is excellent and there is no cutaneous involvement of the newborn (12). Lesions are self-limited and PEP tends not to recur; the exception to this is multiple pregnancies, when both earlier presentation and manifestation in a subsequent pregnancy may occur.

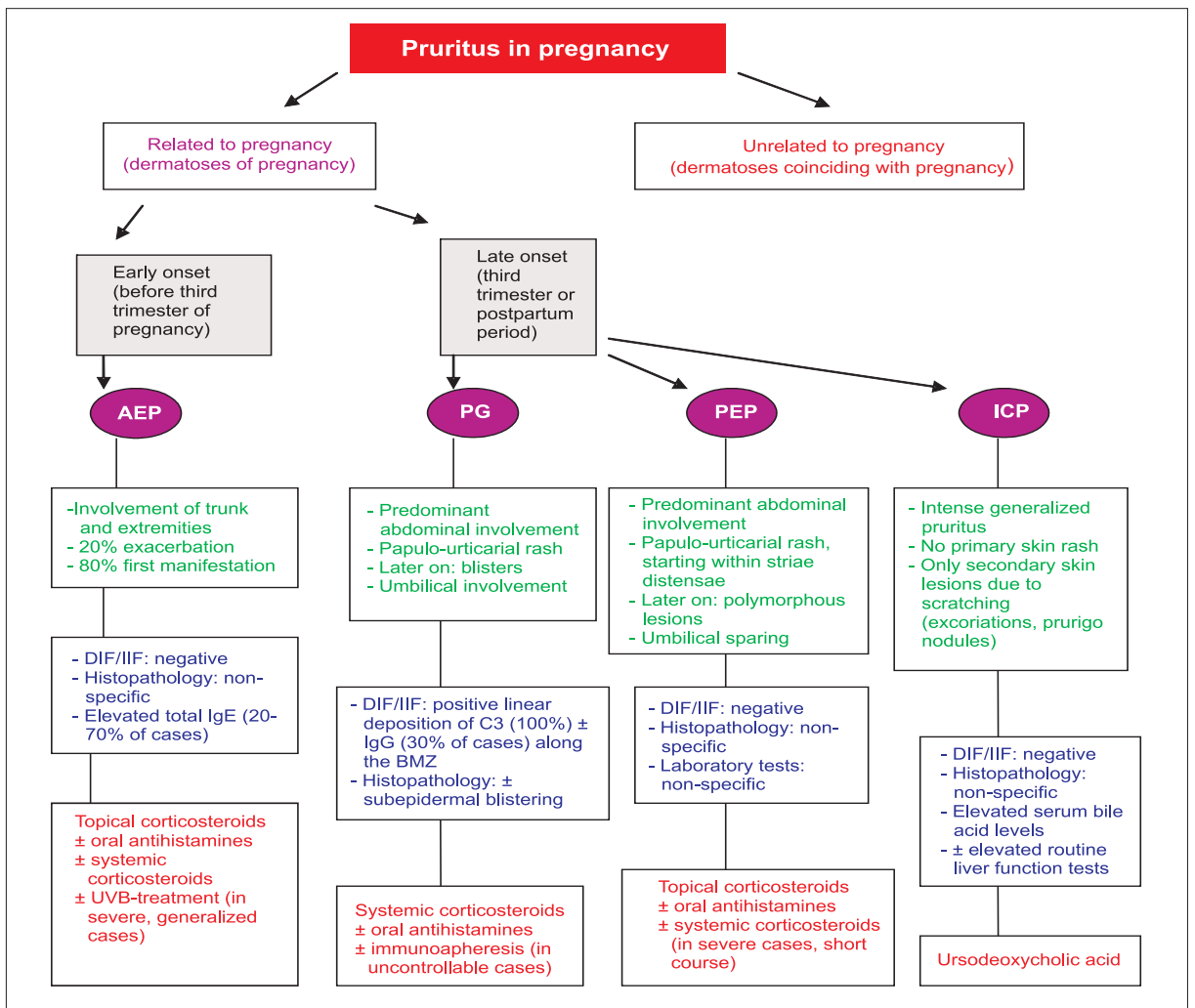
Therapy and management

Symptomatic treatment with topical corticosteroids with or without antihistamines is usually sufficient to control pruritus and skin lesions (12). If systemic antihistamines are needed during pregnancy, older sedating substances such as dimethindene, clemastine, and pheniramine are preferable due to greater experience with their use. This especially applies to the first trimester. If a non-sedating antihistamine is required, loratadine and cetirizine can be administered safely in the second and third trimesters (8, 9). If topical corticosteroids are ineffective to relieve pruritus, and in severe generalized cases, a short course of systemic corticosteroids (prednisolone, 40–60 mg/day, for a few days) may be necessary and is usually very effective (12).

Intrahepatic cholestasis of pregnancy

Intrahepatic cholestasis of pregnancy (ICP), also known as obstetric cholestasis, cholestasis of pregnancy, jaundice of pregnancy, pruritus/prurigo gravidarum) is a reversible form of hormonally triggered cholestasis that typically develops in genetically predisposed indi-

Table 2. Algorithmic approach to pregnant patients with pruritus.



AEP = atopic eruption of pregnancy, PG = pemphigoid gestationis, PEP = polymorphic eruption of pregnancy, ICP = intrahepatic cholestasis of pregnancy, DIF = direct immunofluorescence, IIF = indirect immunofluorescence, BMZ = basal membrane zone.

viduals in late pregnancy. In contrast to the other dermatoses of pregnancy, it presents with pruritus and exclusively secondary skin lesions due to scratching.

The incidence of ICP shows a striking geographical pattern; whereas its prevalence in Central Europe is around 0.2 to 2.4%, it is particularly frequent in Scandinavia and



Figure 1. Polymorphic eruption of pregnancy.



Figure 2. Atopic eruption of pregnancy).

South America, with the highest rates in Chile (15–28%) (5). ICP runs in families and tends to recur in subsequent pregnancies (45–70%) (5, 14).

Pathogenetically, there is a defect in the excretion of bile salts resulting in elevated serum bile acids in the serum. This leads to severe pruritus in the mother, and, because toxic bile acids can pass into fetal circulation, may have deleterious effects on the fetus due to acute placental anoxia and cardiac depression. The reason for this defect seems to be multifactorial, with genetic, hormonal, and exogenous factors being involved (5). Endemic clustering and familial occurrence has pointed towards a genetic background; recently, mutations of certain genes encoding for transport proteins necessary for bile excretion (e.g., the ABCB4 [MDR 3] gene) have been identified in some ICP patients (15). With normal hormone levels, this defect has no clinical implications; it only becomes evident with the highest concentrations as in late pregnancy and/or with hormonal contraception. Furthermore, it has been demonstrated that estrogen and progesterone metabolites are cholestatic themselves (16). Some authors also discuss additional environmental and dietary factors influencing the manifestation of ICP, such as decreased serum selenium levels and others (17).

Clinical features

ICP typically presents with sudden onset of severe pruritus that may start on the palms and soles but quickly becomes generalized. It persists throughout pregnancy and may be tormenting. Of importance, ICP is not associated with primary skin lesions. Clinical features correlate with disease duration (18). At the beginning of pruritus, the skin may be unaffected; later on, secondary skin lesions develop due to scratching that range from subtle excoriations to severe prurigo nodules as pruritus persists. Skin lesions usually involve the shins and lower arms, but may also be present on other sites such as on the buttocks and abdomen. Jaundice, due to concomitant extrahepatic cholestasis, occurs in only 10% of patients, usually after 2 to 4 weeks, complicating the most severe and prolonged episodes (19). These patients are at risk of developing steatorrhea with malabsorption of fat-soluble vitamins, including vitamin K, and potential bleeding complications, as well as cholelithiasis (5).

Diagnostic tests

Histopathology is non-specific; direct and indirect immunofluorescence are negative. The most sensitive indicator for the diagnosis of ICP is a rise of serum bile acid levels, whereas routine liver function tests (including transaminases) may be normal in up to 30% (5, 18). In healthy pregnancies, total serum bile acid levels are slightly higher than in non-pregnant women, and levels up to 11.0 $\mu\text{mol/l}$ are accepted as normal in late gesta-

tion (20, 21). Hyperbilirubinemia is noted in only 10 to 20%; it should always lead to close surveillance of prothrombin time and an ultrasound examination of the liver may be necessary in such cases.

Prognosis

The prognosis for the mother is generally good. After delivery, pruritus disappears spontaneously within days to weeks but may recur with subsequent pregnancies and oral contraceptive use (5). In cases of jaundice and vitamin K deficiency, there is an increased risk for intra- and postpartum hemorrhage in both mother and child (5). However, the key consideration in this disease is not maternal pruritus but the significantly impaired fetal prognosis. ICP is associated with an increased risk of prematurity (19–60%), intrapartum fetal distress (22–33%), and stillbirths (1–2%), which correlate with higher bile acid levels, in particular if in excess of 40 $\mu\text{mol/l}$ (5, 22). Therefore, prompt diagnosis, specific therapy, and close obstetric monitoring as well as maternal counseling, in particular on the expected recurrence in subsequent pregnancies, are essential.

Therapy and management

The aim of treatment is the reduction of serum bile acid levels in order to prolong pregnancy and reduce both fetal risks and maternal symptoms. Ursodeoxycholic acid (UDCA) is the only treatment that has been shown not only to reduce maternal pruritus but to also improve fetal prognosis (5, 18, 23–26). It is a naturally occurring, hydrophilic, non-toxic bile acid that has been successfully employed in Chinese medicine for over 5,000 years in treating various liver diseases and nowadays plays a key role in treating hepatobiliary disorders. In ICP, a dose of 15 mg/kg/day or, independent of body weight, 1 g/day is administered either as single dose or divided into two to three doses until delivery, when it usually can be stopped. With the exception of occasional mild diarrhea, no adverse effects occur. However, UDCA is not licensed for use in pregnancy; thus, it requires special patient information (“off-label use”). Other drugs, including antihistamines, S-adenosyl-L-methionine, dexamethasone, and cholestyramine, do not improve fetal prognosis (5). Of note, cholestyramine and other bile acid exchange resins may contribute to malabsorption of vitamin K with possible consecutive bleeding complications and should therefore be avoided (27). In addition to UDCA treatment, close obstetric surveillance is indicated and includes weekly fetal cardiotocographic (CTG) registration at least from 34 weeks’ gestation on; early delivery as soon as lung maturity is achieved (36–37 weeks) is recommended by some authors (28). Interdisciplinary management of ICP by dermatologists, hepatologists, gynecologists, and pediatricians is absolutely mandatory.

Atopic eruption of pregnancy

Atopic eruption of pregnancy (AEP), also known as prurigo of pregnancy, prurigo gestationis, early-onset prurigo of pregnancy, pruritic folliculitis of pregnancy, eczema in pregnancy) is a benign pruritic disorder of pregnancy which includes eczematous and/or papular lesions in patients with a personal and/or family history of atopy and/or elevated IgE levels after exclusion of the other dermatoses of pregnancy. This term has been introduced based on the results of a large two-center study, in which significant overlap has been observed clinically and histopathologically between patients formerly diagnosed as suffering from eczema in pregnancy, prurigo of pregnancy, and pruritic folliculitis of pregnancy (3). It is the most common dermatosis in pregnancy, accounting for 50% of patients, usually starts early – in 75% before the third trimester – and, due to its atopic background, tends to recur in subsequent pregnancies (3).

The pathogenesis of AEP is thought to be triggered by pregnancy-specific immunological changes; reduced cellular immunity and reduced production of Th1 cytokines (IL-2, interferon gamma, IL-12) stands in contrast to the dominant humoral immunity and increased secretion of Th2 cytokines (IL-4, IL-10) (29). Thus, the exacerbation of preexisting atopic dermatitis as well as the first manifestation of atopic skin changes can be explained by a predominant Th2 immune response that is typical for pregnancy. (Figure 2.)

Clinical features

20% of patients will suffer from an exacerbation of pre-existing atopic dermatitis with a typical clinical picture. The remaining 80% will experience atopic skin changes for the first time ever or after a long remission (e.g., since childhood). Of these, two-thirds present with widespread eczematous changes (so-called E-type AEP) often affecting typical atopic sites such as face, neck, upper chest, and the flexural surfaces of the extremities, whereas one-third have papular lesions (P-type AEP) (3). These lesions include small erythematous papules disseminated on trunk and limbs, as well as typical prurigo nodules, mostly located on the shins and arms. A key finding is the often extreme dryness of the skin and frequent atopic “minor features” according to Hanifin and Rajka (30).

Diagnostic tests

Histopathology is non-specific and varies with the clinical type and stage of the disease. Direct and indirect immunofluorescence are negative. Laboratory tests may reveal elevated serum IgE levels in 20 to 70% (3).

Prognosis

Maternal prognosis is good even in severe cases because skin lesions usually respond quickly to therapy; recurrence in subsequent pregnancies is common. Fetal prognosis is unaffected, but there the infant faces a higher risk of developing atopic skin changes later on.

Therapy and management

Basic treatment is essential and consists in regular application of emollients, often with urea (3–10%) or antipruritic additives such as menthol or polidocanol. Together with topical corticosteroids for several days, this will usually lead to quick improvement of skin lesions. Severe cases may require a short course of systemic corticosteroids and antihistamines; phototherapy (UVB) is a helpful additional measure and considered safe in pregnancy.

Algorithmic approach to pregnant patients with pruritus

Pruritus in pregnancy should never be neglected and should always lead to a precise work-up of the patient. It may be the leading symptom of the dermatoses of pregnancy, but it can also be associated with other dermatoses coinciding by chance with pregnancy. These include scabies, pityriasis rosea, drug rashes, and cutaneous infections that, as a first step, should be excluded. In the second step, the four specific dermatoses of pregnancy must be differentiated. Here, the onset and localization of skin lesions as well as the history and clinical characteristics may offer helpful clues towards the right diagnosis (Table 2). In pemphigoid gestationis and intrahepatic cholestasis of pregnancy, specific diagnostic tests such as immunofluorescence and laboratory investigations will further confirm the diagnosis. Although polymorphic and atopic eruption of pregnancy do not impair maternal or fetal prognosis, pemphigoid gestationis and intrahepatic cholestasis of pregnancy may be associated with fetal risks. Corticosteroids and antihistamines are used to treat pemphigoid gestationis and polymorphic and atopic eruption of pregnancy, whereas intrahepatic cholestasis of pregnancy should be treated specifically with ursodeoxycholic acid.

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