Specific dermatoses of pregnancy: An evidence-based systematic review

George Kroumpouzos, MD, PhD,[a] and Lisa M. Cohen, MD[b,c]

Worcester, Newton, and Boston, Mass

OBJECTIVE: We conducted an evidence-based systematic analysis of the literature on specific dermatoses of pregnancy.

STUDY DESIGN: The bibliographic databases *MEDLINE* and *EMBASE* were screened for studies and reports in all languages about herpes gestationis, pruritic urticarial papules and plaques of pregnancy, pruritic folliculitis of pregnancy, and prurigo of pregnancy from January 1962 to January 2002. As main index terms, including analogs and derivatives, we used the names of specific dermatoses of pregnancy. Intrahepatic cholestasis of pregnancy, not a primary dermatosis, was included herein because this disorder is associated with pregnancy and its secondary skin manifestations must be differentiated from specific dermatoses of pregnancy. Other sources were abstract books of symposia and congresses, theses, textbooks, monographs, reviews, editorials, letters to the editor, free or rapid communications, and the reference lists from all the articles that were retrieved. All articles selected for inclusion in this review were evaluated critically with regard to their impact factor and evidence-based contribution to this field, as measured by their citation index and impact factor of the journal in which they were published. Approximately 39% of articles met the selection criteria.

RESULTS: The clinical features and prognosis of the specific dermatoses of pregnancy have been delineated through a number of retrospective and cohort studies. The molecular biologic and immunogenetic properties of herpes gestationis, pruritic urticarial papules and plaques of pregnancy, and intrahepatic cholestasis of pregnancy have been further clarified. A meta-analysis in this review reveals a higher prevalence of multiple gestation pregnancy (11.7%) among patients with pruritic urticarial papules and plaques of pregnancy. Several investigations have unraveled the fetal complications in intrahepatic cholestasis of pregnancy and herpes gestationis. New treatment modalities in intrahepatic cholestasis of pregnancy (cholestyramine, ursodeoxycholic acid) and herpes gestationis (cyclosporin, intravenous immunoglobulin, and tetracyclines postpartum) have shown promise and warrant further evaluation.

CONCLUSION: During the past few decades, a significant amount of new data has provided new insights into the classification, pathogenesis, treatment, prognosis, and fetal risks that are associated with the specific dermatoses of pregnancy. (Am J Obstet Gynecol 2003;188:1083-92.)

Key words: Intrahepatic cholestasis of pregnancy, herpes gestationis, pruritic urticarial papules and plaques of pregnancy, pruritic folliculitis of pregnancy, prurigo of pregnancy

The terminology of specific dermatoses of pregnancy has been confusing and misleading,[1-5] as a result of the poor definition of these entities, with the exception of herpes gestationis (HG). A number of eponyms have been used for intrahepatic cholestasis of pregnancy (ICP),[6] including obstetric cholestasis, recurrent jaundice of pregnancy, pruritus gravidarum, icterus gravidarum, and idiopathic jaundice of pregnancy. The nomenclature of pruritic urticarial papules and plaques of pregnancy (PUPPP) has been equally confusing[1,5]: polymorphic eruption of pregnancy (favored in the British literature), Bourne's toxemic rash of pregnancy, toxemic erythema of pregnancy, late prurigo of pregnancy, and Nurse's late prurigo of pregnancy all refer to various presentations of the same entity. Finally, denominations (such as Besnier's prurigo gestationis, Nurse's early prurigo of pregnancy, and papular dermatitis of Spangler) have been used to describe prurigo of pregnancy (PP).[1]

From the Division of Dermatology, Department of Medicine, Saint Vincent Hospital at Worcester Medical Center,[a] Cohen Dermatopathology, PC,[b] and the Department of Dermatology, New England Medical Center, Tufts University School of Medicine.[c]

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Holmes and Black[3,4] attempted to solve the problem of obsolete nomenclature by proposing a classification of specific dermatoses of pregnancy into HG, PUPPP, PP, and pruritic folliculitis of pregnancy (PFP). Most authors agree that the previously reported immunoglobulin M dermatosis of pregnancy[7] and papular dermatitis of Spangler[8] are not distinct entities. The former is now considered to be a subtype of PUPPP[9] or PP,[10] and the latter should be included within the spectrum of PP.[10] Moreover, impetigo herpetiformis, which has been considered by some authors to be a dermatosis unique to pregnancy,[11] is believed to be a variant of pustular psoriasis that is triggered by pregnancy rather than a specific dermatosis of pregnancy. An isolated case of progesterone dermatitis of pregnancy has been reported,[12] but this disorder is not unique to pregnancy. The classification of Holmes and Black[3,4] has facilitated the clinical investigation in the field of specific dermatoses of pregnancy[13,14] and is now widely accepted. The specific dermatoses of pregnancy are summarized in Table I.

ICP

The incidence of ICP in Europe ranges from 10 to 150 per 10,000 pregnancies; in the United States the incidence of ICP is approximately 70 per 10,000 pregnancies.[15] The disorder used to be very common in Chile, Bolivia, and Scandinavia,[16] a finding that was attributed to dietary factors.[17] ICP usually manifests in the third trimester by itching (pruritus gravidarum) and skin lesions caused by scratching. Jaundice develops in 20% of cases (intrahepatic jaundice of pregnancy).[6] There is a family history in 50% of cases and an association with multiple gestation.[18] Recurrence in subsequent pregnancies occurs in 60% to 70% of cases. The condition usually resolves within the first month after delivery.

Jaundice can be complicated by subclinical steatorrhea with subsequent vitamin K deficiency and prolongation of prothrombin time[9]; the latter may result in an increased risk of hemorrhage.[10] An association with increased risk of cholelithiasis remains debatable. Elevation in serum bile acids, especially postprandial levels,[19] is the most sensitive marker of ICP.[16] Mild liver function abnormalities are commonly found, and there is a modest elevation of bilirubin levels in patients with jaundice. A skin biopsy is nonspecific; a liver biopsy reveals cholestatic changes.[20]

Hormonal, genetic, environmental, and probably alimentary factors play a role in the pathogenesis of the condition.[15] Estrogens, in particular glucuronides, such as estriol-16α-D-glucuronide and estradiol-17β-glucuronide, have shown cholestatic effects in animal studies.[21] These compounds reduce the sodium-dependent bile acid uptake into the hepatocyte[22] and inhibit basolateral transport proteins.[23] Furthermore, the increased levels of sulfated progesterone metabolites in the serum[24] may saturate the maximal transport capacity of membrane transport proteins of the hepatocyte.[15]

A genetic predisposition for ICP is supported by familial clustering and geographic variation.[15] Recent studies indicate a higher incidence of ICP in mothers of patients with progressive familial intrahepatic cholestasis or benign recurrent intrahepatic cholestasis.[25,26] Patients with progressive familial intrahepatic cholestasis 3 display mutations of the multidrug resistance 3 gene, which encodes the canalicular phosphatidylcholine translocase, a transport protein.[27] Moreover, heterozygosity for the same deletion (1712delT) in the multidrug resistance 3 gene was found in six women with ICP, all of whom were relatives of a patient with 3.[28,29] Finally, progesterone has been shown to bind to and regulate the activity of multidrug resistance translocases.[30]

Fetal risks in ICP include distress, stillbirth, and preterm delivery,[31] which are all the result of placental anoxia.[32] Decreased fetal elimination of toxic bile acids may cause vasoconstriction of placental chorionic veins in vitro[33] and meconium passage.[34] Stillborn infants in ICP often lie in meconium-stained amniotic fluid,[35] and meconium can cause acute umbilical vein constriction.[36] Most authors recommend early cardiotocographic fetal monitoring and the induction of labor in week 38 of gestation in mild cases and in week 36 of gestation in severe cases.[37] Some authors, however, recommend the evaluation of lung maturity and delivery if a patient is at ≥36 weeks of gestation and if the cervix is favorable but recommend pharmacologic treatment if the patient is at <36 weeks of gestation.[38] The cost-effectiveness of these protocols has not been determined.

Mild ICP may respond to symptomatic treatment with emollients and topical antipruritics.[1,6] Antihistamines are rarely effective. Epomediol,[39] silymarine,[40] phenobarbital,[41,42] activated charcoal,[43] and S-adenosylmethionine[44,45] have had limited success. UVB has been occasionally effective.[10] Dexamethasone suppression of fetoplacental estrogen production has been successful in a small uncontrolled trial.[46] Cholestyramine binds bile acids and decreases their enterohepatic circulation. Small uncontrolled studies[41,42] indicate that cholestyramine may be effective in one half of the patients with mild ICP. Preliminary results of a recent large uncontrolled cholestyramine trial[47] showed a clinical response in 70% of patients with ICP who were receiving cholestyramine therapy. Nevertheless, the lack of placebo-controlled cholestyramine trials makes it difficult to assess its efficacy in ICP. The disadvantages of cholestyramine are that it may be ineffective in severe ICP, it needs to be administered for several days before pruritus improves, and that it fails to improve the biochemical abnormalities of ICP.[6,34,41,43] Furthermore, cholestyramine may precipitate vitamin K that leads to coagulopathy.[6,15] A severe case of fetal intracranial hemorrhage during cholestyramine therapy has been reported.[48]

Ursodeoxycholic acid (UDCA), a naturally occurring hydrophilic bile acid, enhances the excretion of hydrophobic bile acids and other hepatotoxic compounds and sulfated progesterone metabolites.[15] UDCA reduces bile acid levels in cord blood, amniotic fluid,[49] and colostrum.[50] The results of four randomized UDCA trials in ICP[51-54] (Table II) show that UDCA, when administered in daily doses between 450 and 1200 mg, is very effective in the control of the pruritus and the serologic abnormalities in ICP. UDCA works faster than cholestyramine and has a more sustained effect on pruritus. The efficacy of UDCA may increase further when it is coadministered with S-adenosylmethionine.[54] UDCA has been safe for mother and fetus[51-54] and may decrease fetal mortality associated with ICP.[55] Large randomized, placebo-controlled trials may be necessary before UDCA can be approved by the Food and Drug Administration for the treatment of ICP.

HG (pemphigoid gestationis)

HG is a rare autoimmune bullous disease that is associated with pregnancy and rarely with trophoblastic malignancy[56] or molar pregnancy.[58] The incidence of HG is estimated between 1 in 10,000[60] and 1 in 50,000 pregnancies.[59] The disease manifests itself most commonly during the second or third trimester[60,61] (mean onset 21 weeks), although initial onset in the immediate postpartum period occurs in approximately 20% of cases.[58] HG starts with abdominal urticarial lesions in one half of the cases.[62,63] A generalized bullous reaction ensues that spares the face, mucous membranes, palms, and soles.[59,64]

The disease runs a variable clinical course. A flare at the time of delivery is a typical feature, seen in 75% of cases.[10,65] In most patients, the disease spontaneously regresses in the postpartum period. Nevertheless, a protracted course,[66,67] "conversion" to bullous pemphigoid (BP),[67,68] and recurrence with menses[69] or subsequent use of oral contraceptives[62,69] have been reported. Furthermore, cases with features of both HG and BP have been described,[70] and the differentiation between the two entities can be a challenge. HG often occurs in subsequent pregnancies, often appearing earlier in gestation and in a more severe form.[64] The postpartum duration of HG may increase with the number of involved pregnancies.[71] Skip pregnancies occur (8%)[61,62,69] for which there has been no satisfactory explanation. The effects of breast-feeding[69] and prolactin[14,60] on prolonging the duration of HG deserve further investigation.

The histopathologic and immunofluorescence findings are similar to those of BP.[60] The most common histopathologic features of HG include a subepidermal vesicle, a spongiotic epidermis, and a mild perivascular infiltrate of lymphocytes, histiocytes, and many eosinophils.[59,64] Early urticarial lesions may show edematous dermal papillae that have a characteristic inverted teardrop shape.[72] Electron microscopic studies have shown more basal cell necrosis in HG than in BP.[73] Direct immunofluorescence of perilesional skin shows linear C3 along the basement membrane zone.[10] In fewer than 40% of cases, immunoglobulin G is also present but is less intense than C3.[73] Immunoglobulin G is, however, always positive when indirect complement-added immunofluorescence is used.[73,74] The autoantibody seen in HG, although present in low titer, is distinctive in its ability to fix complement.

HG is an autoimmune-mediated bullous dermatosis that is closely related to the pemphigoid group of disorders in terms of molecular biologic and immunogenetic properties.[60,67] The antibody in HG belongs to the immunoglobulin G1 subclass,[75,76] and the antigenic target is BP180, a 180-kd hemidesmosomal glycoprotein.[77,78] The autoantibody is believed to activate complement through the classic pathway,[10,79] which causes chemoattraction of eosinophils and degranulation with subsequent damage to the hemidesmosome.[80] Serum anti–basement membrane zone antibody levels[81] and eosinophilia[82] do not correlate with the severity of the disease. Antibody titers and direct immunofluorescence for C3 may remain positive even after clearance of the skin lesions[83] or in subsequent disease-free pregnancies,[62] which indicates that factors other than antibody to BP180 may play a role in blister formation.

The major antigenic epitopes are restricted to the noncollagenous domain (NC16A)[84] of the transmembrane 180-kd antigen (epitopes A1, A2, A.25 and A3).[85] Lin et al[85] recently showed that autoantibodies and autoimmune T lymphocytes from patients with HG recognize the NC16A2 (MCW-1) epitope. These T cells express a T_H1 cytokine profile,[85,86] indicating that they may promote the production of immunoglobulin G_1 HG autoantibodies. These findings indicate that the NC16A2 (MCW-1) epitope may play a key role in triggering the immune response in patients with HG. A considerable body of literature supports the hypothesis that an immunologic insult occurs against class II antigens[87-89] of paternal haplotype[90] at the placental basement membrane zone, and that the antibody then cross-reacts with the skin. The finding of anti-HLA antibodies in all patients with HG[91] supports a possible immunologic response against placental antigens during gestation,[92] because placental tissue is derived from paternal genes, and abnormal expression of paternal class II antigens[93] would probably lead to an increase in anti-HLA antibodies. Nevertheless, it appears that anti-HLA antibodies are an epiphenomenon in the disease process and do not contribute to its pathogenesis.[60]

HG is associated with alleles of the human leukocyte antigens HLA-DR3 (61%-80%), HLA-DR4 (52%), or both (43%-50%).[89,94,95] These associations support an autoimmune process. Most patients with HG carry the C4 null allele, possibly because of linkage dysequilib-

Table I. Summary of specific dermatoses of pregnancy

Dermatosis	*Clinical data*	*Skin findings*
ICP	Third trimester Resolution postpartum	Skin lesions caused by scratching Jaundice in severe cases
HG	Second or third trimester or after delivery Flare at delivery Resolution after delivery	Abdominal urticarial lesions progress into a generalized bullous eruption
PUPPP	Third trimester or after delivery Primigravidas Resolution postpartum Association with multiple gestation	Polymorphous eruption starts in abdominal striae and shows periumbilical sparing
PP	Second or third trimester Resolution postpartum	Grouped excoriated papules over extremities and occasionally on abdomen
PFP	Second or third trimester Resolution after delivery	Follicular papules and pustules

Table II. Controlled UDCA trials in ICP

Study	*Patients*	*Control subjects*	*Dose*
Diaferia et al[51]	8 UDCA*	8 Placebo	300 mg, orally, twice daily
Floreani et al[52]	10 UDCA	10 S-adenosylmethionine	UDCA: 450 mg, orally, daily; S-adenosylmethionine: 100 mg, intramuscularly daily
Palma et al[53]	8 UDCA	8 Placebo	1 g, orally, daily
Nicastri et al[54]	4 UDCA, 4 UDCA + S-adenosylmethionine	4 Placebo, 4 S-adenosylmethionine	UDCA: 300 mg, orally, twice daily; S-adenosylmethionine: 400 mg, intravenously, twice daily

*Bilirubin and transaminases.

rium with HLA-DR3 or HLA-DR4.[96] For some women, a change in consort has been associated with the onset of the disease.[69] Interestingly, an increased incidence of HLA-DR2 among husbands has been associated with HG among their wives and was most pronounced in HLA-DR3/DR4 female patients.[95] Nevertheless, an association between a change in partner and the development of HG has not been found in other studies[61,62]; and skip pregnancies, despite having the same partner,[62] would argue against this association. The importance of paternal factors in disease production awaits further clarification.

An increased risk of autoimmune diseases, in particular Graves' disease, has been reported in patients with a history of HG.[97] There have been no other maternal risks in HG. Neonatal vesicles occur in 10% of cases,[98,99] most likely because of passive transfer of HG antibody.[62] The eruption is usually mild and self-limited, but the lesions may become superinfected as the immune system of the neonate is not fully developed. Although an association with small-for-gestational age infants and preterm delivery has been reported,[82,100] no increase in fetal morbidity or mortality has been documented, with the exception of one case of fetal cerebral hemorrhage.[101] Still, once the diagnosis of HG is established, the pregnancy should be considered to be high risk.[60,102] The pathophysiology of fetal complications is thought to be due to mild placental insufficiency,[103] because placental antigens may be targeted by the immune response that targets the skin.

Early urticarial lesions may respond to topical corticosteroids,[1,59] but more advanced lesions require oral corticosteroids.[104] Although doses up to 180 mg of prednisone daily have been reported,[82] most patients respond to lower doses (20-40 mg daily). Refractory cases during the postpartum period may respond to adjunctive cyclophosphamide,[105] pyridoxine,[106] gold,[66] or methotrexate.[66] The response to these agents, however, has been variable and their safety questionable. Plasmapheresis,[61,64] chemical oophorectomy with goserelin,[107] and ritodrine[108] have been exceptionally used in chronic HG with some success. Intravenous immunoglobulin combined with cyclosporin has been successfully used to treat HG.[109] Case reports indicate some benefit from tetracyclines in postpartum HG.[83] The effectiveness of cyclosporin, intravenous immunoglobulin, and tetracyclines in HG requires further investigation.

Histology/laboratory findings	*Recurrence in future pregnancies*	*Fetal risks*
Biopsy nonspecific ↑Serum bile acids Mild liver function test abnormalities ↑Bilirubin when jaundice Vitamin K in severe cases	++	Fetal distress Stillbirth Preterm delivery
Biopsy: subepidermal vesicle,infiltrate with eosinophils Direct immunofluorescence: linear C3 ± immunoglobin G along basement membrane zone Indirect immunofluorescence: low-titer immunoglobin G when complement added	+++	Neonatal HG Small-for-gestational-age infants Preterm delivery
Biopsy: spongiotic dermatitis, infiltrate with eosinophils Serologic test results negative Immunofluorescence test results negative	—	None
Biopsy nonspecific Serologic test results negative Immunofluorescence test results negative	0	None
Biopsy: sterile folliculitis Immunofluorescence test results negative Serologic test results negative	±	None

Length of treatment	*Results*
20 d	Pruritus, bile salts and liver function tests* significantly improved over placebo
15 d	Pruritus and bile salts significantly improved over S-adenosylmethionine
21 d	Pruritus and liver function tests significantly improved over placebo
20 d	Pruritus and liver function tests* significantly improved over placebo or S-adenosylmethionine, UDCA + S-adenosylmethionine better than either alone

PUPPP

PUPPP (also known as "polymorphic eruption of pregnancy") is the most common specific dermatosis of pregnancy; its incidence ranges between 1 in 130 pregnancies and 1 in 300 pregnancies.[14] The condition occurs predominantly in primigravidas in the third trimester (mean onset, 35 weeks of gestation) and exceptionally postpartum.[110] Recurrence in subsequent pregnancies, with menses or oral contraceptives is uncommon. A familial occurrence has been reported.[111] The eruption is polymorphous, showing urticarial and, at times, vesicular, purpuric, polycyclic or targetoid lesions. The lesions start in the abdominal striae in two thirds of the cases and show periumbilical sparing.[110,112,113] Lesions may spread over the trunk and extremities, usually sparing the palms and soles. Involvement of the face[114] has been debated,[115] although dyshidrosis-like lesions on the extremities are unusual.[116]

PUPPP remains an ill-defined entity because of its variable clinical presentation, lack of pathognomonic diagnostic features, and lack of laboratory abnormalities. The immunofluorescence and serology are negative,[113,117] and the histopathology is often nonspecific.[118] The treatment is symptomatic with antipruritic topical medications and topical corticosteroids.[1] Rarely, a short course of oral prednisone may be necessary.[13,119] UVB can be effective (L. M. Cohen, unpublished observation). Early delivery in refractory cases[120] has not gained support.[121] The maternal and fetal prognosis is excellent.

The pathogenesis of PUPPP has not yet been fully established. No immunologic or hormonal abnormalities have been found,[122] with the exception of a decrease in serum cortisol in a recent study.[13] A role for sex hormones has been suggested by clinical reports.[9] A hypothesis that a substance that is produced by the placenta may induce fibroblast proliferation in maternal skin[123] has not been supported by other studies. Several authors[124-128] suggested that rapid abdominal wall distention in primigravidas may cause damage to connective tissue in the striae with subsequent conversion of nonantigenic molecules to antigenic ones, thus triggering an inflammatory process. Giving foundation to this hypothesis, Cohen et al[124] first reported an association with twin pregnancy and abnormal weight gains in the mother and fetus. The association with maternal or fetal weight gain, however, has been debated.[129]

Table III. Multiple gestation pregnancies in patients with PUPPP

Study	*No. of patients*	*No. of twins*	*No. of triplets*	*No. of twins/triplets*
Callen and Hanno[117]	15	0	0	0
Nguera et al[118]	13	1	0	1
Yancey et al[130]	20	4	0	4
Cohen et al[124]	30	3	0	3
Roger et al[129]	22	2	0	2
Pawels et al[128]	12	3	2	5
Roger et al[14]	15	0	0	0
Aronson et al[113]	57	1	0	1
Vaughan Jones et al[13]	44	6	1	7
Case series*	26	3	0	3
Case reports†	28	5	2	7
Total	282	28	5	33

*Each case series includes 4-7 patients.
†Each case report includes 1-3 patients.

The studies that reported multiple gestation pregnancies in patients with PUPPP are summarized in Table III. Our meta-analysis of 282 cases of PUPPP (Table III) confirmed the previously suggested association with multiple gestation. In this analysis, only cases in which the pregnancy outcome was reported were included. We found 29 multiple gestation pregnancies in 282 PUPPP cases (11.7%). This prevalence is at least 10-fold higher than the prevalence of multiple gestation in the United States (1%).[131] The association of PUPPP with multiple gestation is further supported by the recent study of Elling et al.[132] The authors reported a prevalence of 7.89 PUPPP cases out of 200 multiple gestation pregnancies, compared with 1 PUPPP case out of 200 singleton pregnancies.

What makes women with multiple gestation pregnancy susceptible to PUPPP? Multiple gestation is associated with excessive abdominal distention.[133] This, as previously discussed, may cause trauma to the skin triggering an inflammatory reaction. Furthermore, multiple gestation is associated with higher estrogen and progesterone levels.[133] Progesterone has been shown to aggravate the inflammatory process at the tissue level, and increased progesterone receptor immunoreactivity has been detected in skin lesions of PUPPP.[134]

How does the inflammatory process evolve? Several studies[135-137] indicate the activation of the skin immune system to maternal and/or fetal antigens. Histopathology often demonstrates a dermal perivascular lymphohistiocytic infiltrate. Immunohistochemical studies[135,136] show an infiltrate that is composed primarily of T-helper lymphocytes. These studies reveal activated T cells (HLA-DR$^+$, CD25$^+$, LFA-1$^+$) in the dermis that are associated with increased numbers of CD1a$^+$, CD54$^+$ (ICAM$^+$-1$^+$) dendritic cells, and CD1a$^+$ epidermal Langerhans cells in lesional skin compared with perilesional unaffected skin. This immunohistologic profile may imply a delayed hypersensitivity reaction to an unknown antigen.

Fetal DNA was found recently in skin lesions of PUPPP by Aractingi et al.[137] These authors suggested that fetal cells can migrate to maternal skin and lead to the eruption because pregnancy is associated with peripheral blood chimerism, particularly during the third trimester.[138] Increased abdominal stretching increases vascular permeability and, hence, may facilitate the migration of chimeric cells into the maternal skin. The source of fetal DNA, however, was not investigated by Aractingi et al. It must be determined whether the fetal DNA originates from lymphocytes, which may participate in an immune reaction against maternal antigens, or from other fetal cell types, such as trophoblastic cells, which could be the target of a maternal immune reaction.

PP

The incidence of PP varies from 1 in 300 pregnancies[139] to 1 in 450 pregnancies.[14] PP occurs predominantly in the second or third trimester of gestation.[4,139] The clinical picture is that of grouped excoriated or crusted papules over the extensor surfaces of the extremities and occasionally on the abdomen.[10] The lesions may occasionally appear eczematous. The disease runs a protracted course, and although it commonly resolves after delivery, the eruption may persist for up to 3 months.[139] Recurrence during subsequent pregnancies is common.[14] Serologic tests results are normal; the histopathology is nonspecific, and immunofluorescence is negative.[4] The hormonal abnormalities (elevated β-human chorionic gonadotropin and decreased cortisol and estrogen levels) and dismal fetal outcome reported by Spangler et al[8] have not been confirmed by any other studies. There are no maternal risks, and the outcome of pregnancy is favorable.[10] The treatment is symptomatic.[9,10]

At present, there is little information about the etiopathogenesis of PP. PP may be associated with a family history of ICP,[14] and its differentiation from ICP can be a challenge. Occasionally, the only differentiating feature between the two entities is the absence of primary lesions in ICP. Some authors have suggested that PP and ICP may be different levels of severity of the same entity.[2] Other authors have reported an association with an atopic background.[13] Elevation of serum immunoglobulin E has been detected in two studies.[4,13] In these studies, approximately one third of the patients with PP had a personal or family history of atopic dermatitis. The authors suggested that PP might be the result of pruritus gravidarum in women with an atopic predisposition. The association with atopy was not confirmed by other studies.[14] Cohort studies and further investigations are required to clarify the immunoregulation of immunoglobulin E in pregnancy and the relationship among PP, atopic dermatitis, and ICP.[2]

PFP

PFP was described by Zoberman and Farmer[140] who reported six pregnant women with sterile folliculitis. The eruption cleared spontaneously at delivery or in the postpartum period and was not associated with morbidity to the mother or fetus. The histopathology was that of a sterile folliculitis, and the immunofluorescence was negative. Since the original description, 24 cases have been reported.[4,5,13,141-145] The condition may be more common than previously thought and seems to be as common as HG and PP in the United Kingdom.[14] There may be a lack of awareness of the condition among dermatologists, and many cases may go undiagnosed or misdiagnosed as microbial folliculitis or PUPPP. The largest series of patients with PFP indicates a decreased birth weight and a male/female ratio of 2:1.[13] PFP has been associated with premature delivery in one case.[145]

The pathogenesis of PFP has been poorly understood. There is no evidence that the condition is mediated by immunologic or hormonal abnormalities.[13] In one case, increased serum levels of androgens were detected[142]; in other reports, hormone levels were normal for gestational age.[13,143] PFP has been associated with ICP in one case,[144] but this association has not been confirmed by other reports. Wilkinson et al[142] suggested that PFP might be a form of hormonally induced acne, caused by end-organ hypersensitivity to increased serum levels of sex hormones during pregnancy. There has been little additional evidence in favor of this hypothesis.[145,146] Some authors suggested that PFP should be included within the spectrum of "polymorphic eruption of pregnancy."[146] Follicular lesions have been reported in PUPPP,[147] and the distinction between the two entities can be challenging. Further studies are necessary to define PFP as a separate entity and establish its pathogenesis.

Comment

Major advances have contributed to a better understanding of the classification, pathogenesis, and treatment of the specific dermatoses of pregnancy. Molecular biologic studies are awaited to further elucidate the nature of the immune response in HG and PUPPP. Cohort studies will greatly improve our knowledge of PP and PFP. At present, even the most experienced dermatologist may have difficulty distinguishing ICP from PP, PFP from PUPPP, and protracted postpartum HG from conversion to BP. The current clinical diagnostic criteria of these disorders may be insufficient to make these distinctions.

The cost-effectiveness of the laboratory workup has been addressed.[5] We believe that a biopsy for direct immunofluorescence is necessary when HG is a consideration, and serologic tests (bile salts, liver function tests) are important when ICP is suspected because these two dermatoses have been associated with fetal risks. When the diagnosis of PUPPP, PFP, or PP is evident by history and physical examination, a workup may not be necessary because these disorders are mostly benign for the mother and fetus.

Potential fetal and maternal risks, particularly those risks that are associated with HG and ICP, must be discussed with the pregnant woman. A team approach that involves dermatology, pediatrics, and obstetrics is the optimal way to treat the potential maternal, fetal, and neonatal complications of these dermatoses. A better understanding of the pathogenesis of these dermatoses may decrease these complications.

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