

# Dermatoses of Pregnancy

MARK A. BECHTEL, MD, and ALISHA PLOTNER, MD

*Division of Dermatology, Department of Medicine-Clinical,  
Ohio State University College of Medicine, Gahanna, Ohio*

**Abstract:** The dermatoses of pregnancy represent a distinct heterogenous group of cutaneous disorders that can impact the health of the pregnant woman and potentially the fetus. The current classification of pregnancy-specific cutaneous disorders is reviewed, along with important clinical features. Advances in management of these disorders, along with fetal implications, are discussed. The diagnosis of these disorders is challenging, but important clinical features can aid in diagnosis. There have been important advances in the management of these disorders and better understanding of potential fetal risks. Early recognition is critical for appropriate care.

**Key words:** intrahepatic cholestasis of pregnancy, pemphigoid gestationis, polymorphic eruption of pregnancy, atopic eruption of pregnancy, ursodeoxycholic acid

## Dermatoses of Pregnancy

The dermatoses of pregnancy represent a distinct heterogenous group of pruritic skin disorders that can be very distressing for the mother. Some of the disorders have been reclassified (Table 1), which can lead to confusion. They include polymorphic eruption of pregnancy (PEP) [formerly known as pruritic urticarial papules and plaques of pregnancy (PUPPP)],

pemphigoid gestationis (PG) (formerly known as herpes gestationis), intrahepatic cholestasis of pregnancy (ICP), and atopic eruption of pregnancy (AEP). Whereas PEP and AEP can be associated with severe pruritus and discomfort for the mother, PG and ICP are associated with increased fetal complications. The diagnosis and management of these pregnancy-specific disorders can be challenging due to their variation in clinical presentation and lack of definitive diagnostic tests. Early recognition of these disorders is critical to provide symptomatic care for the mother and avoid potential increased fetal risk if the diagnosis is delayed (Tables 2 and 3). Each therapy reviewed in this section will be assigned a letter from A (most evidence) to E (least evidence). An A designation represents at least 1 prospective randomized, double-blinded, controlled trial or meta-analysis, whereas B represents clinical trials with > 20 subjects, but lacks adequate controls. C represents small trials with < 20 subjects, but design limitations or large number of case reports, D reflects at least 5 cases reported in the literature, and E has only anecdotal case reports of < 5 cases.<sup>1</sup>

In 1982, Holmes and Black<sup>2</sup> first described a generalized classification of pregnancy-specific cutaneous disorders. Their classifications included herpes gestationis

*Correspondence:* Mark Bechtel, MD, 540 Officenter Place, Suite 240, Gahanna, OH. E-mail: mark.bechtel@osumc.edu

*The authors declare that they have nothing to disclose.*

TABLE 1. Classification

Preferred Term	Historical Terms
Intrahepatic cholestasis of pregnancy	Obstetric cholestasis Pruritus/prurigo gravidarum Icterus gravidarum Jaundice of pregnancy
Atopic eruption of pregnancy	Eczema in pregnancy Prurigo of pregnancy Pruritic folliculitis of pregnancy Papular dermatitis of pregnancy Prurigo gestationis
Pemphigoid gestationis	Herpes gestationis
Polymorphic eruption of pregnancy	Pruritic urticarial papules and plaques of pregnancy Toxic rash of pregnancy Late-onset prurigo of pregnancy Erythema multiforme of pregnancy

(currently PG), PUPPP (currently PEP), prurigo of pregnancy, and pruritic folliculitis of pregnancy. The latter 2 disorders are now included under the broader current diagnostic classification of AEP.<sup>3</sup> Shornick in 1998 advocated classifying ICP as a specific dermatosis of pregnancy.<sup>3</sup> The current consensus classified 4 disorders as pregnancy-specific dermatoses, including PG, PEP, ICP, and AEP.

## ICP

ICP is a reversible cholestasis that is hormonally triggered in genetically predisposed individuals during late pregnancy.<sup>4</sup> There is a striking geographical variation with prevalence in Europe of 0.1% to 1.5% to a high of 28% in women of Araucanian Indian ancestry in Chile.<sup>5</sup>

A genetic predilection is suggested due to an increased frequency in families and monozygotic twins.<sup>3</sup> ICP tends to recur in subsequent pregnancies (45% to 70%).<sup>4</sup>

Patients with ICP develop a reduced excretion of bile acids, which results in increased

serum levels with toxic bile acids crossing the placenta. This results in the onset of severe pruritus in the mother and fetal compromise due to acute placental anoxia and cardiac depression.<sup>4</sup> Fetal anoxia is secondary to abnormal uterine contractility, vasoconstriction of chorionic veins, along with impaired fetal cardiomyocyte function.<sup>6</sup> Mutations in the gene adenosine triphosphate-cassette transport B4 (*ABCB4*), which encodes transport proteins involved in bile excretion, have been localized in women with ICP.<sup>3</sup>

The pregnant patient with ICP typically presents in the late second or third trimester with the sudden onset of severe pruritus. Involvement of the palms and soles is common. Approximately 10% of the time, the onset of pruritus is in the first trimester.<sup>3</sup> No primary skin lesions are present, but secondary skin changes from scratching develop over time. Skin lesions vary from minor excoriations to thickened prominent prurigo nodularis. There is a predominance of involvement on the extensor surfaces of the extremities and buttocks. Jaundice occurs in over 10% of patients and reflects the most severe and prolonged cases of ICP.<sup>6</sup> Pruritus usually persists until delivery and then gradually resolves over 2 to 3 weeks.

Maternal prognosis in ICP is favorable. Patients who develop steatorrhea and malabsorption of fat-soluble vitamins, including vitamin K, are at increased risk of bleeding problems.<sup>3</sup> These patients are more likely to manifest jaundice. Women with ICP are more often later diagnosed with hepatobiliary disease, including gallstones, cholangitis, hepatitis C, chronic hepatitis, and cirrhosis. There is a strong association between ICP and hepatitis C, both before and after ICP diagnosis. It is important to screen for hepatitis C in women with ICP.<sup>7</sup> Fetal prognosis is a concern in ICP. The risks of preterm delivery, meconium-stained amniotic fluid, and stillbirth are significant and increase with maternal bile acid concentrations.<sup>8</sup>

When ICP is suspected, it is important to evaluate liver function tests and

**TABLE 2. Distinctive Features of the Pregnancy-specific Dermatoses**

	Onset	Clinical Features	Diagnosis	Maternal Risk	Fetal Risk	Treatment
ICP	Late second or early third trimester	Pruritus, no primary skin lesions	Total bile acids > 11 $\mu\text{mol/L}$	Labor induction Cholelithiasis Steatorrhea Intrapartum hemorrhage	Meconium staining Preterm delivery Intrauterine fetal demise	Ursodeoxycholic acid (UDCA)
AEP	First and second trimesters	Ecematous rashes	Clinical appearance	None	None	Emollients, topical steroids
PG	Second and third trimesters	Urticarial papules and plaques, vesicles and bullae	Skin biopsy Direct cutaneous immunofluorescence	Increased risk of Grave disease	Preterm birth Low birthweight	Topical and systemic corticosteroids, antihistamines
PEP	Third trimester Postpartum in 15%	Urticarial papules and plaques initially involve striae gravidarum Spares umbilicus	Clinical diagnosis No specific laboratory or skin biopsy findings	None	None	Emollients Corticosteroids Antihistamines

AEP indicates atopic eruption of pregnancy; ICP, intrahepatic cholestasis of pregnancy; PEP, polymorphic eruption of pregnancy; PG, pemphigoid gestationis.

quantitate serum bile acid levels. Total bile acids > 11.0  $\mu\text{mol/L}$  confirms the diagnosis and serum bile salts > 40  $\mu\text{mol/L}$  portend a poor fetal prognosis.<sup>3</sup> There is a significant difference between serum bile acid profiles in women with severe ICP and those with mild ICP.

Management of patients with ICP requires a timely and accurate diagnosis, along with close obstetric monitoring. Women with ICP are at increased risk for recurrence of ICP with subsequent pregnancies. The first-degree relatives of patients with ICP are also at increased risk.<sup>3</sup>

The goal of management is to reduce serum bile acid levels in an attempt to reduce maternal pruritus, prolong pregnancy, and reduce fetal risks. Ursodeoxycholic acid (UDCA) is the only treatment demonstrated not only to reduce maternal pruritus,

but to also improve fetal prognosis.<sup>4</sup> UDCA corrects the maternal serum bile acid profile

**TABLE 3. Treatment of Pregnancy Dermatoses**

Pregnancy Dermatoses	Treatment	Therapeutic Level of Evidence
Intrahepatic cholestasis of pregnancy	Ursodeoxycholic acid	A
	Emollients	D
	Antihistamines	D
Pemphigoid gestationis	Systemic steroids	B
	Topical corticosteroids	C
	Antihistamines	C
Polymorphic eruption of pregnancy	Topical corticosteroids	B
	Antihistamines	C
	Systemic steroids	D
	Early delivery	E

and decreases the movement of maternal bile acids to the fetal placental unit. The drug is relatively safe for the mother and fetus, but is off-label when used for ICP.<sup>6</sup> A dose of 15 mg/kg/d or 1 g/d is administered either as a single dose or divided into 2 or 3 doses until delivery.<sup>3</sup> The administration of UDCA results in significant improvement in itching at 2 weeks, along with concomitant decreases in total bile acids and alanine aminotransferase.

Because the majority of stillbirths with ICP tend to cluster at the 38th week, it has been suggested that delivery occur by the 38th week.<sup>3</sup> Women with ICP and markedly elevated serum bile acids ( $> 40 \mu\text{mol/L}$ ) should be considered for delivery at 37 weeks or earlier.<sup>8</sup> The induction of labor in women with ICP gestational weeks 37 to 39 did not increase the risks of emergency cesarean section or fetal asphyxia.<sup>9</sup>

## AEP

The term AEP encompasses previously used terms, including eczema in pregnancy, prurigo of pregnancy, and pruritic folliculitis of pregnancy.<sup>10</sup> AEP is defined as an exacerbation or the first occurrence of eczematous and/or papular skin changes during pregnancy in patients with an atopic diathesis.<sup>6</sup> It represents the most common pruritic disorder of pregnancy and the majority of cases present before the third trimester. Approximately 20% of patients suffer from an exacerbation of preexisting atopic dermatitis, whereas the remaining 80% experience eczematous changes for the first time or after a long clinical remission.<sup>4</sup> It is possible the dominant Th2 cytokine production occurring during pregnancy favors the development of AEP.<sup>6</sup>

The most common clinical presentation is the development of an eczematous rash in the classic "atopic sites," such as the face, eyelids, neck, and antecubital and popliteal fossae. Approximately one third present with pruritic papules on the trunk and extremities (Fig. 1). Some



**FIGURE 1.** Pruritic plaques on legs of atopic dermatitis, which recurrently flare during pregnancies.

patients develop prominent prurigo nodularis and xerosis is common. The rash may recur with subsequent pregnancies. There are no increased fetal or maternal risks.

The histopathology of skin biopsies in AEP are nonspecific and direct and indirect immunofluorescence is negative. There are no specific laboratory abnormalities, except an elevation in serum IgE in 20% to 70% of patients.<sup>4</sup>

Management is directed at providing relief of pruritus and xerosis without increasing fetal or maternal risk. Patients benefit from moisturizers, especially applied after the bath, lukewarm showers, and mild soaps. All Free and Clear (The Sun Products Corp., Wilton, CT) detergent is a hypoallergenic detergent for laundry, which can be helpful. Patients should avoid wool and rough polyester fabrics. Low and mid potency topical steroids are first-line agents when emollients alone are not adequate to control symptoms. Systemic first-generation antihistamines, such as chlorpheniramine and diphenhydramine (pregnancy category B), are safe during pregnancy and can help reduce pruritus.<sup>3</sup> Narrow-band ultraviolet B phototherapy can be used in severe cases that are not responding to topical steroids. In recalcitrant and

highly symptomatic cases, a short trial of prednisone can be considered. An alternative to systemic steroids in severe cases is cyclosporine, which is not teratogenic, but can have adverse effects on renal function and blood pressure.

## PG

PG was previously known as herpes gestationis and is a rare autoimmune bullous disease of pregnancy. The majority of cases develop during late pregnancy or the immediate postpartum period. Although the second and third trimester is the most common period of presentation, PG can occur during the first trimester. Recurrences in subsequent pregnancies are common and may be more severe. PG may also flare during menses or with oral contraceptive use. There is an increased risk of preterm labor and intrauterine growth retardation.<sup>11</sup> The incidence occurs in 1 in 50,000 pregnancies. It has also been reported due to trophoblastic tumors, including choriocarcinoma and hydatidiform mole.<sup>4</sup>

PG is associated with abnormal major histocompatibility complex II expression in the amniochorionic stromal cells and trophoblasts, which exposes bullous pemphigoid (BP) 180 antigen to the maternal immune surveillance. Maternal antiplacental IgG antibodies are produced that cross-react with BP180 in the skin.<sup>11</sup> The BP180 NC16a enzyme-linked immunosorbent assay is highly sensitive and highly specific in differentiating PG from PEP. In addition to BP180, antiplacental IgG antibodies also react with BP230 in the skin. BP180 and BP230 are important structural proteins in hemidesmosomes that are critical for dermoepidermal adhesion.<sup>11</sup>

The histology of PG is dependent on the stage and severity of the disease. In the early prebullous stage, when erythematous and urticarial plaques predominate, pathology is characterized by edema of the upper and mid-dermis with a perivascular infiltrate of lymphocytes, histiocytes, and

eosinophils, whereas the bullous stage demonstrates subepidermal blisters.<sup>4</sup> Direct immunofluorescence of perilesional skin is diagnostic and demonstrates linear deposits of complement 3 (C3) with or without immunoglobulin (IgG) along the basement membrane zone, within the lamina lucida, and localized to the proximal part of anchoring filaments of the epidermal component of salt split skin. Indirect immunofluorescence detects antibodies against the basement membrane in 20% of cases.<sup>3</sup>

The clinical presentation of PG is characterized by the acute onset of very pruritic urticarial papules and plaques along with vesicles and bullae. The blisters are usually clear and tense. These lesions present initially on the abdomen and then spread centrifugally, eventually involving the extremities (Fig. 2).<sup>6</sup> Unlike PEP (previously called PUPPP), PG typically involves the umbilicus.<sup>3</sup> The face and mucous membranes are usually spared, but involvement of the palms can sometimes be prominent. During late pregnancy, many patients improve, but can flare immediately postpartum. Spontaneous remission within weeks or months following delivery is common. Intense and often disabling pruritus re-



**FIGURE 2.** Tense bullae overlying the thighs in a postpartum mother with pemphigoid gestationis.

presents the greatest complaint of these patients. There may be an increased risk of Grave disease after delivery.<sup>3</sup>

The early onset of PG, especially with blister formation, is associated with adverse pregnancy outcomes.<sup>12</sup> PG is associated with miscarriage, preterm delivery, and fetal growth restriction.<sup>13</sup> Evaluation of placentas in mothers with PG shows some slight alteration in ultrastructural morphology of the placental basement membrane. Umbilical artery Doppler evaluation demonstrates no functional placental changes.<sup>13</sup>

The primary goal of treatment is to reduce pruritus. Topical emollients containing menthol or pramoxine are helpful and safe along with oatmeal baths (watching for slipping). Washing clothing and bed sheets in mild detergent, such as All Free and Clear, along with mild bathing soaps is beneficial. Mild topical steroids for the face and intertriginous areas, along with moderately potent steroids for the trunk and extremities, is important first-line therapy.<sup>4</sup>

A significant number of patients with PG require systemic steroids to control the pruritus and reduce blister formation. Because prednisone does not easily pass through the placenta, it is preferred during pregnancy.<sup>14</sup> The disease is usually controlled at 20 to 40 mg daily, but 1 to 2 mg/kg/d may be required for refractory cases.<sup>3</sup> New blister formation should be stabilized for 2 weeks before trying to taper the dose. Sometimes the dose needs to be increased at the time of delivery due to typical flares. Calcium and vitamin D supplementation is recommended and stress doses of steroids may be needed, if faced with pregnancy complications while on systemic steroids. Pregnancy-specific morbidities can be exacerbated and can include gestational diabetes, preeclampsia, eclampsia, and hypertension.<sup>14</sup> Patients should be warned of low risk of cleft palates with exposure to oral steroids during the first trimester.

Intravenous IgG can be used during pregnancy and postpartum for refractory

cases. It is often given in conjunction with prednisone. Intravenous IgG is FDA pregnancy class C and is thought to be a safe option during pregnancy.<sup>14</sup> In refractory cases of PG that are not responding to systemic steroids after delivery and while not breastfeeding, other systemic agents can be considered. Tetracycline, nicotinamide, cyclosporine, azathioprine, dapsone, and rituximab have been reported to be therapeutically beneficial.<sup>3</sup>

## PEP

PEP, formerly known as PUPPP, is the most common dermatosis of pregnancy occurring in about 1 in 200 pregnancies.<sup>6</sup> PEP most commonly occurs in primiparous women and particular risk factors are multiple gestation pregnancies and possibly increased maternal weight gain.<sup>15</sup> The incidence is approximately 0.5% in single pregnancies, 2.9% in twin pregnancies, and 14% in triplet pregnancies.<sup>16</sup> Typical onset is during the last month of pregnancy, particularly between 36 and 39 weeks' gestation, but PEP also develops in the immediate postpartum period in about 15% of cases.<sup>15</sup> One study demonstrated an association between multiple gestation pregnancies and earlier onset of PEP, even in the late second trimester.<sup>15</sup>

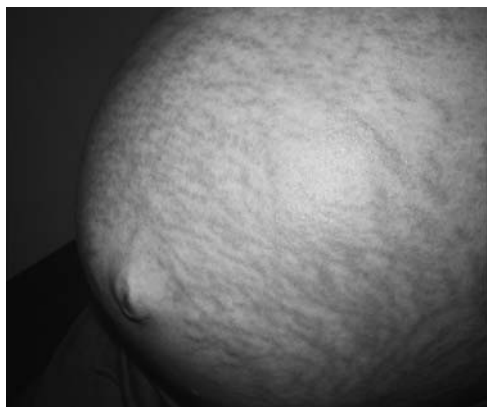
The pathogenesis of PEP is unclear but may involve abdominal distention, immunologic factors, hormonal factors, and/or fetal cell microchimerism. Abdominal distention has been suggested to cause connective tissue damage and exposure of antigens, possibly within collagen, which trigger an abnormal maternal immunologic reaction. This is supported by the onset of PEP within the striae gravidarum and the association of PEP with multiple gestation pregnancies and excessive maternal weight gain.<sup>17</sup>

Hormonal abnormalities have been detected in patients with PEP. In 1 study, women with PEP had a significant reduction in serum cortisol levels but normal levels of  $\beta$ -human chorionic gonadotropin,

estradiol, and androgens compared with unaffected pregnant controls.<sup>18</sup> None of the patients were using oral or topical corticosteroids and the reason for this decreased cortisol level remains unknown.<sup>18</sup>

Microchimerism of fetal cells has been proposed as a possible disease trigger. A study identified male fetal DNA in affected skin of some patients with PEP, which was not found in a control group of healthy pregnant women.<sup>19</sup> The significance of this is unclear: the migration of these fetal cells to maternal skin may be a triggering factor for the ensuing immunologic reaction or may simply be a secondary occurrence.

PEP presents as intensely pruritic urticarial papules and plaques abruptly arising first in striae distensae on the gravid abdomen and then spreading to the trunk and extremities (Fig. 3). There is often sparing of the face, palms, and soles and the mucosa is not involved. The most common sites of involvement are the proximal thighs and abdomen; however, the eruption characteristically spares the umbilicus in contrast to PG.<sup>15</sup> PEP may evolve from the characteristic urticarial papules and plaques to eczematous patches, polycyclic erythema, targetoid lesions, vesicles, and very



**FIGURE 3.** Intensely pruritic dermatitis involving the striae distensae in a patient with polymorphic eruption of pregnancy.

rarely bullae.<sup>15</sup> In PEP cases with bullae formation, the typical immunofluorescence pattern of PG is not seen.<sup>3</sup>

The eruption of PEP lasts on average 4 to 6 weeks and resolves within 7 to 10 days postpartum.<sup>15</sup> Maternal and fetal prognosis is unaffected.<sup>20</sup> Infants do not develop skin lesions. PEP is unlikely to recur in subsequent pregnancies; however, when recurrent it is associated with multiple gestation and tends to be less severe than the first occurrence.<sup>6</sup>

Diagnosis is made by clinical presentation as skin biopsy histopathology is non-specific and laboratory tests are normal. Histopathologic examination shows variable epidermal spongiosis, papillary dermal edema, and a mild to moderate superficial and mid-dermal perivascular inflammatory infiltrate that is primarily lymphohistiocytic. Epidermal changes of acanthosis, hyperkeratosis, and/or parakeratosis may be found in older lesions.<sup>15</sup> Direct immunofluorescence studies of perilesional skin and indirect immunofluorescence studies of patient serum are characteristically negative.

Available treatments can help alleviate pruritus. PEP responds well to corticosteroids and low-potency to mid-potency topical corticosteroids are first-line treatment.<sup>3</sup> Bland emollients and menthol in emollient formulations may be beneficial.<sup>18</sup> In cases with severe, intractable pruritus, systemic corticosteroids and UVB phototherapy have been used with success.<sup>18</sup> Oral antihistamines such as chlorpheniramine may be helpful for pruritus relief, particularly night-time pruritus due to sedating effects. Early delivery may be a treatment of last resort in rare debilitating cases unresponsive to other treatments.<sup>18,21</sup>

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