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INVITED ARTICLE

Specific dermatoses of pregnancy and their treatment

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ABSTRACT: The specific dermatoses of pregnancy represent a diverse group of intensely pruritic dermatoses, occurring only in the puerperal state. The relative rarity of these conditions, the often variable clinical appearance, and the lack of definitive diagnostic tests have led to confusion regarding the appropriate diagnosis and management of the specific dermatoses of pregnancy. Herein we review the clinical characteristics, diagnosis and treatment of five dermatoses occurring during pregnancy: pruritic urticarial papules and plaques of pregnancy, atopic eruption of pregnancy, pemphigoid gestationis, intrahepatic cholestasis of pregnancy, and pustular psoriasis of pregnancy.

KEYWORDS: atopic eruption of pregnancy (AEP), intrahepatic cholestasis of pregnancy (ICP), pemphigoid gestationis (PG), pruritic urticarial papules and plaques of pregnancy (PUPPP), pustular psoriasis of pregnancy (PPP)

Introduction

Cutaneous diseases in pregnancy can be broadly classified into one of three groups: physiologic skin changes in pregnancy, dermatoses, and cutaneous tumors affected by pregnancy, and the specific dermatoses of pregnancy. Herein we aimed to review the specific dermatoses of pregnancy and their treatment. The specific dermatoses of pregnancy have recently been classified into four entities: pruritic urticarial papules and plaques of pregnancy (PUPPP), atopic eruption of pregnancy (AEP), pemphigoid gestationis (PG), and intrahepatic cholestasis of pregnancy (ICP). We would consider a possible fifth, pustular psoriasis of pregnancy (PPP). The specific dermatoses represent a diverse group of intensely pruritic dermatoses, occurring exclusively in the puerperal state. The relative rarity of these conditions, the often variable clinical appearance, and the lack of definitive diagnostic tests have led to confusion regarding the appropriate diagnosis and management of the specific dermatoses of pregnancy.

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Conflict of Interest – None.

Nomenclature

There are four generally accepted specific dermatoses of pregnancy and a fifth dermatosis, which has been included by some (1). The current and most widely used names of the specific dermatoses of pregnancy are PUPPP, AEP, PG, ICP, and PPP.

The first simplified classification of the specific dermatoses of pregnancy was proposed by Holmes and Black in 1982. The four broad categories included herpes gestationis (current preferred term PG), polymorphic eruption of pregnancy (synonymous with PUPPP), prurigo of pregnancy

(PP) and pruritic folliculitis of pregnancy (PFP) (2). The latter two dermatoses are subcategories included in the current broad category of AEP. The term PUPPP reflects the classic morphology of papular urticarial lesions; it does not cover its full range of clinical presentations, prompting our British and European counterparts to prefer the term polymorphic eruption of pegnancy (3). Shornick proposed a refinement of the classification, by suggesting that PFP was not an entity on its own, but a subclassification under the heading PP. Shornick also proposed the addition of cholestasis of pregnancy to the list of specific dermatoses of pregnancy, arguing that it should be added based on the potential fetal risk, especially in the case of delayed diagnosis (4). Ambros-Rudolph et al. in a recent study of over 500 pregnant patients with pruritus, found significant overlap between the diagnoses atopic dermatitis, PP and PFP, leading their group to classify the above under the heading AEP (5). In accordance with these authors, the specific dermatoses of pregnancy to be discussed further will include: PUPPP, AEP, PG, and ICP.

Another entity, potentially worthy of inclusion in this established classification scheme, is PPP, also known as impetigo herpetiformis (IH). There is controversy whether PPP is truly specific to pregnancy (6–8). For the same reasons, Shornick included ICP, we believe the potential maternal and fetal risk warrant its inclusion in this schema. Some historical eponyms are included for reference in Table 1. We recommend against using these historical terms as they often lack descriptive terms and contribute to the existing confusion and difficulty differentiating the specific dermatoses of pregnancy.

Table 1. Nomenclature

Preferred term	Historic synonym
Pruritic urticarial papules and plaques of pregnancy or Polymorphic eruption of pregnancy	Bourne's toxemic rash of pregnancy Late-onset prurigo of pregnancy Erythema multiforme of pregnancy
Pemphigoid gestationis	Herpes gestationis
Atopic eruption of pregnancy: Eczema in pregnancy Prurigo of pregnancy Pruritic folliculitis of pregnancy	Papular dermatitis of pregnancy (widespread) Prurigo gestationis of Besnier (favor extensor surface, grouped) Nurse's early-onset prurigo of pregnancy
Intrahepatic cholestasis of pregnancy	Obstetric cholestasis Pruritus gravidarum Icterus gravidarum
Pustular psoriasis of pregnancy	Impetigo herpetiformis

PUPP

PUPPP was first described in seven similar cases and so named by Lawley et al. in 1979 (9). Approximately, 1 in 200 pregnancies will develop PUPPP (10,11). It is the most common distinct dermatosis of pregnancy.

PUPPP occurs most often in primiparous women, generally during the last month of pregnancy or in the immediate postpartum period. The presentation of intensely pruritic urticarial papules and plaques is typically abrupt. Lesions of PUPPP routinely spread to the trunk and extremities, but rarely involve the face, palms, or soles. Most patients with PUPPP present with the stereotypical urticarial papules and plaques; a small minority may present with erythematous patches. Later, in the disease course, patients may develop eczematous lesions, polycyclic erythema, or even targetoid or erythema multiforme like lesions (12). Tiny vesicles or pseudovesiculated papules can be seen in a minority of cases (10). Lesions characteristically spare the umbilicus and arise within striae distensae, (FIG. 1) (12). No reports of mucosal involvement were noted during review of the literature. PUPPP tends not to recur with subsequent pregnancies.

As a rule, laboratory tests are normal and help only to exclude other conditions. The histopathologic findings are nonspecific and diagnosis is best made on clinical grounds. Direct immunofluorescence of lesional skin is usually negative, distinguishing PUPPP from PG. However, occasionally deposits of c3 or immunoglobulin M (IgM) in blood vessel walls or granular deposits of c3 at the dermoepidermal junction have been described (9,12–14). Indirect immunofluorescence for circulating antibodies to the basement membrane are uniformly negative in cases of PUPPP (12).

In one series the mean duration of eruption was 4 weeks with a standard deviation of 3 weeks, while others have reported an average duration of 6 weeks (12,15). PUPPP tends to resolve within 7–10 days postpartum. Maternal and fetal prognosis is comparable with pregnancies without PUPPP (Table 2) (16). The eruption tends not to recur with subsequent pregnancies. The goal of treatment is relief of symptoms, and PUPPP typically responds

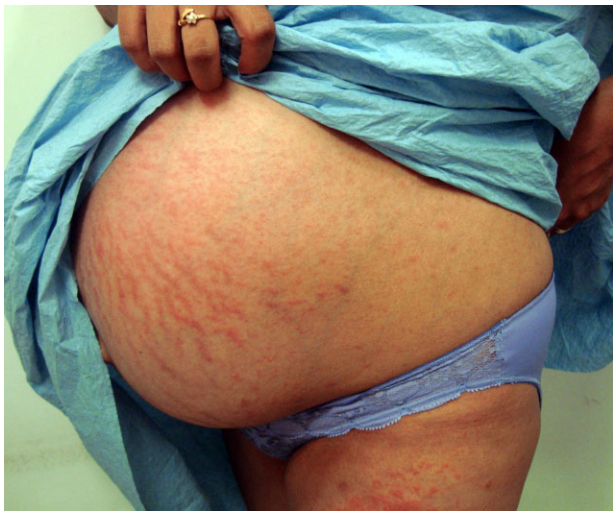

FIG. 1. Pruritic urticarial papules and plaques of pregnancy. Note the erythematous urticarial papules within the striae distensae along the left side of the gravid abdomen with additional streaks of erythematous urticarial papules on the proximal lateral thigh. Also note the halos of hypopigmentation surrounding the urticarial papules on the thigh.

well to topical corticosteroids (Table 3) (4). Low- to mid-potency topical steroids are suggested as initial therapy. Bland emollients and anti-pruritic emollient formulations containing menthol have also been used alone with success (17). For severe and intractable pruritus, systemic corticosteroids have been effective and safe in such cases (17). Rarely, early delivery has been used for relief of intractable pruritus (18). However, PUPPP is generally not considered an indication for early delivery.

AEP

AEP is a heterogeneous grouping of dermatoses with eczematous and/or papular lesions occurring in pregnant patients with an atopic diathesis after exclusion of other dermatoses of pregnancy (19). The term was introduced into the literature by Ambros-Rudolph to encompass the clinical entities eczema in pregnancy (EP), PP, and PFP (5). The clinical overlap among these entities, the lack of understanding of the underlying pathogenesis, as well as the shared treatment strategies led to their grouping as a new disease complex.

EP, the most common dermatosis of pregnancy and the largest contributor to the grouping AEP, accounts for 50% of all pruritic dermatoses of pregnancy. It could be debated if this is really a dermatosis of pregnancy or simply eczematous eruption occurring in pregnancy. Twenty percent of patients have an exacerbation of existing atopic dermatitis; the remaining 80% of patients experience atopic skin changes for the first time or after a prolonged latency of atopic dermatitis (5). AEP usually develops prior to the third trimester. AEP is divided into two types: E-type (eczematous changes) and P-type (papular changes). The eczematous type occurs in two-thirds of cases affecting typical sites of atopic dermatitis including face, neck, and flexural surfaces. One-third of cases present with papular lesions, usually small erythematous papules on extremities and trunk. Histopathology is nonspecific; immunofluorescence is negative; laboratory tests are normal with the possible exception of an elevated IgE level (5).

PP was previously reported to occur in about 1 in 300 pregnancies. PP has been reported in all three trimesters. Characteristic lesions are erythematous papules and nodules on the extensor surfaces of the extremities and occasionally the trunk and resemble prurigo nodularis in nonpregnant patients (FIG. 2). Recurrence during subsequent pregnancies is variable (20). In Ambros-Rudolph's article suggesting the terminology AEP, only 4 of 255 patients lumped under the heading AEP were considered to have true PP (5). As is the case in PFP and EP the pathogenesis is not yet elucidated. There are no specific histopathological, immunofluorescence, or other diagnostic tests, and thus PP remains a clinical diagnosis.

PFP, a rare dermatosis of pregnancy and the most uncommon of the distinct entities under the umbrella of AEP, occurs in about 1:3000 pregnancies (21). PFP typically presents during the second trimester of pregnancy with follicular, pustular, and papular lesions on the trunk or generalized (1). The etiology of PFP remains unclear. Often, the lesions begin as small 3–5-mm erythematous papules on the upper trunk that generalize and form follicular and erythematous papules and pustules. Pruritus is usually present and may be severe, but sometimes PFP is asymptomatic. Cultures should be done to rule out infectious causes of folliculitis. Skin biopsy is unnecessary as histopathology is nonspecific. Immunofluorescence is also negative. As is the case in the other distinct entities of AEP, maternal and fetal prognosis is excellent (Table 2). Lesions continue during gestation, but disappear within weeks after delivery.

Given the clinical similarities among the distinct entities within AEP, it is not surprising that similar management strategies are employed. The goal of treatment is relief of symptoms, without undue maternal or fetal risk. Emollients, tepid baths, and avoidance of harsh soaps are important in the

Table 2. Maternal and fetal risk in the specific dermatoses of pregnancy

Pregnancy dermatosis	Maternal Risk	Fetal Risk
Pruritic urticarial papules and plaques of pregnancy	None	None
Atopic eruption of pregnancy	None	None
Pemphigoid gestationis	Long-term increased risk of Graves's disease	Preterm birth, low birthweight[a]
Intrahepatic cholestasis of pregnancy	Induction of labor, cholelithiasis and cholesterol gallstones, steatorrhea and intrapartum hemorrhage[b]	Meconium staining, preterm delivery, Intrauterine fetal demise
Pustular psoriasis of pregnancy	Constitutional symptoms, hypocalcemia with tetany, seizures	Intrauterine fetal demise, stillbirth, neonatal death

[a]Particularly in patients with bullae and pemphigoid gestationis.
[b]More likely in patients with jaundice and vitamin K deficiency.

Table 3. Recommended treatment for specific dermatoses of pregnancy

Pregnancy dermatosis	Treatment of mild disease	Treatment of severe disease
Pruritic urticarial papules and plaques of pregnancy	Bland emollients Anti-pruritic lotion with menthol Low to mid potency topical steroids	High-potency topical corticosteroids Short course of systemic corticosteroids
Atopic eruption of pregnancy	Emollients Tepid baths Avoidance of harsh soaps Low to mid potency topical corticosteroids First-generation antihistamines such as chlorpheniramine, diphenhydramine[a]	High-potency topical corticosteroids Narrowband ultraviolet B Short course of systemic corticosteroids
Pemphigoid gestationis	Mid to high potency topical corticosteroids	Systemic corticosteroids in doses ranging from 20 to 40 mg per day up to 1–2 mg/kg/day
Intrahepatic cholestasis of pregnancy	UDCA given at 15 mg/kg/day in two to three divided doses or independent of weight, a dose of 1 g/day, may be given once a day or in divided doses Delivery at 38 weeks Close monitoring by Maternal Fetal Medicine Specialist	UDCA given at 15 mg/kg/day in two to three divided doses or independent of weight, a dose of 1 g/day, may be given once a day or in divided doses Delivery at 38 weeks Close monitoring by Maternal Fetal Medicine Specialist
Pustular psoriasis of pregnancy	Topical corticosteroids for localized disease	Calcium Prednisone/prednisolone at high doses 60–80 mg /day [b]Cyclosporine [b]Infliximab

[a]Due to the potential risk of retrolental dysplasia, these should be avoided after viability up to full maturity, ~27–37 weeks gestation.
[b]Considered by some to be first-line agents in cases of acute severe disease.
UDCA, ursodeoxycholic acid.

routine management of all eczema patients including pregnant patients. Generally accepted first-line agents for AEP include low- to mid-potency topical corticosteroids and antihistamines. Systemic first-generation antihistamines such as chlorpheniramine and diphenhydramine are safe during pregnancy (Pregnancy Category B) and can be helpful for the control of pruritus (Table 3). However, a single study did find the use of antihistamines during the final 2 weeks of pregnancy to be associated with an increased risk of retrolental fibroplasia in premature infants, although subsequent studies have not confirmed this association (22). Therefore caution should be

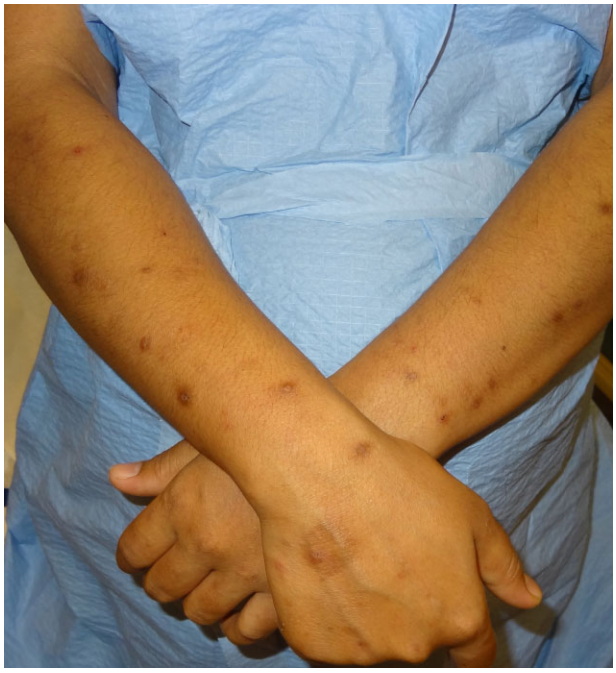

FIG. 2. Prurigo of pregnancy. Note the hyperpigmented lichenified and excoriated papules on bilateral extensor forearms.

used when prescribing antihistamines post-viability, but prior to maturity, approximately 27–37 weeks gestation. For patients with severe AEP that has not responded to first-line treatment, narrow band ultraviolet B phototherapy can be added (23). A short course of prednisone or prednisolone for severe, recalcitrant AEP can be considered during the third trimester. The maternal fetal gradient of prednisone and prednisolone is 10:1, making risk of adrenal suppression very low (24,25). Prednisone, more commonly prescribed in the United States, is converted to prednisolone in the liver by the enzyme 11 beta-hydroxysteroid dehydrogenase (26). If a systemic agent other then prednisone or prednisolone is required, the safest option is cyclosporine. Although cyclosporine is not a teratogen, it is nephrotoxic and readily crosses the placenta, and should be used for the shortest duration possible. Regular monitoring of blood counts, blood pressure, and renal function is obligated (27). Another important consideration in AEP is the risk of bacterial superinfection and bacterial infection leading to disease exacerbation. Prompt diagnosis and treatment with systemic antibiotics safe for use in pregnancy should be pursued (28). Penicillin, cephalosporins, and erythromycin are safe during pregnancy (24). Acyclovir is also safe and acceptable in the case of herpetic superinfection (29).

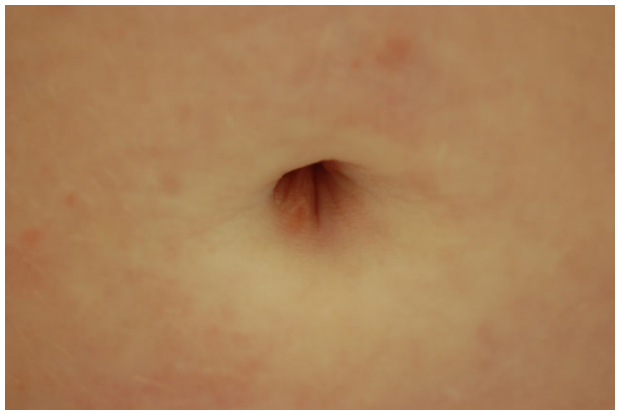

FIG. 3. Pemphigoid gestationis. As is typical in pemphigoid gestationis note the erythema directly involving the umbilicus.

PG

PG, previously referred to as herpes gestationis, is a rare pruritic specific dermatosis of pregnancy, affecting on the order of 1 in 50,000 pregnancies (30). Although rare, this dermatosis is the most well defined of the specific dermatoses of pregnancy. Onset of the eruption typically occurs during the second or third trimester, although first trimester onset has been reported. Initial postpartum onset occurs in upwards of 25% of cases, usually within hours of delivery. PG may flare postpartum, during menses or with oral contraceptives (31–33). Unlike PUPPP, PG often recurs in subsequent pregnancies, sometimes earlier in gestation and possibly more severely.

The acute eruption of intensely pruritic urticarial papules, plaques, vesicles, and bullae typically begins on the abdomen and then spreads centrifugally to involve the extremities (30). Unlike PUPPP, PG classically involves the umbilicus (FIG. 3). In late stages, vesicles and bullae predominate, generally sparing the face, mucous membranes, and palms and soles. A majority of cases improve considerably during late pregnancy, but then go on to flare immediately postpartum (4).

Multiple laboratory tests are available to confirm the diagnosis of PG. Routine histopathology and direct immunofluorescence is often enough to establish the proper diagnosis. PG is distinguished from the other specific dermatoses of pregnancy and in particular from PUPPP, by the presence of linear deposits of complement 3 (c3) with or without immunoglobulin (IgG) along the basement membrane on direct immunofluorescence. Routine indirect immunofluorescence detects an anti-basement membrane antibody in

only 20% of cases of PG (34). A complement binding indirect immunofluorescence technique is able to detect the presence of IgG antibodies to the basement membrane, specifically of the IgG1 subclass historically termed the herpes gestationis factor (35). More recently, a commercially available BP180-NC16a domain enzyme-linked immunoassay can be used for the serodiagnosis of PG, and has been found to have similar specificity to indirect immunofluorescence with increased sensitivity (36,37).

Spontaneous remission, even without treatment, within weeks to months post-delivery is typical. However, several cases of persistent PG lasting for years after delivery have been reported (38). There is evidence that early onset PG and bullae is associated with adverse fetal outcomes in the form of preterm birth and small-for-gestational-age infants (Table 2) (39,40).

During pregnancy, the maternal systemic health risks are negligible; however, the degree of pruritus can be disabling. After pregnancy, there is an increased risk of secondary autoimmune disease in patients with a history of PG. Graves's disease is the most common secondary autoimmune disease observed (Table 3) (41). In PG, the main goal of treatment is to reduce the pruritus and prevent formation of new blisters. For mild cases, early urticarial lesions or premenstrual flares, potent topical steroids with or without oral antihistamines, are sufficient to keep the disease under control (20). However, most patients require systemic steroids and as such are considered first-line agents. They are both highly effective and historically safe during pregnancy. Usually prednisone is dosed 20–40 mg daily, but 1–2 mg/kg/day may be required in severe or refractory cases (Table 3). Once the clinical lesions are cleared, the dose of prednisone should be maintained for 1–2 weeks before attempting to taper. The dose should be increased at the time of delivery corresponding to the typical disease flare that occurs at the time of delivery. Intravenous IgG (IVIG) has a history of safety during pregnancy. IVIG has been used in PG during pregnancy and postpartum, and is often added to an existing regimen of prednisone (42–45).

Rarely, systemic steroids alone are not effective or not desired, especially in refractory postpartum cases. Several alternative regimens for postpartum PG have been reported with variable success in the literature. Tetracyclines and nicotinamide have been used with some success (46,47). (Of course, tetracycline should not be considered during pregnancy, only postpartum in women who are not breast feeding.) A single case of cyclophosphamide used for a patient with severe and persistent PG who also had antiphospholipid antibody syndrome had an excellent clinical response (48). Cyclosporine 100 mg per day, along with low-dose prednisolone and IVIG was started 7 months postpartum in a Kuwaiti woman whom developed PG at 20 weeks gestation and unfortunately suffered in utero fetal death at 30 weeks gestation (42). Azathioprine and dapsone have been used as an adjunctive agent in severe persistent postpartum PG, although not during breast-feeding (39,43,44,49). Another case of severe persistent PG failing treatment with a combination of immunosuppressant agents was successfully treated with rituximab. The patient went into a 6-month remission after four weekly infusions of 375 mg/m^2. Another four infusions of rituximab were needed to treat a subsequent flare until complete remission (49).

ICP

ICP is a rare pruritic specific dermatosis of pregnancy occurring with variable prevalence in a geographical pattern. South America, specifically Chile, claims the highest prevalence rates, especially in women of Araucanian Indian descent (28%) (50). In central Europe, rates of 0.2–2.4% have been observed. ICP also runs in families, with increased frequency in mothers and sisters of patients with ICP and in monozygotic twins suggesting a genetic predilection. Recently, mutations of the gene multidrug resistant-3 or adenosine triphosphate-cassette transport B4 (ABCB4), which encodes transport proteins necessary for bile excretion, have been identified in patients with ICP (51). Increased levels of estrogen and progesterone during pregnancy have also been implicated in the pathogenesis of ICP (50).

Classically, ICP presents with sudden onset pruritus in late second or third trimester, usually including the palms and soles. About 10% of the time, pruritus develops in the first trimester. ICP does not have primary skin lesions, but this dermatosis is crucial for the dermatologist to recognize, as it may in some cases portend a poor fetal prognosis. Initially, patients may have pruritus alone without skin changes. As the disease progresses and generalizes, secondary skin changes develop from scratching and can range from minor excoriations to severe prurigo nodules. Skin lesions tend to concentrate on the extremities, although may involve other sites such as the buttocks and abdomen. Patients with ICP

experience jaundice because of extrahepatic cholestasis 10% of the time (52). Typically, this occurs within 2–4 weeks of the onset of pruritus. These patients may develop steatorrhea and malabsorption of fat soluble vitamins such as vitamin K, increasing the risk for bleeding complications (50).

Every pregnant patient with pruritus should have an evaluation of liver function tests. A separate test to quantitate the serum bile acid level should be undertaken in those patients where ICP is suspected. In healthy pregnant patients total serum bile acids are slightly higher than in nonpregnant patients and late in pregnancy levels as high as 11.0 μmol/L (normal range, 0–6 μmol/L) are accepted as normal (53,54). Total bile acids >11.0 μmol/L confirms the diagnosis. Serum bile acid levels greater than 40 μmol/L in particular portend a poorer fetal prognosis (55). Less specific tests such as alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, and also bilirubin levels may be elevated in patients with ICP as compared with healthy pregnancy controls (50). We also recommend evaluation for hepatitis C especially in patients presenting with cholestasis earlier than usual (56). An abdominal ultrasound should be considered in patients with abdominal symptoms to exclude cholelithiasis. Liver and skin biopsies are not necessary to establish the diagnosis of ICP. Histopathology is nonspecific in ICP and immunofluorescence studies are negative. The clinical diagnosis of ICP is based upon the presence of severe pruritus and elevated bile acids in the absence of any other signs or symptoms of liver disease.

Maternal prognosis is mostly favorable in ICP, and pruritus typically resolves within days to weeks after delivery. For patients with vitamin K deficiency because of steatorrhea and absorption deficits, intrapartum hemorrhage is a concern. Cholelithiasis and cholesterol gallstones are increased in patients with ICP. There is a 2.7-fold increased risk for gallstones in primigravidae with ICP as compared with pregnant women without cholestasis (57). Fetal prognosis is a major concern in patients with ICP. It has been associated with an increased risk for prematurity, intrapartum fetal distress and still births. The most alarming sequelae is a three- to fivefold increased risk of fetal death in utero (58). The exact mechanism of fetal morbitity and mortality in ICP is incompletely understood. Autopsies show signs of acute anoxia but lack signs of chronic anoxia from placental insufficiency (58–60). There is also an increase in meconium stained amniotic fluid (Table 2) (52,58,61). Birthweight for gestational age and umbilical artery flow is not affected in ICP (62).

Accurate and timely diagnosis, close obstetric monitoring, and maternal counseling are imperative in caring for patients with ICP. Notably, subsequent pregnancies are at an increased risk for recurrence of ICP. Pregnancies occurring in first-degree relatives of patients with ICP are also at increased risk. Ursodeoxycholic acid (UDCA) is the only treatment in use which has been shown to decrease the serum bile acid levels, improve maternal pruritis, and may also improve fetal outcomes (63,64). UDCA is a hydrophilic bile acid, which is thought to decrease the passage of maternal bile acids to the fetoplacental unit, as well as protect against injury to bile ducts and stimulate the excretion of other potentially hepatotoxic compounds. UDCA normalizes the cholic acid/chenodeoxycholic acid (CA/CDCA) ratio and decreases the delivery of bile acids to the fetus (53,65–70). A dose of 15 mg/kg/day or 1 g/day is administered either as a single daily dose or divided into two to three doses until delivery (Table 3). UDCA is very well tolerated, with the exception of mild diarrhea in rare cases. No adverse fetal events have been reported.

The majority of stillbirths associated with ICP tend to cluster at the 38th week (71). Therefore, there is general agreement to deliver by 38 weeks. For severe disease, delivery may be undertaken earlier. The exact time of delivery is debated. Although, antepartum surveillance is unable to prevent intrauterine death, these patients are often closely managed by maternal fetal medicine specialists. Amniocentesis can be utilized to assess fetal lung maturity and meconium staining. Meconium staining is common in ICP and may portend a poor fetal prognosis (71). The timing of delivery is complicated as one trades the risk of intrauterine fetal demise for increased risk of premature morbidity and complications associated with induction of labor (72).

PPP (IH)

PPP is a rare variant of generalized pustular psoriasis occurring during the puerperal state that merits mention as a potential specific dermatosis of pregnancy because of its maternal and fetal morbidity and the importance of recognizing and properly treating this condition. This entity was first described by Von Hebra in 1872, and named IH (73). To date only approximately 130 cases have

been published describing this disease entity (74). Although historically, there has been controversy as to whether IH is a separate pregnancy-specific disease or a variant of generalized pustular psoriasis occurring in pregnancy, it is now considered by most to represent the latter (75–77).

Although presentation as early as first trimester has been reported, PPP typically presents during the third trimester with symmetric erythematous plaques studded with sterile pustules at the margins of the plaques in a circinate pattern. It is often associated with hypocalcemia. The eruption tends to begin in flexural areas and spread centrifugally with new pustules at the margins while older central pustules dry with desquamative collarettes of scale or crusts (75,78). Subungual pustules may lead to onycholysis or rarely onychomadesis (79). Mucous membranes including the esophagus may have erosive or exfoliative plaques (77). Associated constitutional symptoms are often noted including malaise, fever, delirium, diarrhea, vomiting, and symptoms of tetany (77). Patients with PPP often lack a previous or family history of psoriasis. PPP may recur with subsequent pregnancies with increased severity.

Commonly, patients may have leukocytosis with neutrophilia, elevated erythrocyte sedimentation rate, low maternal serum calcium, phosphate, and vitamin D because of hypoparathyroidism and hypoalbuminemia (77,78). Although patients may demonstrate systemic symptoms, blood cultures and pustules are sterile. Punch biopsy is recommended, given the potential consequences of the disease for maternal and fetal health. Histopathology demonstrates spongiform pustules with neutrophils. Psoriasiform hyperplasia and parakeratosis can also be seen (75). Immunofluorescence is negative in PPP.

Clinical history, morphology, histopathology, and negative immunofluorescence help to differentiate PPP from other similar appearing entities such as impetigo, subcorneal pustular dermatosis, dermatitis herpetiformis, and acute generalized exanthematous pustulosis (20,74).

Maternal prognosis is usually favorable with early treatment and close monitoring of serum calcium levels to prevent sequelae of hypocalcemia such as seizures and tetany. Fetal prognosis is less predictable, even in treated patients. Intrauterine fetal demise, stillbirth, and neonatal death have all been reported to be associated with PPP (Table 2) (75,80).

Systemic corticosteroids were historically recommended as first-line agents for the treatment of PPP, but now cyclosporine may be used by some preferentially. Prednisone can be given up to a max dose of 60–80 mg/day. Cyclosporine has been successfully used to treat PPP in several patients having first failed systemic corticosteroids (Table 3) (81–83). Anti-tumor necrosis factor inhibitors have also been used safely and effectively in a patient with a history of PPP during a subsequent pregnancy without recurrence of PPP and with normal fetal development (79). In a recent review from the Medical Board of the National Psoriasis Foundation, cyclosporine and infliximab were included as first-line agents for the treatment of PPP (84). Cyclosporine at doses of 2–3 mg/kg have been shown to be safe in pregnant transplant patients, and thus the authors extrapolate safety in the PPP population (85). Of note, the doses with proven efficacy in generalized pustular psoriasis in nonpregnant patients often exceed the 2–3 mg/kg/day of cyclosporine (86). Infliximab has been used with success, has a rapid onset and carries a category B pregnancy status (84,85). For persistent cases, post-delivery in non–breast-feeding mothers, other therapies may be tried including retinoids and methotrexate.

Conclusion

PUPPP, AEP, PG, ICP, and PPP can each be alarming to the patient suffering with it. Patients with PUPPP and AEP can be reassured that their disease will not affect their fetus and can generally be treated with topical therapies. Although PG, ICP, and PPP can all have detrimental effects on the pregnancy, we can comanage these patients with obstetricians to help minimize the risks and alleviate the symptoms. Our ability to accurately diagnose these diseases as well as treat their symptoms will be a great benefit to our patients.

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