Abstract and Introduction

Abstract

The pregnancy-specific skin disorders are pruritic, inflammatory eruptions. The current classification by Ambros-Rudolph et al. includes four entities: pemphigoid gestationis (PG), polymorphic eruption of pregnancy (PEP), atopic eruption of pregnancy (AEP), and intrahepatic cholestasis of pregnancy (ICP). Although these disorders are all characterized by intense pruritus during pregnancy, they can be distinguished by timing, morphology, histopathology, treatment and potential for fetal complications. Diagnosis is made by clinical presentation, histology, and immunofluorescence. PEP and AEP typically resolve without sequelae; however, PG may lead to prematurity and low birth weight, and ICP is associated with an increased risk of prematurity, fetal distress, and intrauterine fetal demise. The potential for serious fetal complications necessitates a thorough evaluation of pregnancy-related pruritus. This article will discuss the skin disorders specific to pregnancy, with a focus on clinical presentation, potential for fetal complications, pathogenesis, diagnosis, and treatment.

Introduction

While pregnancy may result in a number of skin changes, there are pruritic eruptions that occur specific to pregnancy and the postpartum period.[1–3] In 1983, Holmes and Black proposed a classification of pregnancy-specific skin disorders, which included pemphigoid gestationis, polymorphic eruption of pregnancy, prurigo of pregnancy, and pruritic folliculitis of pregnancy.[4] In 1998, Shornick proposed the addition of intrahepatic cholestasis of pregnancy.[5] The current classification was proposed by Ambros-Rudolph et al. in 2006 on the basis of a large retrospective study of 505 patients, and includes four entities: pemphigoid gestastionis, polymorphic eruption of pregnancy, atopic eruption of pregnancy (encompassing prurigo of pregnancy and pruritic folliculitis of pregnancy), and intrahepatic cholestasis of pregnancy.[2]

A major etiology of skin changes in pregnancy involves alterations in the maternal immune system. To prevent fetal rejection, an imbalance is created between cellular and humoral immunity.[1–3] T helper type 2 (Th2) cytokine production is favored over Th1, enhancing humoral immunity and stunting cell-mediated immunity. The changes in maternal hormones are also believed to have an effect, as many skin disorders develop during the third trimester.[3]

This article will discuss the skin disorders specific to pregnancy, with a focus on clinical presentation, potential for fetal complications, pathogenesis, diagnosis, and treatment.

Pemphigoid Gestationis

Pemphigoid gestationis (PG), previously known as herpes gestationis, is the most rare of the pregnancy-specific disorders, with incidence of 1:2,000 to 1:60,000, varying with the prevalence of human leukocyte antigens (HLA)-DR3 and HLA-DR4.[1,3] PG initially presents with pruritic, erythematous urticarial papules and plaques that progress to a vesiculobullous eruption. PG characteristically involves the umbilicus, and often spreads to the chest, back, and extremities.[3,4,6] Palms and soles can be affected, but not typically the face and mucosa.[3,4] The eruption develops most often in the third trimester.[3] The course fluctuates throughout pregnancy and, in 75% of patients, a flare occurs at delivery.[1] PG usually clears spontaneously within a few months after delivery. Recurrence during subsequent pregnancies is common, and is often characterized by earlier presentation and increased severity.[1,3] There have also been reports of flares during menstruation or with the use of oral contraceptives.[1,6,7] There is an increased incidence of prematurity and small-for-gestational age infants, especially with more severe maternal disease, marked by blister formation and onset before the third trimester.[1,3] Approximately 10% of infants develop a transient, bullous eruption due to the transfer of antibodies via the placenta.[1,3,4]

Autoimmune diseases commonly present during pregnancy due to the immunosuppression required to maintain fetal life. PG is an autoimmune condition in which antibodies develop against the NC16A domain of collagen XVII (BPAG2, BP180), which is present in the amniotic, placental, and umbilical cord tissues, in addition to the basement membrane of the skin.[3] The antibodies activate the complement cascade leading to inflammation and bullae formation.[1,3,8] Immunoglobulin G (IgG) is the main crossreacting antibody seen in PG, specifically IgG4.[3,8] Women who present with this disorder are at a higher risk of autoimmune disease, particularly Grave's disease.[1] An association with HLADR3 and HLA-DR4 has been observed.[3]

Histologically, pre-bullous PG is characterized by dermal edema and perivascular inflammation with lymphocytes, histiocytes, and eosinophils. A sub-epidermal split is observed in the vesiculobullous lesions, with an eosinophil-predominant infiltrate.[1,4,6] Direct immunofluorescence of peri-lesional skin shows linear deposition of complement 3 (C3) along the basement membrane zone in all patients.[1,3]Some patients also have IgG deposition along the basement membrane.[1] Enzyme-linked immunosorbent assay (ELISA) detects the specific antibodies against collagen XVII, which correlates with disease activity and can be monitored to assess treatment effectiveness.[1,3]

Treatment of PG is focused on managing pruritus and bullae formation.[1,3] In mild cases, topical corticosteroids and antihistamines are effective. In severe bullous PG, it is appropriate to use systemic corticosteroids. The dose can be decreased after adequate control is attained, however, it is often increased prior to delivery due to the high risk of flare.[3] Use of systemic corticosteroids does not increase fetal risk, and may actually decrease risk due to control of placental inflammation.[9]

Polymorphic Eruption of Pregnancy

Polymorphic eruption of pregnancy (PEP), previously called pruritic urticarial papules and plaques of pregnancy, is a benign, pruritic inflammatory disorder that affects approximately 1 in 160 pregnancies.[1,4,10] It is typically observed during the late third trimester or immediate postpartum period of first pregnancies, and the risk is increased with multiple gestations and rapid weight gain. Urticarial papules and plaques first appear within striae distensae on the abdomen, and unlike PG, spare the umbilicus. The eruption commonly spreads to the thighs and buttocks, and rarely may generalize.[1–3,10] One-to-two millimeter vesicles may develop, but in contrast to PG, bullae are not observed.[1] Target lesions and widespread erythema may also be present.[4] The eruption is self-limited and clears spontaneously in 4–6 weeks without relation to delivery. It does not typically recur; however, there have been recurrences with earlier presentation of the lesions in subsequent pregnancies that are multiple gestations. No adverse fetal outcomes have been described.[1,3]

It is theorized that connective tissue damage from excessive stretching plays a major role in the pathogenesis of the disorder. The stretching may elicit an immune response to the damaged connective tissue antigen.[1,3]

Histological findings are similar to PG. In early PEP, a superficial to mid-dermal perivascular infiltrate of lymphocytes, histiocytes, and sporadic eosinophils is observed with edema of the dermis. Later stages of PEP demonstrate epidermal spongiosis.[1,3,4,6] Immunofluorescence is negative, distinguishing PEP from PG.[1–3,10]

Treatment of PEP is based on symptomatic relief with the use of topical corticosteroids and antihistamines. If the rash becomes generalized, a short systemic corticosteroid taper can be used.[1,3]

Atopic Eruption of Pregnancy

Atopic eruption of pregnancy (AEP) is the most common pregnancy-specific skin disorder, accounting for almost 50% of cases. It has also been referred to by several other names including prurigo of pregnancy, prurigo gestationis, early-onset prurigo of pregnancy, Spangler's papular dermatitis of pregnancy, pruritic folliculitis of pregnancy, and eczema of pregnancy.[1–

[3] AEP is a benign disorder characterized by a pruritic eczematous or papular eruption.[1] It usually presents before the third trimester, in contrast to the other dermatoses of pregnancy.[1,4] Two-thirds of AEP cases are characterized by eczematous skin changes in the common atopic sites such as neck and flexor surfaces. The remaining cases are characterized by a papular eruption of the abdomen and extremities.[1] Lesions typically respond well to treatment and spontaneously clear postpartum; however, AEP is likely to recur in future pregnancies.[1,3] The fetus is unaffected, but is at increased risk for atopic dermatitis as an infant.[1]

It is thought that the pathogenesis of atopic eruption of pregnancy is initiated by pregnancy-related immune system changes.[1,3] There is a shift towards humoral immunity, with increased Th2 activation.[1]Patients who develop AEP may have an existing predisposition to atopic dermatitis, but 80% of the patients develop these skin changes for the first time during their pregnancy.[1] A family history of atopic dermatitis is frequently observed.[3]

AEP is commonly a diagnosis of exclusion, as diagnostic testing is nonspecific. Serum IgE levels are elevated in 20–70% of patients.[1] Other pregnancy-specific skin disorders, particularly ICP, must be excluded. Additionally, pruritic eruptions not specific to pregnancy, such as scabies and drug eruptions, must be considered in the differential diagnosis of AEP.

Topical corticosteroids are the mainstay of treatment. In severe cases, systemic corticosteroids and antihistamines may be indicated for short-term use. Phototherapy can also be considered.[1]

Intrahepatic Cholestasis of Pregnancy

Intrahepatic cholestasis of pregnancy (ICP), known previously as obstetric cholestasis, cholestasis of pregnancy and jaundice of pregnancy, is a reversible cholestasis that appears to be hormonally triggered towards the end of pregnancy in predisposed women. It is characterized by pruritus of acute onset that often starts on the palms and soles and then generalizes. On exam, there are only secondary lesions, such as excoriations and prurigo nodules. Ten percent develop jaundice due to concomitant extrahepatic cholestasis. After delivery, pruritus resolves within a few weeks. There is a risk of recurrence in future pregnancies and with the use of oral contraceptives.[1,11]

Recognition of ICP is critical due to its association with serious sequelae. Potential fetal complications include prematurity, intrauterine fetal distress, and intrauterine fetal demise.[1,11]Fetal complication rates correlate with total bile acids in maternal serum, but do not increase significantly until bile acid levels exceed 40 µmol/L.[12] In cases of severe ICP complicated by jaundice, there is risk of maternal or fetal hemorrhage due to malabsorption of vitamin K.[1,11]

The severe pruritus present in ICP is due to elevated conjugated bile salts in the blood caused by impaired secretion, a multifactorial process influenced by genetics, environment and hormones.[1] There is a higher incidence of ICP in twin pregnancy.[11]

ICP is diagnosed by elevated bile acid level. Hyperbilirubinemia is noted in only the most severe cases, about 10–20%, and liver function tests can be normal in 30%. Histology is nonspecific and immunofluorescence is negative.[1,11]

Treatment targets serum bile acid levels to reduce fetal risk and control maternal symptoms.[1,11]Recommended treatment is ursodeoxycholic acid (UDCA).[1,3,11] Other drugs have been found to decrease pruritus but not fetal risk, including antihistamines, S-adenosyl-L-methionine, dexamethasone, and cholestyramine.[1] Anion exchange resins, such as cholestyramine, can cause a vitamin K deficiency independent of ICP and, therefore, should be avoided.[11]

Conclusion

The four skin disorders specific to pregnancy, pemphigoid gestationis, polymorphic eruption of pregnancy, atopic eruption of pregnancy, and intrahepatic cholestasis of pregnancy, can be distinguished by clinical presentation, histopatholgy, pathogenesis, and potential for fetal complication. Only pemphigoid gestationis and intrahepatic cholestasis of pregnancy are associated with significant risk to the fetus. As these dermatoses are all characterized by pruritus, careful evaluation of any pregnancy related pruritus is essential to appropriately treat the mother and manage any potential risk to the fetus.