21 Dermatologic diseases and pregnancy

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DERMATOLOGIC DISEASES AND PREGNANCY

The skin during pregnancy undergoes profound changes that are associated with multiple endocrine, metabolic, and immunologic adjustments to this state. Pregnant patients develop physiologic or endocrine-induced skin changes, dermatoses specifically related to pregnancy, and skin diseases seen in the nonpregnant state. The physiologic changes occur with such regularity during pregnancy that they are considered virtually normal, but these changes sometimes become pathologic when severe. The physiologic changes often occur in the general population but are increased in frequency among pregnant women, and most regress postpartum. The most common physiologic changes affect pigmentation, striae formation, the vascular system, the pilosebaceous unit, oral mucosa, and sweat glands (Table 1).

The specific dermatoses of pregnancy include pemphigoid gestationis (herpes gestationis), pruritic urticarial papules and plaques of pregnancy (PUPPP), pustular psoriasis of pregnancy (impetigo herpetiformis), cholestasis of pregnancy (CP; prurigo gravidarum), prurigo of pregnancy (PP; papular dermatitis of pregnancy), and pruritic folliculitis of pregnancy (PFP) (Table 2). These diseases are discussed later in the chapter.

PHYSIOLOGIC CHANGES ASSOCIATED WITH PREGNANCY

Pigmentary Changes

Ninety percent of pregnant patients develop hyperpigmentation, usually mild and generalized. There is accentuation of normally hyperpigmented regions such as the areolae, nipples, axillae, genitalia, perineum, anus, and inner thighs (1–3). Generally, hyperpigmentation appears during the first trimester, progresses until delivery, and regresses postpartum. However, anatomic sites already hyperpigmented (areola, nipples, and genitalia) usually do not return to their previous color. The cause of hyperpigmentation is controversial. Most investigators agree that an increase in the production of pituitary, placental, and ovarian hormones is responsible (4–6). Melanocyte-stimulating hormone (MSH), estrogen, and progesterone are strong melanogenic stimulants and may play an important role. MSH is increased during pregnancy and decreases postpartum (7–9). Studies have also shown that the placenta contains other bioactive molecules that stimulate melanocytes by upregulating tyrosinase activity (10).

Pigmentary changes during pregnancy include darkening of the areolae, producing what is known as secondary areolae. This is usually seen as pigmentation between the two areolae. Areolar pigmentation is readily distinguished from nevoid hyperkeratosis of the nipple and areola, a rare condition which also develops during pregnancy (11). The linea alba often darkens and is renamed the linea nigra; this is most notable in

dark-skinned women. Linea nigra is often accompanied by the shifting of the umbilicus to the right side of the patient at term, known as the “ligamentum teres sign,” which persists postpartum until the abdominal muscles redevelop normal tone (11,12). Pigmentary demarcation lines, seen as borders of abrupt transition between more deeply pigmented skin and that of lighter pigmentation, may occur on the lower limbs during pregnancy (13). Severe generalized hypermelanosis is rare and its occurrence suggests hyperthyroidism.

Melasma (chloasma), or the “mask of pregnancy,” presents as blotchy, irregularly shaped, usually sharply demarcated patches of light to dark brown pigmentation of the face. It occurs in greater than 50%, with some studies reporting up to 75%, of pregnant women and in up to 34% of women taking oral contraceptives (14,15). Melasma usually begins during the second trimester and is more common in dark-skinned (skin types IV–VI) women (16). The most commonly affected sites are the nose and cheeks followed by the upper lips, forehead, chin, and eyebrows (17). Three clinical patterns exist, which can be distinguishable by examination with the Wood’s lamp. The causative agent for melasma is unknown. Contributing factors, aside from pregnancy and oral contraceptives, include genetics, skin type, exposure to UV radiation, nutrition, hepatic diseases, thyroid dysfunction, drugs, and cosmetics (16). Preventive measures such as avoidance of sun, usage of broad-spectrum sunscreens, and non-allergenic cosmetics are recommended. Treatment is frequently deferred until after delivery, since gestational melasma usually regresses within a year postpartum but may persist in less than 10% of patients (11). If melasma does persist, treatment options (in addition to consistent daily use of broad-spectrum SPF 30 sunscreen and sun protective hats) include topical hydroquinone products, or hydroquinone in combination with tretinoin and topical steroid creams, azelaic acid topical preparations, laser therapy, and chemical peels.

Freckles, melanocytic nevi, and recent scars may also darken. Although melanocytic nevi may appear somewhat darker during pregnancy, an increase in size, significant change, or variation in color, or irregular shape of a nevus is always of concern and therefore warrants an excisional biopsy. Data support the finding that women with previously diagnosed dysplastic nevus syndrome demonstrate an increased rate of changing nevi during pregnancy compared with their non-pregnant counterparts (18). Other studies have demonstrated that women who are pregnant or on oral contraceptives have an increased number of estrogen and progesterone receptors on their nevi cells similar to those observed in malignant melanoma and severely dysplastic nevi (19). Histopathologic evaluation of malignant melanoma diagnosed during pregnancy shows an increased tumor thickness. This may be associated with growth factor accelerating tumor growth

Table 1 Physiologic Skin Changes of Pregnancy

Pigmentary changes
Hyperpigmentation
Melasma
Hair changes
Hirsutism
Telogen effluvium
Male pattern baldness
Nail changes
Transverse grooving
Distal onycholysis
Striae distensae
Vascular and hematologic changes
Spider angiomas
Palmar erythema
Varicosities
Non-pitting edema
Mucous membrane changes
Cutaneous tumors
Granuloma gravidarum
Hemangiomas
Molluscum gravidarum
Glandular activity

Table 2 Dermatoses of Pregnancy

Pemphigoid gestationis
Pruritic urticarial papules and plaques of pregnancy
Pustular psoriasis of pregnancy
Cholestasis of pregnancy
Prurigo of pregnancy
Pruritic folliculitis of pregnancy

or may reflect a delay in diagnosis. However, there has been no study that has shown a difference in anatomic location or histologic type when comparing malignant melanoma in the pregnant and nonpregnant patients (18).

Striae Distensae

Striae distensae, or stretch marks, are linear violaceous bands, which progress over time to pink or white atrophic lines. Striae develop opposite to skin tension lines on the abdomen, breast, upper arms, lower back, buttocks, thighs, and groin and are reported to occur in 55% to 90% of pregnant women during the 6th and 7th months (1–3,20–22).

The exact etiology is unknown, but several contributing factors include hormonal changes (adrenocorticotropins, relaxin, and estrogens) affecting connective tissue formation, maternal weight gain, degree of abdominal distension, and genetic predisposition (11). A recent study by Atwal et al. showed that the most significant risk factor for developing striae is low maternal age (due to increased fragility of fibrillin), followed by BMI greater than 26, maternal weight gain greater than 15 kg, and high neonatal birth weight (23). Postpartum, the purplish striae improve cosmetically, becoming flesh-colored or hypopigmented, although striae generally do not disappear entirely. No treatment has proven definitive to prevent or decrease the occurrence of striae; topical agents have been tried (11) with minimal success.

Hair and Nail Changes

Some degree of hirsutism develops in many women early in pregnancy and is most pronounced in women with preexisting abundant body hair or dark hair. Excessive hair growth is most pronounced on the face (upper lip, chin, and cheeks); however, the arms, legs, back, and suprapubic areas may be affected. Within 6 months postpartum, excess vellus-type hairs disappear, but coarse terminal hairs may remain.

The cause of hirsutism is unknown, but it is thought to be due to increased ovarian androgen secretion or increased adrenocorticotrophic hormone secretion (24,25). Patients with marked persistent hirsutism should have an appropriate evaluation to exclude virilizing tumors. Therapy consists of reassuring the patient, although when hirsutism persists more than 6 months postpartum, cosmetic treatment (hair removal lasers or electrolysis) may be considered.

Lynfield reported an increased proportion of anagen hair follicles (growth phase) during pregnancy, which is thought to be secondary to a decreased rate of conversion of anagen to telogen hairs (resting phase), producing a thicker than normal growth (26). This increased proportion of anagen to telogen hairs is due to the increased estrogen levels during pregnancy, which prolong the anagen phase (4). The mean percentage of anagen hairs in the first trimester is comparable with the nonpregnant state at 85% and is increased to 95% by the second trimester (26). Postpartum, a greater than usual number of hairs enter the telogen phase manifesting clinically as a sudden increased shedding of telogen hairs, known as telogen effluvium. Telogen effluvium begins classically 3 months after delivery, but may start 1 to 5 months postpartum and usually persists for approximately 1 year with complete regrowth by 15 months. The causes of telogen effluvium include the stress of delivery and changes in postpartum hormone balance. There is an abrupt decrease in estrogen after delivery probably leading to the dramatic shift from anagen to telogen phase. Lynfield found the percentage of anagen hairs dropped from 95% to 76% shortly after delivery. Therapy involves reassurance, with most patients returning to baseline hair growth and thickness within 1 to 2 years.

A mild degree of frontoparietal recession in a male pattern distribution may develop toward the end of pregnancy. This may not be fully reversible postpartum (11). Diffuse thinning of the hair during the last trimester is also seen. The causes of male pattern frontal recession and hypotrichosis are unknown, but inhibition of gonadotropic activity secondary to high steroid levels occurring late in pregnancy may play an important role.

Nail changes seen during pregnancy include Beau’s lines (transverse grooving), brittleness or softening, distal onycholysis, subungual keratosis, and accelerated nail growth (1–3, 24,27). The pathogenesis of these pregnancy nail changes is unclear. It is important to consider nail changes associated with psoriasis, lichen planus, and onychomycosis. Treatment consists of careful nail trimming and avoidance of external sensitizers and infections.

Vascular and Hematologic Changes

Vascular changes occur during pregnancy and are related to distention, fragility, and proliferation of vessels. Elevated

levels of circulating estrogens and angiogenesis factors are believed to be important in the pathogenesis of "spider" angiomas, palmar erythema, hemangiomas, and pyogenic granulomas.

A spider angioma is a bright red macule or papule, with a telangiectatic puncta, radiating branches, and surrounding erythema, easily blanchable with pressure. Spider angiomas appear most commonly in areas drained by the superior vena cava (neck, throat, periorbital, and arms) (28). These changes appear in 67% of white and 11% of black women between the 2nd and 5th months of pregnancy and regress within 3 months postpartum in 75% of cases (29). Persistent spider angiomas may be best treated for cosmetic purposes with electrodesiccation or vascular lasers (28). Treatment is usually deferred until after delivery.

Palmar erythema may be localized to the thenar or hypothenar area or can present as a diffuse mottling of the hand with cyanosis and pallor. It is seen in 66% of white and 33% of black women beginning in the first trimester (1–3). The erythema may be accompanied by a burning sensation and therefore mistaken for erythromelalgia (12). Palmar erythema usually resolves 1 week postpartum. Diffuse palmar erythema is indistinguishable from that seen in hyperthyroidism and hepatic cirrhosis.

Varicosities involving the saphenous, vulvar, and hemorrhoidal veins appear in 40% of women starting from the 3rd month of pregnancy (2,3,21). A familial tendency for increased elastic tissue fragility in conjunction with increased venous pressure may account for varicosities. However, because most varicosities develop toward the end of the first trimester when intrapelvic pressure is not significant, vascular fragility may be the more important factor (28). Partial regression tends to occur postpartum. Prevention or minimizing the risk of development of varicosities is the focus of therapy. Leg elevation, lying in the left lateral decubitus position, sleeping in Trendelenburg position, compression stockings, and avoidance of tight-fitting clothes are recommended but no studies definitively show their efficacy (28).

Other vascular changes occur less commonly in pregnancy. Cutis marmorata and livedo reticularis of the legs, facial flushing, and pallor are presumably due to vasomotor instability secondary to increased estrogens. Patients with preexisting Raynaud's phenomena may improve because of vasomotor relaxation. Non-pitting edema of the eyelids, face, hands, and feet is common during the third trimester. The edema tends to decrease during the day and is due to sodium and water retention in conjunction with increased capillary permeability. Small purpuric lesions on the legs secondary to increased capillary permeability are common during the last half of pregnancy.

Mucous Membrane Changes

Gingival hyperemia is present in up to 80% of pregnant women with an increased incidence of gingivitis beginning in the 2nd month of pregnancy (1–3,30). The gingivae enlarge, darken, become red, swollen, and may bleed spontaneously. The causes are unclear, although poor oral hygiene, local gingival irritation, nutritional deficiencies, and progesterone-induced vascular proliferation are thought to be important in the pathogenesis.

Cutaneous Tumors

Proliferation of capillaries in hypertrophied gingivae results in granuloma gravidarum (pyogenic granuloma of pregnancy or pregnancy tumor). In 27% of women, it appears as a deep-red friable nodule arising from the gingiva during the 2nd to 5th month of pregnancy (30). Clinically and histologically, it is identical to pyogenic granuloma in nonpregnant women, but tends to regress postpartum. If regression does not occur, surgical removal of the nodule is a reasonable therapy.

Mollusum gravidarum (skin tags) may appear on the neck, chest, axillae, and inframammary areas in the latter stages of pregnancy and may spontaneously regress after delivery. Persistent bothersome skin tags are easily removed by simple scissoring, cryotherapy, or electrodesiccation if desired.

Hemangiomas, hemangioendotheliomas, glomangiomas, glomus tumors, neurofibromas, dermatofibromas, and leiomyomas may arise during gestation. Except for neurofibromas, these tumors tend to regress postpartum, but may recur during subsequent pregnancies. Keloids may grow rapidly and desmoid tumors may also develop during pregnancy. Desmoid tumors should be treated by wide local excision if there is rapid enlargement and resultant local tissue destruction.

Glandular Activity

Eccrine sweating progressively increases during the third trimester accounting for occasional hyperhidrosis and increased incidence of miliaria rubra (heat rash). The cause is unknown, but it is believed that these changes are due to increased thyroid activity. By contrast, palmar sweating is decreased, which may be secondary to increased adrenocortical activity. If eccrine sweating is significantly increased, topical treatment with a solution of 20% aluminum chloride hexahydrate in ethyl alcohol applied every night for 1 week may be helpful and then as necessary. Careful application to dry skin reduces potential irritation.

Apocrine gland activity decreases during pregnancy, improving preexisting Fox–Fordyce disease and hidradenitis suppurativa, but there may be a rebound postpartum. Sebaceous gland activity increases in some patients during the third trimester. Acne and oily skin may develop, but the effects of pregnancy on acne are unpredictable. Sebaceous glands are associated with lactiferous ducts on the areolae hypertrophy in 30% to 50% of women, beginning during the 6th week of gestation, and appear as elevated brown papules called Montgomery's tubercles (1–3,13,25). The cause of the glandular changes is not well understood, but estrogen, progesterone, and cortisol are implicated. Breast changes during pregnancy include enlargement, tenderness, erect nipples, hyperpigmentation of nipples and areolae, prominence of veins, striae, and Montgomery's tubercles. Most of these changes regress postpartum.

DERMATOSES OF PREGNANCY

The dermatoses of pregnancy can be divided into two main categories: dermatoses without fetal risk and dermatoses with fetal risk. Terminology of the disease processes continues to be an ongoing controversy. The newest terminology will be used to discuss each entity. Fetal risk is associated with pemphigoid gestationis, pustular psoriasis of pregnancy, and CP.

Pemphigoid Gestationis

Pemphigoid gestationis is the least common, but best characterized disease of pregnancy and the puerperium. It is an autoimmune disease characterized by an intensely pruritic, urticarial eruption, which rapidly progresses to bullae. The disease is most commonly associated with pregnancy, although rare occurrences have been reported with hydatidiform mole and choriocarcinoma (31,32). The incidences of pemphigoid gestationis range from 1:1700 deliveries to 1:50,000 deliveries (33–35). The older term “herpes gestationis” is a misnomer, reflecting the “herpetic” clinical appearance reported by JL Milton in 1872 (36), although the condition is not related to any known viral infection. Mayou and colleagues have proposed that the term “pemphigoid gestationis” is more appropriate given its clinical and histologic resemblance to bullous pemphigoid (37). Both names can be found in the literature.

The etiology of pemphigoid gestationis appears to be autoimmune in pathogenesis, and it is associated with C4Q0 allele in 90% of affected patients. However, the clinical relevance of the presence of a C4Q0 allele remains to be elucidated (38). All women with a history of pemphigoid gestationis have anti-HLA antibodies, with 50% exhibiting both HLA-DR3 and HLA-DR4 (38–40). Circulating maternal autoantibodies react with an “antigenic” constituent of the cutaneous basement membrane as well as the chorionic epithelium and amnion of the placenta. This antigen is a normal constituent of the basement membrane and may be found in the placenta as early as the second trimester. Subepidermal blisters develop from tissue damage incurred by this antigen–antibody reaction with resultant complement activation. A recent finding of abnormal expression of paternal major histocompatibility complex (MHC) II region molecules in the placenta suggests that the maternal immune system evokes an allogeneic reaction (41). This has been theorized to be the etiology for the production of maternal antibodies to the amniotic basement membrane. The amniotic basement membrane is antigenically similar to skin thus leading to a cross-reaction causing maternal and occasional newborn disease (38).

The pemphigoid gestationis antigen has been characterized as a 180-kDa glycoprotein found in the lamina lucida of the basement membrane of skin and placenta (42,43). It is an interesting observation that pemphigoid gestationis antigen may first appear in the placenta during the second trimester of pregnancy, coinciding with the time course of the development of pemphigoid gestationis (44). This 180-kDa antigen is also known as bullous pemphigoid antigen 2 and most recently as type XVII collagen. This is a transcellular glycoprotein in the hemidesmosome with both a cytoplasmic and extracellular domain. The function of the hemidesmosome is to anchor the basal cells of the epidermis to the basement membrane thus keeping it attached to the dermis. The NC16A segment of the 180-kDa antigen is the immunoreactive site in the majority of affected patients (38).

Pemphigoid gestationis presents as an extremely pruritic, urticarial, and bullous eruption that may begin at any time during the pregnancy, but most commonly occurs during the second and third trimesters. It frequently begins during the first pregnancy and has a tendency to recur earlier and with

greater severity in subsequent pregnancies. Initial onset in the postpartum period has also been well documented in up to 25% of patients and is often explosive, occurring within hours of delivering. A frequent observation is a relative remission in the weeks prior to delivery followed by a postpartum flare.

Early lesions of pemphigoid gestationis begin as erythematous, edematous papules and plaques, which rapidly develop into vesicles and tense bullae (Fig. 1). The vesicles and bullae may be grouped, hence the historical description of “herpetic,” and develop into erosions with crusting. The eruption begins in and around the umbilicus in the majority (50%) of patients and then spreads to involve the abdomen and thighs (Fig. 2). The back, breast, palms, and soles are frequently affected. The head and mucosa are involved less frequently (<20%). A constant feature of pemphigoid gestationis is pruritus. Itching is often extreme and may begin days or weeks prior to the appearance of clinical lesions.

Two skin biopsies are needed to establish the diagnosis: one punch biopsy of an intact bullous lesion for routine H & E histology and a second punch biopsy taken from perilesional skin for direct immunofluorescence. Histology of an early urticarial lesion shows a perivascular infiltrate consisting of lymphocytes and many eosinophils. Papillary dermal edema with spongiosis and intracellular edema of the overlying

Figure 1 Early lesions of herpes gestationis.

Figure 2 Periumbilical distribution of herpes gestationis.

epidermis are seen. Histology of a bulla reveals basal cell necrosis with a resultant subepidermal bulla. There is a pronounced inflammatory infiltrate containing many eosinophils. The presence of eosinophils is the most constant feature of pemphigoid gestationis (45).

Using a direct immunofluorescence assay, patients with pemphigoid gestationis have a linear deposition of complement 3 (C3) along the basement membrane zone in clinically normal and involved skin (46). This finding traditionally is the hallmark of the disease, remaining the most sensitive and specific test for pemphigoid gestationis (45). Immunoglobulin G (IgG) deposition is seen as well (30–40% of patients), and less frequently IgA and IgM.

The sera of patients with pemphigoid gestationis contain an antibody to a basement membrane constituent of normal skin. This antibody, known as “herpes gestationis factor,” avidly binds complement and is an IgG1 molecule (47). Using conventional indirect immunofluorescence, only 25% of patients show evidence of “herpes gestationis factor,” and usually in low titers. However, complement added indirect immunofluorescence reveals the circulating anti-basement membrane zone IgG in nearly all patients, thus this technique is much more sensitive (38). Salt split skin studies reveal the immunoreactants to localize in the epidermal side of the lamina lucida, a finding similar to that seen in bullous pemphigoid (48). Placental studies reveal a similar deposition of C3 and immunoglobulin along the amniotic basement membrane. As in lesional skin and plasma, IgG1 is the most frequently found immunoglobulin (49).

Laboratory evaluation is not necessary for the diagnosis of pemphigoid gestationis, although there is an increase in incidence of antithyroid antibodies detected in affected patients but clinically apparent thyroid dysfunction is rare (38,50). ELISA testing is now available and will potentially replace direct immunofluorescence for diagnosis in the future.

The primary disease entity in the differential diagnosis of pemphigoid gestationis is PUPPP. There is clinical overlap between the two diseases in that they are both pruritic dermatoses of pregnancy presenting with urticarial plaques, wheals, and vesicles. Pemphigoid gestationis is distinctive, however, in developing grouped bullae (PUPPP occasionally is vesicular), in its initial periumbilical distribution (PUPPP classically arises in abdominal and thigh striae), and its earlier appearance within the second trimester (PUPPP usually begins in the third trimester). On H & E histology, one cannot definitively differentiate them. However, direct immunofluorescence of pemphigoid gestationis is consistently positive for linear deposits of C3 at the basement membrane, while PUPPP shows nonspecific direct immunofluorescence. Indirect immunofluorescence studies in PUPPP are negative (51).

Other vesiculobullous diseases, such as dermatitis herpetiformis, bullous pemphigoid, and bullous erythema multiforme, are easily differentiated from pemphigoid gestationis by clinical presentation and routine immunofluorescence. Bullous pemphigoid has many similarities to pemphigoid gestationis both in its clinical appearance and in its ultrastructural findings. However, bullous pemphigoid is a disease of the elderly and would rarely be seen in the reproductive years. The dominant Ig subclass in bullous pemphigoid is IgG4 compared with IgG1 in pemphigoid gestationis (45).

Systemic steroids are the mainstay of therapy for moderate to severe pemphigoid gestationis. Recommended prednisone dosing is 0.5 mg/kg/day. One can frequently taper to a daily prednisone dose of 10 mg. Fortunately, the use of low-dose systemic steroids in the second and third trimester of pregnancy is not associated with increased risk of congenital anomalies, although careful monitoring is needed for gestational diabetes and hypertension (52). Mild cases are often treated with mid- to high-potency topical glucocorticoids and oral antihistamines (some studies have shown these medications to be ineffective, but they may offer symptomatic relief) (38). Alternative therapies include dapsone, cyclosporine, plasmapheresis, and cyclophosphamide, each variably effective at best, and all with significant potential for morbidity (38,53,54).

The usual course of pemphigoid gestationis is extremely variable. Many experience complete remission several weeks after delivery and mild flaring with resumption of menses. Rarely, severe cases of pemphigoid gestationis will persist far beyond the postpartum period and require corticosteroid therapy. Recurrent disease flares are reported from 2 weeks up to 12 years postpartum (38,45). Monthly perimenstrual flares, ovulatory flares, and flares with the use of birth control pills or estrogen therapy have all been reported in up to 25% of patients. These reports support the contention that once pemphigoid gestationis is initiated, it is hormonally mediated. Once a patient has pemphigoid gestationis, there is a clear tendency for it to recur in subsequent pregnancies (there are also reports of “skip pregnancies” in 5–10% of cases) with an earlier onset and more severe disease, but there are no good data to support this (38,55).

The impact of pemphigoid gestationis on perinatal morbidity and mortality is controversial. While Lawley and colleagues noted an increase in fetal morbidity and mortality, Shornick and coworkers found no increase in maternal or fetal complications (34,56). More recent data suggested an increase in preterm delivery and fetal growth retardation (57,58). No studies show that treatment with systemic steroids alters the risk of preterm delivery in these patients (38). In any case, good obstetrical and perinatal care gives a favorable outcome in the great majority of cases. Rarely do infants born to mothers with pemphigoid gestationis have vesicles or bullae (<10%). When present, the eruption is mild and transient. There appear to be no ill effects on the child nor evidence of increased incidence of other autoimmune diseases (46). Women with a history of pemphigoid gestationis have an increased risk for the development of Grave's disease (38).

Pruritic Urticarial Papules and Plaques of Pregnancy

PUPPP is the most common of the dermatoses of pregnancy with an incidence varying from 1 in 160 to 1 in 300 pregnancies (50,59). In the first report of PUPPP, a woman was described with all the clinical features: a pruritic, urticarial eruption developing within abdominal striae during the third trimester and generalizing to the thighs and buttocks. While it was termed toxemic rash of pregnancy, there is no association of PUPPP with pre-eclampsia, and this terminology was not accepted (60). In 1979, Lawley and colleagues (61) reported seven cases in which they carefully defined the clinical features of PUPPP and gave it its widely accepted, yet controversial, name of pruritic urticarial papules and plaques of pregnancy.

Later Holmes and Black suggested the name polymorphic eruption of pregnancy based on the varying morphology of the lesions (62). Both names are now found in the literature.

While the etiology remains unknown, there are several current theories, one of which involves an inflammatory reaction to connective tissue damaged within striae secondary to late abdominal wall distension (63,64). Hormonal modulation may be involved as evidenced by patients with PUPPP having higher prevalence of multiple gestations compared with the general population. One study found a 13% incidence of PUPPP in multiple gestational pregnancies compared with 1% incidence in single gestational pregnancies (65). Other theories include maternal weight gain, fetal weight, infant sex (males more common), and fetal DNA (66,67).

The onset of PUPPP varies from as early as 17 weeks to 1 week postpartum, with the majority of patients presenting within the third trimester (mean onset 35 weeks) (38). The mean duration of the disease is 6 weeks, but it may persist as long as 16 weeks. Severe symptoms usually last 1 week. PUPPP classically presents with erythematous urticarial plaques on the abdomen usually in association with striae and always sparing the periumbilical region (Fig. 3) (38,65). Other presentations include vesicular, purpuric, targetoid, or polycyclic lesions, hence the polymorphous nature. This cutaneous eruption then spreads rapidly to involve the thighs, buttocks, breasts, and arms while the face, palms, and soles are rarely involved. Pruritus is localized to the involved skin.

Histopathologic findings of an early urticarial lesion reveal epidermal and upper dermal edema with a superficial lymphohistiocytic perivascular infiltrate. Eosinophils often are present in the infiltrate. However, blood eosinophilia is a less common feature. Vesicles are present in the most florid examples, in which case intense focal spongiosis is seen in the epidermis. Direct immunofluorescence studies are nonspecific, and indirect immunofluorescence studies are negative, which helps differentiate PUPPP from pemphigoid gestationis.

Treatment of PUPPP is symptomatic due to its self-limiting course and lack of serious outcomes. Management of pruritus, often very intense and unremitting, is usually accomplished with medium-potency topical steroid preparations and oral antihistamines. Systemic corticosteroids are sometimes used. Reassurance to the patient about this common cutaneous

Figure 3 Pruritic urticarial papules and plaques of pregnancy developing in striae.

disease of pregnancy is important, because it usually resolves within a few weeks without risk to the fetus.

Maternal and fetal prognosis is excellent (68). Recurrence during subsequent pregnancies, with menses, or oral contraceptives is uncommon. If it does recur, the disease tends to be attenuated.

Pustular Psoriasis of Pregnancy (Impetigo Herpetiformis)

Pustular psoriasis of pregnancy is rare, with fewer than 350 cases reported. It was first described by Von Hebra in 1872, and it consists of an acute pustular eruption resembling pustular psoriasis arising suddenly in a patient without prior history of psoriasis (69). Pustular psoriasis of pregnancy continues to be debated as to whether this disease is a variant of pustular psoriasis or a distinct clinical entity truly specific to pregnancy. Several factors favor a pregnancy-specific dermatosis. These include the absence of a positive family history of psoriasis, abrupt cessation of symptoms after delivery, and the tendency for recurrence with subsequent pregnancies and oral contraceptives (38).

The onset of pustular psoriasis of pregnancy is usually during the last trimester of pregnancy, but it may occur as early as the third month. Skin lesions begin as circinate erythematous macules or plaques, with 1 to 3 mm pustules advancing along the peripheral edge, preferentially occurring in intertriginous areas. It may spread to mucous membranes as well as to the entire integument, sparing only the face, hands, and feet. Pruritus is usually not present or very mild. The lesions heal with non-scarring post-inflammatory hyperpigmentation. Systemic symptoms are common including fever, chills, malaise, nausea, diarrhea, and arthralgias. Rarely does the patient present with tetany, delirium, and seizures secondary to hypocalcemia. Other potential lab abnormalities include leukocytosis with neutrophilia, elevated erythrocyte sedimentation rate, hypoalbuminemia, and iron deficiency anemia (70–72).

Histologically, pustular psoriasis of pregnancy is identical to pustular psoriasis and is characterized by parakeratosis, elongation of the rete ridges, and subcorneal collections of neutrophils. Immunofluorescence studies are all negative. It is important to remember that these pustules are sterile unless the skin becomes secondarily bacterially infected.

Early recognition of pustular psoriasis of pregnancy is crucial, with both maternal and fetal morbidity and mortality increased (73). Maternal complications may include profound hypocalcemia and the risk of bacterial sepsis, due to failure of skin barrier function. Fetal complications include placental insufficiency with sequelae such as miscarriage, fetal growth restriction, and possible stillbirth (73,74). Fetal well-being should be monitored with nonstress tests, biophysical profiles, and ultrasound studies as indicated (70).

First-line treatment during pregnancy is oral corticosteroids. A prednisone dose as high as 60 mg/day may be required, with a careful slow taper to prevent a rebound phenomenon. Therapeutic consideration may be given to cyclosporine (class C), depending on the severity of the clinical situation (38,73). After delivery, treatment options are broader with oral retinoids (isotretinoin or etretinate), narrowband ultraviolet B phototherapy, and methotrexate more commonly used (71).

CP

CP, also known as prurigo of pregnancy and prurigo gravidarum, is characterized by sudden onset of intense pruritus in the absence of primary cutaneous lesions, although secondary excoriations may occur (Fig. 4). It classically presents during the third trimester in 80% of cases (with 10–20% during first and second trimesters). Symptoms remit within 2 to 4 weeks after delivery but can recur with successive pregnancies (38,51). The incidence of this disorder ranges from 0.02% to 3% depending on the region, with the highest incidence in Chile at 14% to 16% (4,38,75).

The etiology of CP is secondary to maternal intrahepatic bile secretory dysfunction with the pathogenesis remaining unclear. Hormonal alterations most likely play a large role in CP. Increased levels of estrogen and progesterone during pregnancy have been shown to inhibit the enzyme glucuronyl transferase, resulting in impaired bilirubin conjugation and excretion leading to intrahepatic cholestasis. Disease onset and resolution correlating with elevation and reduction of hormones also favor hormonal alterations. However, several other factors including genetic, environmental, and alimentary etiologies may play a role in inducing cholestasis, which results in elevated levels of bile acids in serum and skin in genetically predisposed women (76).

Clinical presentation is moderate to severe pruritus, which may be intermittent initially, occurring only at night. Pruritus may be localized to the palms and soles, but tends to become generalized. Occasionally, patients may have anorexia, nausea, vomiting, and diarrhea. The progression to jaundice occurs in approximately one in five patients (38). Jaundice is usually mild and may be associated with dark urine and light-colored stools. It becomes detectable 1 to 4 weeks after the onset of pruritus. The symptoms resolve rapidly postpartum (within 2 to 4 weeks), but may recur in subsequent pregnancies or with the use of oral contraceptives in 45% to 70% of patients (38).

CP should be highly suspected in a patient who presents in the third trimester with the complaint of pruritus, but with few or absent skin findings. Skin biopsy is of little benefit. Laboratory evaluation is necessary for diagnosis, with elevation of bile acid the most sensitive indicator of CP (levels greater than 11.0 M are significant) (77). The degree of pruritus tends to correlate with the bile acid level. Other liver function tests may be elevated including transaminases, alkaline phosphatase, and bilirubin (76). It is also important to rule out other causes of liver abnormalities, jaundice, and pruritus.

Maternal and fetal risks are associated with CP. Maternal outcomes are generally favorable, but severe cases may lead to postpartum hemorrhage secondary to low vitamin K (38). Other complications include an increased tendency toward cholelithiasis and cholecystitis. Fetal risk includes fetal distress in 20% to 30% of cases, premature birth in 20% to 60% of cases, and stillbirth in 1% to 2% of cases. Fetal risks are thought to be due to the result of placental anoxia secondary to decreased fetal elimination of toxic bile acids (38,51,76).

Medical management of CP is twofold: fetal monitoring and treating maternal symptoms. Fetal monitoring should begin around the 34th week of gestation. Delivery may need to be induced depending on the severity of fetal distress. Topical therapy with steroid preparations, emollients, and oral antihistamines provides some relief to mild pruritus. In

patients with intense pruritus, ursodeoxycholic acid has replaced cholestyramine as first-line therapy. Ursodeoxycholic acid treatment is the only medical therapy shown to decrease both maternal pruritus and fetal mortality (38,51,78). Doses range from 450 to 1200 mg/day (38).

PP and PFP

In the past, these two dermatoses of pregnancy were viewed as separate entities by the majority, but recently Ambros-Rudolph et al. have proposed the term “atopic eruption of

Figure 4 Excoriations in pruritus gravidarum.

Figure 5 Allergic contact dermatitis, a common dermatosis, which also occurs in pregnant patients.

pregnancy" (51). This term encompasses PP, PFP, and eczema in pregnancy. Though discussed separately, PP and PFP may best be considered part of a spectrum.

PP has an incidence of 1 in 450. It tends to manifest during the second or third trimester. Clinically, the patient presents with erythematous, excoriated papules or nodules along the extensor surfaces most commonly. The lesions can appear eczematous or crusted. This is more common in patients with a history of atopy (79). A laboratory workup is usually not necessary. PP resolves postpartum, but may persist for up to 3 months. Fetal and maternal prognoses are excellent. It may recur in subsequent pregnancies (79). Treatment for pruritus is symptomatic including topical steroids and antihistamines.

PFP has an incidence of approximately 1 in 3000 (79). Clinical presentation occurs during the second or third trimester with pruritic, follicular, monomorphous papules and occasionally pustules. The skin findings tend to be on the trunk but may become generalized. PFP is a sterile folliculitis; however, evaluation to rule out other infectious etiologies is warranted. Fetal and maternal outcomes appear to be unaltered. One study reported decreased birth weight and a male to female ratio of 2:1 (80). Treatment is aimed at symptomatic relief. Topical medium potency steroids and narrowband ultraviolet B phototherapy have proven beneficial (38).

CONCLUSION

Pregnancy affects the majority of the biologic systems, and the skin is not an exception. It is important to remember that many common dermatoses also occur in pregnant patients (Fig. 5) as well as significant dermatoses specific to pregnancy. Risks to both mother and fetus, associated with specific dermatoses of pregnancy, may be identified quickly and treated appropriately with accurate dermatologic diagnosis.

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