Pregnancy dermatoses are inflammatory skin disorders that occur during pregnancy or immediately postpartum. This heterogenous group of disorders includes pemphigoid gestationis, polymorphic eruption of pregnancy, intrahepatic cholestasis of pregnancy, atopic eruption of pregnancy, and pustular psoriasis of pregnancy. Prompt diagnosis and treatment is important to decrease maternal and fetal morbidity and, in some diseases, mortality. In this article, we provide a comprehensive literature review of each condition focusing on nomenclature, epidemiology, pathogenesis, clinical presentation, diagnosis, differential diagnosis, maternal risk, fetal risk, and treatment. We aim to increase awareness and help clinicians recognize, diagnose, and manage these unique conditions.
Maternal immunoglobulin (Ig) G antibodies bind to the BP180 antigen in the placenta and then cross-react with the BP180 antigen found in the basement membrane of the skin.\textsuperscript{5,13,14} This leads to activation of the inflammatory complement cascade, ultimately causing splitting of the epidermis and the dermis.\textsuperscript{1,5,13,14} The splitting of the epidermis and dermis clinically reveals tense bullae, a hallmark of PG.\textsuperscript{15,16}

Pemphigoid gestationis is an autoimmune disease more prevalent in patients with HLA-DR3 and HLA-DR4.\textsuperscript{1} Shornick et al compared human leukocyte antigen typing of 23 patients with a history of PG with that in a healthy control population. HLA-DR3 was found in 61\% of patients with PG (22\% of those in the control group), HLA-DR4 was found in 52–53\% of patients with PG (33\% of those in the control group), and a combination of HLA-DR4 and HLA-DR3 was found in 43\% of patients with PG (3\% of those in the control group).\textsuperscript{2,17,18}

Clinical Presentation, Diagnosis, and Differential Diagnosis

The clinical presentation of PG is an abrupt onset of pruritic papules and annular plaques followed by clustered vesicles with or without tense bullae on an erythematous base. The duration of time between the onset of pruritic papules and plaques to the formation of large, tense bullae ranges from days to 4 weeks.\textsuperscript{2} The initial lesions classically develop peri-umbilically, and then over time they spread to involve the trunk and extremities.\textsuperscript{9,10,19} The face and mucous membranes are typically spared.\textsuperscript{10,19} In a study of 23 patients with PG, 65\% of cases began along the periumbilical area. In 100\% of cases, the lesions involved the extremities and in 96\% of cases the lesions involved the trunk.\textsuperscript{14} There were no patients with mucous membranes involvement, and pruritus was the most common symptom in all patients.\textsuperscript{14}

Skin lesions typically spontaneously regress during the final weeks of pregnancy. However, 75\% of patients develop flares immediately after delivery and 10\% of patients develop flares with oral contraceptive usage.\textsuperscript{9,20} Postpartum flares typically resolve within weeks to months after delivery.\textsuperscript{9}

The diagnosis of PG is confirmed by obtaining two skin biopsies, one for histology and one for direct immunofluorescence (DIF). On histology, early prebullous PG reveals dermal edema with perivascular lymphocytic, histiocytic, and eosinophilic infiltration. Bullous stage will reveal a subepidermal split and bullae. Direct immunofluorescence is a diagnostic technique, performed on fresh (not formalin fixed) tissue, that detects deposits of immunoglobulins and complement proteins.

Table 1. Nomenclature of Dermatoses of Pregnancy

<table>
<thead>
<tr>
<th>Current Name</th>
<th>Previous Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pemphigoid gestationis</td>
<td>Herpes gestationis, gestational pemphigoid</td>
</tr>
<tr>
<td>Polymorphic eruption of pregnancy</td>
<td>Pruritic urticarial papules and plaques of pregnancy, Bourne’s “toxemic rash of pregnancy,” Nurse’s late onset prurigo of pregnancy, toxic erythema of pregnancy, linear immunoglobulin M dermatosis of pregnancy, late prurigo of pregnancy</td>
</tr>
<tr>
<td>Intrahepatic cholestasis of pregnancy</td>
<td>Pruritus gravidarum, prurigo gravidarum, cholestasis of pregnancy, obstetric cholestasis, cholestatic jaundice of pregnancy, pruritus or prurigo gravidarum, recurrent jaundice of pregnancy, icterus gravidarum, idiosyncratic jaundice of pregnancy</td>
</tr>
<tr>
<td>Atopic eruption of pregnancy</td>
<td>Prurigo of pregnancy, Besnier’s prurigo gestationis, Nurse’s “early onset prurigo” of pregnancy, Spangler’s papular dermatitis of pregnancy, pruritic folliculitis of pregnancy, eczema in pregnancy, linear IgM disease of pregnancy</td>
</tr>
<tr>
<td>Pustular psoriasis of pregnancy</td>
<td>Impetigo herpetiformis, generalized psoriasis of pregnancy</td>
</tr>
</tbody>
</table>
complement proteins in skin biopsies by binding antibody-fluorophore conjugate molecules to the abnormal protein deposits. In PG, all patients have the pathognomonic linear deposition of complement 3 along the basement membrane of perilesional skin.\textsuperscript{19} In addition, about 25–50\% of patients will also have deposition of IgG autoantibodies along the basement membrane.\textsuperscript{5,19}

Routine indirect immunofluorescence (IIF) and enzyme-linked immunoassay are other tests that are

<table>
<thead>
<tr>
<th>Disease</th>
<th>Disease Onset</th>
<th>Clinical Findings</th>
<th>Maternal Risk</th>
<th>Fetal Risk</th>
<th>1st-Line Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pemphigoid gestationis</td>
<td>2nd trimester, 3rd trimester, or immediately after delivery</td>
<td>Pruritic urticarial papules and plaques followed by clustered vesicles or tense bullae; starting periumbilical and spreading to involve trunk and extremities; spares the face and mucous membranes</td>
<td>Recurrence, development of autoimmune diseases (ie, Grave’s disease)</td>
<td>Premature birth, small-for gestational age neonates, neonatal pemphigoid gestationis</td>
<td>Corticosteroids, antihistamines</td>
</tr>
<tr>
<td>Polymorphic eruption of pregnancy</td>
<td>3rd trimester</td>
<td>Extremely pruritic, erythematous, and edematous papules and plaques within the abdominal striae followed by evolution of polymorphic features, such as targetoid lesions, vesicles, and eczematous plaques in some cases</td>
<td>None</td>
<td>None</td>
<td>Corticosteroids, antihistamines</td>
</tr>
<tr>
<td>Intrahepatic cholestasis of pregnancy</td>
<td>Late 2nd or 3rd trimester</td>
<td>Intense pruritus with no primary skin changes. Secondary changes include excoriations and prurigo nodules</td>
<td>Recurrence, intrapartum or postpartum hemorrhage in severe cases</td>
<td>Preterm birth, meconium staining, sudden intrauterine death, respiratory distress syndrome</td>
<td>Ursodeoxycholic acid, some recommend early delivery of fetus</td>
</tr>
<tr>
<td>Atopic eruption of pregnancy</td>
<td>1st or 2nd trimester</td>
<td>Eczematous patches and plaques involving the face, neck, and flexural areas or a papular eruption on the trunk or extremities</td>
<td>Recurrence</td>
<td>No</td>
<td>Corticosteroids, emollients, antihistamines</td>
</tr>
<tr>
<td>Pustular psoriasis of pregnancy</td>
<td>3rd trimester or postpartum</td>
<td>Symmetric, erythematous plaques with sterile pustules, often in circumferential rings. Systemic symptoms such as fever, malaise, nausea, vomiting</td>
<td>Recurrence, electrolyte imbalance, dehydration from fluid loss, sepsis from secondary infections, hypocalcemia, tetany, seizures</td>
<td>Stillbirth, neonatal demise, premature birth, intrauterine growth restrictions, premature rupture of membranes</td>
<td>Corticosteroids (though some experts consider cyclosporine or TNF inhibitors also 1st-line for severe cases) Early delivery of fetus if medically necessary or among patients near term or at term with severe or recalcitrant disease</td>
</tr>
</tbody>
</table>

TNF, tumor necrosis factor.
used to diagnose PG. Indirect immunofluorescence detects circulating antibodies in patient’s serums. Although routine IIF can detect an antibasement membrane antibody in only approximately 20% of cases, a complement binding IIF technique can detect IgG antibodies to the basement membrane in nearly all patients with PG. 5, 21, 22 Enzyme-linked immunosassay is a newer, now more commonly used test that can detect serum levels of antibodies against NC16A, the extracellular domain of BP180. Enzyme-linked immunosassay has shown to have similar specificity as IIF with increased sensitivity. 22–24 Enzyme-linked immunosassay is useful in diagnosis, monitoring disease activity, and evaluating therapeutic efficacy. 22–27

Lastly, a recent study evaluated the utility of using routine immunohistochemistry for anti-C4d in formalin-fixed paraffin-embedded tissue to differentiate PG from polymorphic eruption of pregnancy (PEP), a late onset, benign inflammatory skin disorder of pregnancy. In 100% of DIF-proven cases of PG (8/8), linear C4d immunoreactant deposition was seen along the basement membrane zone compared with 0% of patients with PEP (0/11). Although further testing is necessary given the small sample size, these results raise the possibility of using immunohistochemistry to differentiate PG and PEP without having to perform a second biopsy for DIF. 22, 27

The differential diagnosis for PG includes polymorphous eruption of pregnancy, allergic contact dermatitis, bullous drug eruption, urticaria, bullous pemphigoid, erythema multiforme, dermatitis herpetiformis, and atopic eruption of pregnancy. 28

Maternal and Fetal Risk

The greatest maternal risk is recurrence of PG in future pregnancies. Recurrence has been reported in 30–50% of patients. Typically, recurrences have earlier onset and more severe disease manifestations. Additionally, “skipped” pregnancies have been reported in 8% of cases. 2, 3, 9, 29 Mothers with PG are also at increased risk of developing autoimmune disease, most frequently Grave’s disease. 1, 30

Fetal risks include premature birth and small-for-gestational-age neonates. These risks are likely a result of chronic placental insufficiency from antibody deposition within the chorionic villi of the placenta. 29, 31 In a retrospective cohort study of 61 pregnancies complicated by PG, 34% of neonates were born prematurely compared with 6% in the general population. Additionally, 34% of neonates were born small-for-gestational-age compared with 6% in the general population. 32 In another retrospective study of 32 patients with PG, six pregnancies were complicated by preterm labor and two by fetal growth restriction. 10

About 10–13% of newborns present with mild skin blistering, known as neonatal pemphigoid gestationis. 1 Neonatal pemphigoid gestationis is thought to result from passive transfer of maternal IgG autoantibodies to the fetal skin. The eruption resolves spontaneously within weeks of birth. 1, 33, 34

Treatment

The main goals of treatment are to suppress blister formation and to relieve pruritus. High-potency topical corticosteroids are the first-line therapy for blister suppression. 35 Examples include fluocinonide 0.05% cream or ointment, which is classified as a group 2, high-potency topical steroid, and clobetasol propionate 0.05% cream or ointment, which is classified as a group 1, super-high-potency topical steroid. If PG persists, systemic corticosteroids are recommended. In pregnant women who are recalcitrant to oral corticosteroids, treatment with intravenous immune globulin, azathioprine and dapsone have shown to be effective. Rituximab has also shown to suppress disease but is only used in postpartum women. 1

A systematic review of 190 articles evaluating treatment approaches to PG found that 54% of patients (74/137) received systemic corticosteroids with or out without topical corticosteroids or antihistamines, and 80% (59/74) achieved complete remission. Twenty-six percent of patients (35/137) received systemic corticosteroids combined with steroid-sparing treatments with or without topical corticosteroids or antihistamines, and 86% (30/35) achieved complete remission. Prednisone was the most frequently administered systemic steroid (43%, 47/109), followed by prednisolone (36%, 39/109), and betamethasone (7%, 8/109). The mean initial prednisone-equivalent dosage was 50 mg/day, with mean maximum dosage of 70 mg/day. Intravenous immune globulin was the most prescribed steroid sparing agent (22%, 12/54), followed by azathioprine (15%, 8/54), and dapsone (13%, 7/54). 1

A study performed by Chi et al investigated the risk of systemic corticosteroid use among patients with PG. In this retrospective study of 61 pregnancies, there was no significant association between adverse pregnancy outcomes and systemic corticosteroid use even after stratifying for duration or trimester of treatment. Therefore, Chi et al concluded that the benefit of reducing inflammation with systemic corticosteroids usage outweighs the potential harm.
Symptomatic control of pruritus is commonly attained using antihistamines. Most pregnant women are treated with second-generation antihistamines given the lower risk of sedation and cholinergic side effects. Loratadine (10 mg once daily) is most commonly recommended. A multicenter study of 161 loratadine exposed pregnancies and a prospective controlled cohort study of 210 loratadine exposed pregnancies both reported that loratadine does not represent a major teratogenic risk.

**Polymorphic Eruption of Pregnancy**

Polymorphic eruption of pregnancy, also known as pruritic urticarial papules and plaques of pregnancy, is a self-limited inflammatory disorder that occurs in the 3rd trimester of pregnancy (Fig. 2 and Table 1). It is characterized by pruritic, erythematous, and edematous papules and plaques that over time can develop polymorphic features. There are no increased maternal or fetal risks associated with PEP (Table 2).

**Epidemiology and Pathogenesis**

The incidence of PEP is estimated at 1 in 200 pregnancies. Polymorphic eruption of pregnancy typically occurs in the third trimester of pregnancy in primigravid women. Two large studies found 70% (76/109) and 73% (132/181) of women with PEP were primigravidas.

The pathogenesis of PEP is poorly understood, but it is thought to be related to increased maternal weight and thus is seen more frequently in multiple gestation pregnancies. A meta-analysis found that 12% (29/282) of cases of PEP occurred in multiple gestations, a frequency much higher than the background rate of multiple gestation in the United States. One hypothesis is that the abdominal distension damages underlying connective tissue. This leads to exposure of dermal antigens, activation of an inflammatory response, and cross-reactivity to collagen in skin of other areas of the body. Polymorphic eruption of pregnancy commonly initiates within the abdominal striae, which further supports this theory.

Another hypothesis is that PEP is an immune response to circulating fetal antigens within maternal blood. Chimerism, which is the presence of fetal cells in maternal blood, is thought to produce a graft-versus-host–like reaction against maternal tissue. In a study performed by Aractinig et al, male fetal DNA was detected in skin lesions of patients with PEP but was absent in nonaffected patients. Polymorphic eruption of pregnancy is seen more commonly among male fetuses, which further supports this hypothesis.

**Clinical Presentation, Diagnosis, and Differential Diagnosis**

Polymorphic eruption of pregnancy clinically presents as extremely pruritic, erythematous, and urticarial papules and plaques within the abdominal striae. In a retrospective analysis of 44 patients with PEP, 91% of cases clinically developed within or adjacent to striae of the abdomen or proximal thighs. Only 3% of patients did not have any abdominal involvement. The skin eruption typically spreads over days to involve the extremities, chest, and back. The face, palms, and soles are often spared. As the disease progresses, about 50% of patients develop more polymorphic features, such as targetoid lesions, vesicles, and eczematous plaques. It is important to note that PEP spares the periumbilical area, which helps differentiate PEP from PG.

Diagnosis is primarily based on clinical history and physical examination. Skin biopsies can be performed in cases of diagnostic uncertainty; however, histopathologic examination is generally nonspecific. Epidermal changes are seen among 30–50% of cases, and can include spongiosis, acanthosis, hyperkeratosis, and parakeratosis. The dermis commonly reveals nonspecific perivascular and interstitial
lymphocytic infiltrate, dermal edema, neutrophils, and eosinophils.\textsuperscript{40,47} Direct immunofluorescence can reveal nonspecific, granular deposition of complement 3, IgM, or IgA deposits at the dermo-epidermal junction or perivascular. Indirect immunofluorescence is negative.\textsuperscript{40,47}

The differential diagnosis of PEP is broad because the clinical features change as the disease evolves. The early urticarial phases of PEP, PG, and intrahepatic cholestasis of pregnancy can appear clinically similar. Additionally, the latter appearance of targetoid lesions can resemble erythema multiforme. Other common dermatologic diseases that can present with erythematous papules and urticarial plaques include drug reactions, viral exanthemas, scabies, arthropod bites, atopic eruption of pregnancy, urticaria, and contact dermatitis.\textsuperscript{48–50}

**Maternal and Fetal Risk**

There are no increased fetal or maternal risks associated with PEP.

**Treatment**

Polymorphic eruption of pregnancy is a benign and self-limiting disease that generally resolves spontaneously within 4–6 weeks. The main goal of treatment is symptomatic relief. Low-to mid-potency topical steroids, emollients, and oral antihistamines are used as initial therapy. Examples of low-potency topical steroids include hydrocortisone 2.5% ointment or cream and desonide 0.05% ointment or cream. Examples of mid-potency topical steroids include triamcinolone acetonide 0.1% ointment or cream, mometasone furoate 0.1% cream, and fluocinolone acetonide 0.025% ointment. If pruritus is recalcitrant to the above treatments, a short course of systemic corticosteroids has shown to be safe and effective.\textsuperscript{22,45}

**INTRAHEPATIC CHOLESTASIS OF PREGNANCY**

*Intrahepatic cholestasis of pregnancy* (ICP), also known as pruritus gravidarum, is a liver disorder that occurs in the late second or third trimester of pregnancy (Fig. 3, Table 1). It is characterized by elevation in serum bile acid levels and acute onset of generalized pruritus, classically involving the palms and soles. Intrahepatic cholestasis of pregnancy is associated with an increased maternal and fetal risk, so prompt diagnosis and treatment is critical (Table 2).

**Epidemiology and Pathogenesis**

The incidence of ICP varies greatly among geographic regions, likely resulting from differences in genetic predisposition, susceptibility among ethnic groups, environmental factors, and reporting.\textsuperscript{51,52} In Europe, the incidence of ICP ranges from 0.5% to 1.5% with highest rates among Scandinavia and the Baltic states (1–2%).\textsuperscript{53} In the United States, incidence ranges from 0.32% in the predominately White communities of Bridgeport, Connecticut, to 5.6% in the primarily Latina populations of Los Angeles.\textsuperscript{52,54} South America has the highest incidence at 28% among Araucanian Indian women, a group of indigenous Chilean people.\textsuperscript{55}

Genetic predisposition, hormonal factors, and underlying liver disease have been shown to play a role in the pathogenesis of ICP. The increased incidence of ICP among first-degree relatives, certain ethnic groups, familial clustering, and high recurrence rates support an underlying genetic predisposition.\textsuperscript{56,57} In a U.K. study, the rate of ICP was more than 10 times higher in the mothers and sisters of the affected women than in the general obstetric population.\textsuperscript{57,58} Reports of small pedigrees have also reported an autosomal dominant, sex-limited inheritance pattern.\textsuperscript{57,58} Moreover, several studies have found mutations in genes encoding the bile transporter proteins, bile acid receptor, and bile salt export pump can predispose women to ICP. One study reported a 16% prevalence of variations in the ABCB4 gene among White women with ICP.\textsuperscript{59} Other genes that have been associated with ICP include ABCB11, ATP8B1, ABCC2, and NR1H4.\textsuperscript{57,60–62}
Hormonal factors, such as increased levels of estrogen and progesterone, have also been associated with the development of ICP. Intrahepatic cholestasis of pregnancy is most common in the second half of pregnancy when estrogen and progesterone levels are highest. Additionally, ICP occurs more frequently with multiple gestations, which are associated with higher levels of estrogen.

The placenta is a major source of estrogen during the second half of pregnancy, and ICP typically resolves after placental removal. Reyes et al administered ethinyl estradiol to both men and women and found a decreased clearance of sulfobromophthalein, a dye used to assess liver function. The clearance was further decreased among women with a personal history of ICP and their male relatives. These findings suggest an independent metabolic interaction between estrogen and the liver that can be genetically transmitted by either sex.

In addition, in vitro studies have found that the cholestatic estrogen metabolite, 17-β-estradiol glucuronide, inhibits the bile salt export pump. Bile acid buildup resulting from increased 17-β-estradiol glucuronide further supports the interplay between elevated estrogen levels and the development of cholestasis.

Alterations in progesterone expression and metabolism have also been associated with the development of ICP. Excess progesterone metabolites have been found in the serum and urine of women with ICP. These metabolites saturate the hepatic transport system and reduce excretion of bile. In addition, multiple studies have concluded that administration of exogenous progesterone may trigger ICP in predisposed women. Specifically, in a study of 13 women with ICP, 12 women had received progesterin for uterine contractions or cervical modifications.

There are other environmental, maternal, and liver diseases that have been associated with higher incidences of ICP. Environmental factors include selenium deficiency and low vitamin D levels. Rates of ICP increase in winter months, which is when natural selenium and vitamin D levels are low. Maternal factors include multiple gestation, advanced maternal age, and family history of cholestasis in pregnancy. Liver diseases associated with ICP include hepatitis C infection, progressive fibrosis, nonalcoholic cirrhosis.

Clinical Manifestations, Diagnosis, and Differential Diagnosis
Intrahepatic cholestasis of pregnancy typically develops during the late second or third trimester of pregnancy, with 80–86% of affected women presenting after 30 weeks of gestation. Intrahepatic cholestasis of pregnancy is characterized by sudden onset of intense generalized pruritus, typically including the palms and soles. Pruritus is often worse at night, and it gradually improves throughout pregnancy. There are no primary skin lesions associated with ICP; however, secondary excoriations and prurigo nodules are often seen. Jaundice occurs in 14–25% of patients, typically within 2–4 weeks after the onset of pruritus. Systemic symptoms of cholestasis can also develop, including pale stools, dark urine, steatorrhea, malabsorption of fat-soluble vitamins, and increased bleeding.

Intrahepatic cholestasis of pregnancy is diagnosed in pregnant women with pruritus and elevated serum bile acids after all other causes are excluded. For pregnant women, elevated serum bile acids are defined as greater than 11.0 micromoles/L. Severe cholestasis is defined as serum bile acids greater than 40 micromoles/L, and accounts for about 20% of cases of ICP. In a systematic review on 11 studies, elevated serum bile acids were found to have sensitivity of 91% and a specificity of 93% in diagnosing ICP.

Other laboratory abnormalities seen among patients with ICP include serum aminotransferases (elevated in up to 70% of cases), alkaline phosphatase, and total and direct bilirubin concentrations (elevated in 10–20% of cases). Pruritus often precedes elevation in serum bile levels by several weeks; thus, it is important to repeat laboratory tests if ICP is suspected. If treatment is initiated empirically, elevation in serum bile acid levels may not be detectable. Hepatic ultrasonography can be useful to exclude other causes of cholestasis in pregnancy.

The differential diagnosis includes both primary liver diseases and primary cutaneous diseases. Liver diseases that should be considered include gallstones, biliary disease (cholecytitis and cholangitis), hepatitis, and acute fatty liver of pregnancy. Skin disorders include atopic dermatitis, PEP, and scabies.

Maternal and Fetal Risks
Maternal pruritus typically resolves within days to weeks of delivery, significantly decreasing the morbidity associated with ICP. The most common maternal risk is recurrence with subsequent pregnancies, which has been reported in up to 45–70% of cases. There have also been reports of flares with oral contraceptive use. In severe cases of ICP, with jaundice and vitamin K deficiency, there is increased risk of
The greatest risk of ICP is to the fetus. The risk of fetal complications is thought to be related to the maternal serum bile acid levels, with a study showing a 1–2% increased risk for every 1 micromoles/L of bile acid above 40 micromoles/L. Intrahepatic cholestasis of pregnancy is associated with increased risk of prematurity, meconium staining, stillbirth, and respiratory distress syndrome. Preterm labor is seen in 30–40% of cases of ICP. Meconium staining, a sign of fetal distress, is seen in 16–58% of cases of ICP and in all cases of ICP that are complicated by stillbirth. A systematic review and meta-analysis found that there is an increased risk of stillbirth among women with ICP, with the highest risks occurring among women with total bile acid levels of 100 micromoles/L or more. Respiratory distress syndrome is considered an independent fetal risk of ICP, estimated at a rate of 29% of newborns born to women with ICP. Elevated levels of bile acids were found in the bronchoalveolar fluid of 10 neonates with respiratory distress syndrome, further supporting the role of bile acids in respiratory distress syndrome.

Treatment
The primary goal of treatment is to decrease serum bile acid levels in order reduce maternal and fetal morbidity and mortality. Oral ursodeoxycholic acid (UDCA) remains the preferred method of treatment despite conflicting data in the literature. Oral ursodeoxycholic acid has shown to decrease serum bile acid levels, reduce passage of maternal bile acids to the fetus and placenta, and improve function of the bile acid transporter. Additionally, some studies have found that UDCA reduces both maternal symptoms and prevents adverse perinatal outcomes. In a randomized controlled trial of 125 women with ICP who received UDCA, UDCA significantly reduced pruritus when compared with the placebo group. Similarly, a meta-analysis that compared ICP pregnancies treated with various therapeutic agents, including UDCA (n=207) or placebo (n=70), found that UDCA improved pruritus. The meta-analysis also reported a reduction in prematurity, fetal distress, respiratory distress syndrome, and neonatal intensive care unit hospitalizations among patients treated with UDCA. Although the data were limited by a small sample size, similar findings were seen in a bigger meta-analysis that synthesized 12 randomized controlled trials with 662 patients with ICP. In this report, UDCA was associated with resolution of pruritus, reduced serum levels of bile acid, fewer premature births, reduced fetal distress, less frequent respiratory distress syndrome, and fewer neonatal intensive care unit hospitalizations.

In contrast, other studies have shown that UDCA does not improve outcomes among women with ICP. A double-blind, randomized, placebo-controlled study of 605 women with ICP showed that treatment with UDCA did not reduce perinatal adverse outcomes. The author concluded that UDCA’s routine use for ICP should be reconsidered. In addition, a meta-analysis of 13 randomized controlled trials with 625 participants comparing maternal and fetal outcomes after UDCA, S-adenosylmethionine, or both showed no favorable effect on symptoms including pruritus in patients with ICP.

Despite the conflicting data, the Society for Maternal-Fetal Medicine (SMFM) recommends, “UDCA can be used as the first-line agent for the treatment of maternal symptoms,” and states that, “UDCA has not been demonstrated to improve fetal outcomes.” The SMFM 2021 ICP guidelines also recommend a starting dose of 10–15 mg/kg per day, which can be divided into two or three daily doses. If symptoms do not improve after 1 week of treatment, the dose can be increased to a maximum of 21 mg/kg per day. Improvement in pruritus is typically seen within 1–2 weeks, and improvement in laboratory findings are seen within 3–4 weeks.

The SMFM recommends considering the use of alternative therapies, such as antihistamines, S-adenosyl-l-methionine, rifampin, and cholestyramine, in cases in which UDCA cannot be prescribed or if patients continue to have symptoms while receiving the maximum dose of UDCA. S-adenosyl-methionine, rifampin, and antihistamines may improve pruritus in refractory cases. Cholestyramine reduces reabsorption of bile acids. However, it has been shown to have minimal effect on pruritus, and it has a significant side-effect profile, which includes gastrointestinal symptoms and vitamin K deficiency.

Early delivery has also been recommended as a treatment for women with ICP. However, guidelines regarding timeline of delivery are not universally standardized given the lack of sufficiently powered randomized controlled studies evaluating the risks and benefits of early delivery. In 2014, a decision-analytic model evaluated 18 studies and found that delivery at 36 weeks of gestation is the optimal delivery strategy for women with ICP. These findings were further supported by a retrospective cohort study in 2015 that reported delivery at 36 weeks of gestation would reduce perinatal mortality.
In contrast, a systematic review of 16 articles from 1967 to 2011 found no clinically significant reduction in fetal risk with early delivery. Lastly, a randomized controlled trial in 2012 compared UD-CA compared with placebo and early term delivery compared with expectant management and revealed no significant difference between early term delivery and expectant management.

Currently, the SMFM recommends timing of delivery based on the level of total bile acids. For patients with total bile acid levels 100 micromoles/L or greater, delivery should be offered at 36 weeks of gestation because of the increased risk of stillbirth as discussed above. For patients with total bile acid levels below 100 micromoles/L, delivery is recommended between 36 and 39 weeks of gestation. The SMFM also recommends antenatal fetal surveillance should occur at a gestational age when delivery would be performed if the results are abnormal or at the time of diagnosis if the diagnosis is made at a later gestational age.

**Epidemiology and Pathogenesis**

Atopic eruption of pregnancy is the most common skin disorder of pregnancy, accounting for 50% of all pregnancy dermatoses. Atopic eruption of pregnancy commonly develops in the first trimester of pregnancy, with 75% of patient presenting before the third trimester. Atopic eruption of pregnancy can develop as a flare or a first occurrence of atopic dermatitis. A study of 256 patients with AEP found that 20% had a personal history of atopic dermatitis and 80% developed initial lesions during pregnancy. Moreover, a study evaluating 72 patients with AEP found that a personal or family history of atopy (asthma, eczema, or hay fever) was seen in 51% of women who developed atopic lesions for the first-time during pregnancy.

The pathogenesis of AEP is thought to result from a shift in immune response that occurs during normal pregnancy. To prevent fetal rejection during normal pregnancy, there is a downregulation of maternal cell-mediated immune function and T-helper 1 cytokine production and an upregulation of maternal humoral immune response and T-helper 2 (Th2) cytokine production. Atopic dermatitis is considered a Th2-dominant disease. Thus, the shift toward the dominant Th2 response in pregnancy worsens the imbalance already present in patients who are atopic, leading to the development of AEP.

**Clinical Presentation, Diagnosis, and Differential Diagnosis**

Atopic eruption of pregnancy is characterized by intense pruritus associated with either patchy eczematous lesions, known as E-type, or papular eruptions. These eruptions are localized to flexural surfaces and do not involve the abdomen. In contrast, a systematic review of 16 articles from 1967 to 2011 found no clinically significant reduction in fetal risk with early delivery. Lastly, a randomized controlled trial in 2012 compared UD-CA compared with placebo and early term delivery compared with expectant management and revealed no significant difference between early term delivery and expectant management.

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**ATOPIC ERUPTION OF PREGNANCY**

Atopic eruption of pregnancy (AEP) encompasses diseases previously known as prurigo of pregnancy, pruritic folliculitis in pregnancy, and early eczema of pregnancy (Figure 4A and B and Table 1). It is defined as a flare or first occurrence of eczema during pregnancy. It typically occurs in the first trimester of pregnancy and presents as a patchy eczematous or papular eruption. Atopic eruption of pregnancy is diagnosed clinically after ruling out other causes of pregnancy dermatoses. There are no life-threatening maternal or fetal risks, though it can recur in future pregnancies (Table 2).
(pruriginous or follicular lesions), known as P-type. E-type is seen in 66% of cases and presents with eczematous lesions that often involve classic sites of atopic dermatitis, such as the face, neck, upper chest and flexural aspects of the extremities. P-type accounts for 33% of cases of AEP and presents with small, erythematous, and grouped papules or prurigo lesions that are most commonly seen on the trunk and extensor extremities. In both subtypes, secondary manifestations such as excoriation from scratching or superimposed bacterial or viral infections can be seen due to the intense pruritus. Some experts believe that some papular lesions should be classified with the original prurigo of pregnancy, because some of these patients do not have an atopic background and, thus, they do not fit classically under the umbrella term “AEP.”

Atopic eruption of pregnancy is a clinical diagnosis that cannot be confirmed until ruling out other dermatoses of pregnancy. The diagnosis is based on pattern of skin eruption, an early onset in pregnancy, a personal or family history of atopy, or elevated IgE levels. In a study of 143 patients with AEP, serum IgE levels were elevated in 71% of cases. Skin biopsies can be performed to rule out other causes of dermatoses in cases of diagnostic uncertainty. Histopathology is generally nonspecific, with the epidermis revealing spongiosis, acanthosis, hyperkeratosis, or parakeratosis. The dermis is composed of perivascular lymphocytic infiltrate. Eosinophils are a common finding in AEP, with one study reporting eosinophilic presence in 74% of cases. Both DIF and IIF studies are negative. It is also important to note that in patients presenting with follicular pustules, a culture should be performed to rule out bacterial or candida folliculitis.

The differential diagnosis includes allergic contact dermatitis, PEP, early-stage PG, scabies, folliculitis, pustular psoriasis of pregnancy, and urticaria.

Maternal and Fetal Risk

There are no life-threatening maternal or fetal risks associated with AEP. However, recurrence of AEP in subsequent pregnancies is common.

Treatment

The main goal of treatment is symptomatic relief. Atopic eruption of pregnancy typically responds rapidly to low-to mid-potency topical steroids. Emollients, such as topical urea and 1–2% menthol, are recommended to prevent dryness and relieve pruritus. Antihistamines are also used to suppress pruritus. In refractory and severe cases, systemic corticosteroids and narrowband ultraviolet B radiation have been effective in treating AEP.

Pustular Psoriasis of Pregnancy

Pustular psoriasis of pregnancy (PPP), previously known as impetigo herpetiformis, is a rare pregnancy dermatosis that occurs in the third trimester of pregnancy (Fig. 5 and Table 1). It is characterized by erythematous plaques covered with sterile pustules, classically in circumferential rings and can be associated with systemic symptoms. Pustular psoriasis of pregnancy is considered by many to be a variant of generalized pustular psoriasis, and as such, is not included as a true “dermatosis of pregnancy.” However, given the importance of early recognition and treatment in preventing life threatening maternal and fetal risks, some authors include it in discussions of dermatoses of pregnancy (Table 2).

Epidemiology and Pathogenesis

Pustular psoriasis of pregnancy is a rare form of pustular psoriasis. The pathogenesis is poorly understood, but several hypotheses have been reported. Genetic factors may contribute to the development of PPP, with reported cases developing in twins and siblings as well as among women with IL36RN mutations. Others theorize that hypocalcemia, low vitamin D, and hypoparathyroidism, which are commonly seen in late pregnancy, may play a role. Hormonal changes in pregnancy, particularly progesterone, may also contribute to the development of PPP and may account for the flares that can occur postpartum, during menses, and when using oral contraception. Lastly, two case reports describe drug-induced PPP possibly triggered by...
Clinical Presentation, Diagnosis, and Differential Diagnosis

Pustular psoriasis of pregnancy most commonly occurs in the third trimester of pregnancy. The lesions characteristically develop in flexural areas as symmetrical erythematous plaques with circumferential rings of sterile pustules along the periphery.\textsuperscript{22,110,115} The plaques then spread to involve the trunk and extremities, often sparing the hands, feet, and face. Over-time, the plaques can become eroded and crusted in the center. Erosions of the mouth and esophagus may develop, and subungal pustules can result in onycholysis.\textsuperscript{22,114,122} Systemic symptoms can also occur, such as fever, anorexia, nausea, vomiting, diarrhea, malaise, lymphadenopathy, and seizures.\textsuperscript{22,114} Pustular psoriasis of pregnancy is distinct from other pregnancy dermatoses as it is usually seen in the absence of pruritus.\textsuperscript{115}

Although PPP can often be detected clinically, a skin biopsy is recommended for definitive diagnosis given the possibility of life-threatening maternal and fetal consequences.\textsuperscript{22} Histopathology is similar to pustular psoriasis in nonpregnant women, revealing spongiform pustules with neutrophils, epidermal hyperplasia, and parakeratosis.\textsuperscript{22,114,115,121} Laboratory monitoring often shows leukocytosis with neutrophilia, hypocalcemia, hypoalbuminemia, hypoparathyroidism, low vitamin D, and an elevated erythrocyte sedimentation rate.\textsuperscript{22,110,115} Blood cultures and pustules are sterile but should be performed to exclude bacterial and fungal infections.\textsuperscript{22,115} Both DIF and IIF are negative.\textsuperscript{22}

The differential diagnosis includes impetigo, candida, tinea corporis, acute generalized exanthematous pustulosis, IgA pemphigus, subcorneal pustular dermatosis, PEP, AEP (follicular type), PG, and dermatitis herpetiformis.\textsuperscript{28}

Maternal and Fetal Risk

Maternal complications include electrolyte imbalance, dehydration from fluid losses, and sepsis from secondary infections.\textsuperscript{123} Low serum calcium is the most common laboratory abnormality seen in PPP, and it can lead to delirium, tetany, and seizures.\textsuperscript{120} Women may also develop other abnormal laboratory values and constitutional symptoms, as described in the above section.\textsuperscript{120} Additionally, there has been reports of PPP complicated by gestational hypertension, PPP recurring in subsequent pregnancies, and PPP occurring during menstruation and when taking oral contraceptive pills.\textsuperscript{117,120,123,124} When recurrence occurs during future pregnancies, it happens at an earlier gestational age and with a more severe onset.\textsuperscript{115,116,120,125,126} In one case described by Ou-meish et al.,\textsuperscript{123} the patient developed PPP in nine successive pregnancies, each time at an earlier onset and with more severe features.

There is a risk of fetal stillbirth and neonatal demise due to placental insufficiency, premature rupture of membranes, preterm labor, and intrauterine growth restrictions.\textsuperscript{110,120,123,127} Fetal demise has been reported within 3 days of a reactive nonstress test, emphasizing the importance of early treatment if PPP is suspected.\textsuperscript{121}

Treatment

Prompt initiation of treatment is critical to prevent maternal and fetal morbidity and mortality. Currently, there are no standardized guidelines for treating PPP given the rarity of disease; however, several treatment options have shown to be effective.\textsuperscript{128} In all cases, careful laboratory monitoring and fluid and electrolyte resuscitation should be initiated early given the risk of maternal infections, large fluid losses, and electrolyte imbalances.\textsuperscript{128} Additionally, fetal monitoring can be performed to determine whether early delivery is warranted.\textsuperscript{128}

Systemic corticosteroids, specifically prednisolone, have been considered the mainstay of treatment for PPP though some experts consider cyclosporine or tumor necrosis factor inhibitors also first line for severe cases.\textsuperscript{120,128,129} The initial dose for mild-to-moderate cases is 15–30 mg prednisolone daily.\textsuperscript{123,128} If necessary, the dose can be increased up to 60–80 mg per day.\textsuperscript{120,123,128} Most patients remain on oral therapy until the postpartum period, and then the steroids are very slowly tapered down to prevent flaring.\textsuperscript{110}

Cyclosporine is administered in the setting of severe or recalcitrant cases of PPP.\textsuperscript{110} There have been 14 reported cases of PPP in which cyclosporine has been administered in combination with systemic corticosteroids. The prescribed dose of cyclosporine in these cases ranged from 2 mg/kg/day to 7.5 mg/kg/day.\textsuperscript{120} The outcomes among the 14 patients varied, with one patient attaining complete remission, two patients remaining in stable condition, three patients having a partial response, four patients with marked improvement, and four patients with complete resistance to therapy.\textsuperscript{130} A meta-analysis evaluating cyclosporine use during pregnancy found that there may be a small risk of prematurity.\textsuperscript{130,131} There is also an increased risk of maternal hypertension, so
monitoring of maternal blood pressure and creatinine are critical.

Tumor necrosis factor-alpha inhibitors (infliximab and adalimumab) have also shown to be effective in treating PPP in two case reports; however, the fetal risks are still not fully understood.\textsuperscript{132,133} Given that these agents can cross the placenta,\textsuperscript{134} Narrowband ultraviolet B in combination with corticosteroids has shown to be effective and safe among pregnant women with PPP.\textsuperscript{120,135,136} Retinoids and methotrexate are contraindicated in pregnancy but have been successful in treating postpartum nonbreastfeeding women.\textsuperscript{120,137,138} Antibiotics do not control disease completely, but they have shown to be effective for mild cases and in the initial stages before sepsis has been excluded.\textsuperscript{120,139} Older cephalosporins are considered the antibiotic of choice.\textsuperscript{120}

Pustular psoriasis of pregnancy usually spontaneously resolves after delivery.\textsuperscript{110,120} Therefore, induction of labor has also been reported as a treatment option for patients with severe or recalcitrant disease who are near or at term.\textsuperscript{110,140}

**CONCLUSION**

Pregnancy dermatoses are a heterogenous group of inflammatory skin conditions that affect intrapartum and postpartum women. This article offers a comprehensive review of the literature to help clinicians recognize, diagnose, manage, and treat these rare, yet sometimes life-threatening, conditions. In addition, having an in-depth understanding of these disease processes can improve patient safety and improve quality of life during and after pregnancy.

**REFERENCES**


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