

DIAGNOSIS AND TREATMENT OF ATOPIC DERMATITIS, URTICARIA, AND ANGIOEDEMA DURING PREGNANCY

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Evaluation of the pregnant patient with pruritus and clinical findings suggestive of cutaneous disease can be challenging. This article outlines recent advances in the diagnosis and treatment of atopic dermatitis, urticaria, and hereditary angioedema in pregnancy and suggests educational resources to supplement physician answers to the patient's concerns, such as: "How will the condition affect my unborn baby? Will the treatment harm my baby?"

ATOPIC DERMATITIS IN PREGNANCY

Pathophysiology

Atopic dermatitis is an increasingly prevalent skin condition, affecting 3% of infants and 1% to 2% of adults. It is characterized by an eczematous disorder, which includes (1) pruritus, (2) a chronic or recurring course, (3) typical appearing rash and distribution (Fig. 1), and (4) a genetic predilection to develop allergic rhinitis, asthma, and food allergy. The spectrum of symptoms may extend from a mild isolated circumscribed patch (nummular eczema) to severe generalized exfoliative erythroderma. Acutely, the condition evidences erythema, dermal

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Figure 1. Atopic dermatitis. Typical flexural exanthem of atopic dermatitis of the antecubital fossa. Erythema, edema, excoriations, and peripheral hyperpigmentation are present.

edema, excoriations, and weeping while chronically it reveals scaling, thickening, hyperpigmentation, and fissuring. Areas of predilection include the antecubital and popliteal fossae, neck, upper trunk, perioral and periorbital areas, and hands in adults. Abnormal cutaneous findings frequently include the following: white dermographism (a white line rather than a wheal in response to skin stroking); a greater dermal constrictor response to cold; reduced whealing to histamine; reduced delayed hypersensitivity reactions on patch testing; exaggerated response to methacholine; pallor instead of erythema to nicotinic acid; diminished reactions to beta-adrenergic stimulation; and increased dermal mast cells. Some of these findings also may be observed, though less frequently, in patients with other chronic dermatoses.

Observations of atopic dermatitis-like lesions and elevated IgE levels in primary T-cell abnormalities like the Wiskott-Aldrich syndrome have helped to elucidate the immunologic basis for the disorder. The eczematous rash in these patients remits when the immunologic defect is corrected with bone marrow transplantation, suggesting a bone marrow-derived cellular dysfunction rather than an inborn dermal defect. Immunoregulatory dysfunctions are frequent in atopic dermatitis, including increased total and specific IgE production, enhanced spontaneous histamine release, recurrent skin infections due to viruses and bacteria, reduced levels of CD8 suppressor/cytotoxic T cells, increased

production of interleukin (IL)-4 and decreased production of interferon gamma, and reduced reactivity to contact allergens.¹⁹ Other alterations in cell-mediated immunity occur, including increased numbers of circulating FcεRII mononuclear cells, depressed neutrophilic and mononuclear cell chemotactic activity, and elevated mononuclear cell phosphodiesterase activity. Elevated serum IgE levels occur in up to 70% to 80% of subjects with atopic dermatitis. Peripheral eosinophilia and specific IgE to foods (the majority during infancy) and inhalants are frequently seen. An association of sensitization to foods and inhalants with atopic dermatitis has been established.¹⁰ In atopic dermatitis, an abnormal allergic/immunologic mechanism occurs in atopics that leads to the cutaneous release from mast cells of such mediators as histamine, eosinophilic chemotactic factors, leukotrienes, and others. Increased numbers of dendritic Langerhans' cells infiltrate chronic lesions, and an elevated proportion of T-helper to T-suppressor lymphocytes occurs in dermal infiltrates. Greater numbers of mast cells but not basophils are seen in lesions, and large quantities of eosinophil basic protein, a potentially toxic product of eosinophil leukocytes, permeate abnormal skin.¹⁵ In adults, inhalant allergy, particularly to mite, dander, and occasionally foods, may be responsible for IgE-mediated eczema.

Diagnosis

The spectrum of dermatologic findings in atopic dermatitis is broad, but its key components are pruritus and dermatitis. The most important clinical features essential to making the diagnosis of atopic dermatitis include the following⁴:

Pruritus

Chronic or recurring course

Typical appearing rash and distribution

Genetic predilection to develop allergic rhinitis, asthma, and food allergy

Most parturient women with atopic dermatitis are aware of their disease before pregnancy, as atopic dermatitis typically has its onset in infancy or early childhood.

Atopic symptoms may be ameliorated or exacerbated with menses and pregnancy. In a prospective study of 200 women referred to a London specialty clinic for pregnancy dermatoses, eczema accounted for 72 cases; 57 of those cases had a personal or family history of atopy.²⁶ Of 150 Scottish women ages 15 to 45 with atopic dermatitis surveyed, 33% reported skin symptom "deterioration" immediately before or during menstruation, with improvement the week following menses. A subgroup of 50 had been pregnant at least once: 52% noted deterioration in their skin during pregnancy, 24% noted improvement, and 24% noted no change. Four women in the subgroup noted recrudescence of atopic dermatitis during pregnancy after several years without symptoms.¹²

Many dermatoses itch, but in atopic dermatitis, pruritus is the cardinal feature.¹³ There may be an indirect adverse effect of maternal pruritus on the fetus by interfering with maternal dietary intake, sleep patterns, or emotional well being. Differentiating atopic dermatitis from other pruritic dermatoses of pregnancy is important, as therapy must be directed to the specific disorder. Pruritic skin changes due to pregnancy include idiopathic pruritus, prurigo of pregnancy, pruritic folliculitis, and cholestasis of pregnancy.

Idiopathic pruritus (pruritis gravidarum) has its usual onset during the first trimester; only excoriations are seen (Fig. 2). It may be caused by a functional hepatic disturbance induced by estrogens. In *cholestasis of pregnancy*, the skin also is normal, but elevation of serum bile acids triggers pruritus. Pruritus of the palms and soles may be a useful clue.²⁷ Because it is associated with an increased incidence of stillbirth, intrapartum fetal distress, and preterm labor, it is worthwhile to assess liver function in pregnant patients with unremitting pruritus and excoriations. Ursodeoxycholic acid orally gives relief of pruritus, as does induction of delivery at 38 weeks.¹⁷

Prurigo of pregnancy occurs in the second or third trimester and is an erythematous papular eruption with excoriations, primarily localized to the anterior abdomen. The mechanism has not been determined.



Figure 2. Idiopathic pruritus of pregnancy. Linear vertical hyperpigmented papules and erosions are seen on the dorsal forearms.

Pruritic folliculitis usually occurs during the third trimester and shows follicular papules and pustules on the trunk, with spread to arms and legs, resolving before delivery. Surprisingly, biopsy in 12 patients showed histopathology similar to pruritic urticarial papules and plaques of pregnancy (PUPPP) (discussed later), whereas only 2 cases showed "florid folliculitis."²⁶

Dermatoses that may be exacerbated by pregnancy include such inflammatory disorders as atopic dermatitis, contact dermatitis, urticaria, and infections or infestations such as staphylococcal folliculitis and scabies.

Contact dermatitis refers to a delayed onset (hours to several days) of a scaly, red, pruritic, often vesicular, well-demarcated eruption. Identifying a cause, such as vitamin E oil used to ameliorate striae on the abdomen of a pregnant woman (S. Boiko, MD, personal communication, 1987), is important in preventing recurrent exposure. Treatment consists of topical or systemic corticosteroids.

Folliculitis refers to pink or red follicular papules and pustules and implies a bacterial infection of the follicle, such as *Staphylococcus aureus*. Treatment with oral antistaphylococcal antibiotics and avoidance of fomites, such as repetitively used disposable razors and bath sponges, is recommended.

Severe pruritus unrelieved by topical emollients and steroids that worsens at night is typical of *scabies*. Burrows may be seen in the finger webs, elbows, palmar creases, or nipples. Mites, eggs, or feces from a scraping of a burrow placed in mineral oil and examined under the microscope will make the diagnosis.

Xerosis (asteatosis) is common with frequent bathing and decreased humidity. The skin appears flaky and finely crackled, usually over the shins. Atopic dermatitis often shows generalized xerosis. *Keratosis pilaris* is an inherited trait, also associated with atopy and xerosis. Follicular pink scaly papules occur, especially on the outer arms, upper thighs, and buttocks.

Treatment

Treatment of atopic dermatitis must be directed at controlling non-specific and specific allergen triggers, reducing pruritus, eradicating secondary infections, and modulating inflammation.¹¹

Nonpharmacologic

Identification and removal or reduction of both specific and non-specific triggers for atopic dermatitis is essential prior to starting pharmacologic intervention. Irritants such as wool and occlusive clothing, chemicals, overwashing, drying soaps, excessive perspiration, and unwarranted stress need to be avoided. Secondary skin infections with *S. aureus* and, less frequently, herpes simplex, molluscum contagiosum,

and *Pityrosporum ovale*, need to be prevented and, if present, recognized early for specific therapy. Specific inhalant sensitivity to dust mites and, less often, to molds and pollens may be important in some adults, with atopic dermatitis demanding intervention with environmental avoidance techniques. A recent epidemiologic study noted a clear relationship between the severity of atopic dermatitis and dust mite exposure and also between clinical improvement and environmental control.³

For immediate relief of pruritus, cold compresses in the form of refrigerator-temperature aluminum cans filled with liquid or wet compresses of tap water-soaked soft cotton cloths are inexpensive and universally available.

Pharmacologic

It is good practice to discuss the risks and benefits of any medication recommended to the pregnant patient and to document the discussion in the medical record. The mainstays of treatment for any patient with atopic dermatitis are restoring the epidermal barrier with emollients, relieving pruritus with antihistamines, reducing cutaneous inflammation with steroids or other immunomodulators, and treating secondary bacterial or viral infection with antimicrobials. Special consideration must be given to the effect of these treatments on the fetus when treating atopic dermatitis during pregnancy.

Emollients are oil and water preparations that trap water in the stratum corneum, relieving the sensations of dryness and itching. Creams or ointments are preferred to lotions, as lotions have higher water content and may sting; however, some patients prefer the cooling effect of a lotion's rapid evaporation. Emollients should be applied after bathing and may be applied as often as desired.

When clinically indicated, oral antihistamines should be administered at the lowest effective dose, initiating therapy with the first-generation agent chlorpheniramine (4 mg up to every 4 hours or 8–12 mg slow-release up to twice daily), followed by tripeleminamine (25–50 mg four times a day or 100 mg sustained-release twice daily). If the above are ineffective, hydroxyzine (10–50 mg before bedtime) may be tried after the first trimester. If sedation becomes a problem, second-generation antihistamines, such as cetirizine or loratadine (which have reassuring animal studies), could be considered after the first trimester.²³ "Exposure to second generation antihistamines (loratadine, cetirizine) during . . . organogenesis should generally be avoided except when the expected benefit is large."²³

A topical steroid should be selected based on its potency, which reflects the amount of steroid likely to be systemically absorbed (Table 1). The pregnant body surface increases in area as the pregnancy progresses, yielding a possibly larger area of application of the topical steroid. Using the lowest potency topical steroid that is effective is recommended. Even a class V steroid such as 0.1% triamcinolone cream can cause atrophy and striae if applied for prolonged periods to the face or to an occluded area, such as the groin or axilla. Class I topical steroids can cause

Table 1. TOPICAL CORTICOSTEROIDS (IN DECREASING ORDER OF POTENCY)

Group	Generic Name
1	Betamethasone dipropionate, augmented 0.05%§ Clobetasol propionate 0.05%§ Diflorasone diacetate 0.05%§ Halobetasol propionate§
2	Amcinonide* Betamethasone dipropionate* Diflorasone diacetate* Halcinonide† Fluocinonide*† Desoximetasone† Mometasone furoate*
3	Betametasone dipropionate† Betametasone benzoate† Betametasone valerate* Fluticasone propionate*
4	Triamcinolone acetonide* Fluradrenolide* Triamcinolone acetonide* Fluocinolone acetonide†
5	Desonide* Triamcinolone acetonide† Fluradrenolide† Flucinolone acetonide† Triamcinolone acetonide† Betamethasone valerate† Hydrocortisone valerate† Hydrocortisone butyrate†
6	Hydrocortisone 1%, urea 10%† Flumetasone pivalate† Desonide† Alclometasone dipropionate†
7	Hydrocortisone 1%*† Dexamethasone* Methylprednisolone acetate† Prednisolone†
8	Hydrocortisone 0.5%*†

*Ointment.

†Cream.

‡Gel.

§All preparations included.

From Cohen, Bernard A: *Pediatric Dermatology*, ed 2. London, Mosby, 1999, p 10; with permission.

hypothalamic-pituitary axis (HPA-axis) suppression with as little as 45 g/wk.

Corticosteroid treatment should be initiated, when clinically indicated, with the least potentially adrenal suppressive preparations, such as hydrocortisone (0.5%–2.5%). Use of the more potent corticosteroid preparations should be reserved for the more recalcitrant areas or patients. Administration of corticosteroids by intralesional or systemic injections should be avoided. Oral steroids commonly have been used in the pregnant patient to ameliorate severe asthma. With chronic use, such as in asthma, some studies have shown a slight increase in the

incidence of pre-eclampsia, premature deliveries, or low birth weight (see article by Schatz and Dombrowski elsewhere in this issue). Oral steroids are recommended in atopic dermatitis when the symptoms are severe and unrelieved with topical and other therapies, realizing that rebound may occur as the oral steroid is withdrawn.

Infectious exacerbations, generally secondary to *S. aureus* colonization, should be treated with penicillinase-resistant synthetic penicillins or erythromycin in those patients who are allergic to penicillin.

URTICARIA IN PREGNANCY

General

Urticaria refers to circumscribed, elevated pruritic and erythematous wheals formed by superficial dermal edema caused by acute dermal mast cell histamine release and subsequent dermal capillary leakage of plasma into the dermis. Acute urticaria occurs in 20% of the population and is a common response to provocateurs that may be allergic, chemical, infectious, or emotional. For example, two labor and delivery nurses who were in preterm labor were treated with magnesium sulfate intravenously, with rapid and sudden onset of urticaria.²⁴

Angioedema refers to deeper dermal edema extending to the subcutis and submucosa. A case of cyclic angioedema with eosinophilia during pregnancy has been described. Cyclic angioedema with eosinophilia (CAE) is a rare syndrome, with 20 reported cases. Recurrent angioedema and eosinophilia with fever is responsive to prednisone. A patient with CAE noted onset of hand edema before menses, then progression of edema to feet and face, resolving post menses. She was symptomatic twice during pregnancy and was treated with a 3-week taper of 20 mg/d prednisone, which caused diuresis, defervescence, and decreased eosinophil count. The infant was delivered 5 weeks premature.¹⁶

Acute urticaria is defined as less than 6 weeks' duration of symptoms. Chronic urticaria, lasting longer than 6 weeks, is much less common, occurring in less than 2% of the population. Because the cause of urticaria remains undiscovered in more than 80% of cases, the adjective "idiopathic" often describes urticaria/angioedema. A similar syndrome may be secondary to allergic sensitivity to endogenous hormones, especially progesterone, and is termed *autoimmune progesterone dermatitis of pregnancy*.⁵ It is characterized by a papulopustular eruption with transient arthritis, peripheral and tissue eosinophilia, miscarriage, and delayed intradermal sensitivity to aqueous progesterone. Endogenous progesterone also has been implicated in anaphylaxis during pregnancy.¹⁸

Urticarial vasculitis is a subset of urticaria in which lesions persist for days instead of the usual less-than-24-hour individual lesion duration of urticaria. Diagnosis is established by punch biopsy of a persistent lesion which reveals neutrophilic and eosinophilic infiltration of the dermal vessels. Urticarial vasculitis localized to the striae distensae during pregnancy has been described.¹⁴

Diagnosis

The diagnosis of urticaria and angioedema is based on the clinical findings of wheals and dermal and mucosal edema. The search for causative factors begins with a directed history of possible triggers. Foods, drugs, and infections are examples of immunologic (allergic) triggers, whereas physical stimuli, such as sunlight, cold, vibration, pressure, dermatographism, or exercise, are examples of nonimmunologic triggers. Non-IgE-mediated adverse reactions to aspirin and food additives, such as dyes and sulfites, also can occur.

Treatment

Avoidance of identified triggers (i.e., food, pressure, medication) helps prevent future episodes. First-generation antihistamines (discussed earlier in this article) relieve itching and edema. If sedation is a problem, second-generation antihistamines (loratadine, cetirizine) are probably safe to use after the first trimester. Systemic steroids occasionally are needed. Acute, severe urticaria/angioedema requires aggressive therapy with epinephrine, intravenous diphenhydramine, and intravenous corticosteroids, similar to treatment of anaphylaxis.

Pruritic Urticarial Papules and Plaques of Pregnancy

Pruritic urticarial papules and plaques of pregnancy is the term used in the United States to denote an itchy, papulovesicular eruption of unknown origin (Fig. 3). Onset of PUPPP is typically during the third trimester of pregnancy. PUPPP is not associated with fetal morbidity or mortality but is associated with increased maternal weight gain,²⁰ first pregnancy, and twin and triplet pregnancies.^{9, 20, 27} The eruption begins on the abdomen in striae and spreads to the arms, inner thighs, and inframammary skin. Abdominal striae often are marked, and pruritus is the most common symptom, although lesions can be painful.²⁷ Small papules surrounded by blanched halos on the legs are common, regardless of lesion morphology elsewhere. In the British literature, PUPPP is called *polymorphic eruption of pregnancy* (PEP).²⁵⁻²⁷

Histopathology of PUPPP is similar to urticarial vasculitis and shows a perivascular lymphohistiocytic infiltrate with dermal edema and eosinophils. There have been no specific direct immunofluorescence findings.^{2, 26}

Treatment may be as simple as a topical aqueous cream with 1% to 2% menthol or may require medium- to high-potency topical steroids and oral antihistamines for relief of itching. Therapeutic cesarean section near term has been performed for intractable pruritus under most dire circumstances.

The differential diagnosis of PUPPP includes disorders nonspecific

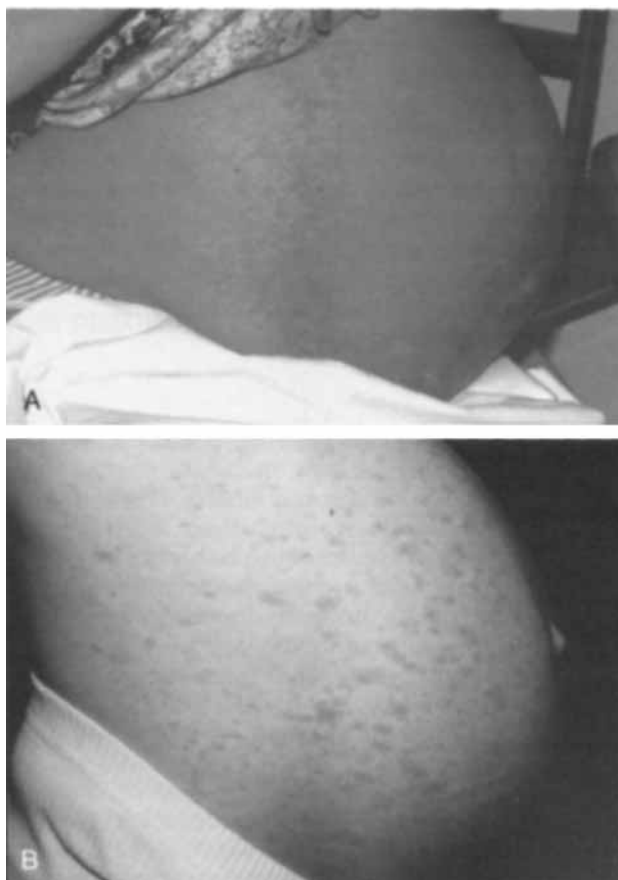


Figure 3. Pruritic urticarial papules and plaques of pregnancy. *A*, Severe eruption in a triplet pregnancy. Multiple erythematous fixed urticarial papules and plaques coalescing into a confluent abdominal plaque centered umbilically. *B*, Mild eruption with discrete oval fixed erythematous papules and plaques.

to pregnancy, including contact dermatitis, drug eruptions, viral exanthems, and pityriasis rosea, as well as dermatoses only occurring in pregnancy, such as impetigo herpetiformis and pemphigoid gestationis.

Impetigo herpetiformis (IH) (pustular psoriasis of pregnancy) is clinically (Fig. 4) and microscopically similar to pustular psoriasis, yet there is no prior history of psoriasis. Unlike PUPPP, IH is clinically and histologically uniform from case to case (hundreds of uniform, sterile pustules at periphery of erythematous plaques, microscopically, an intraepidermal pustule with neutrophilic infiltrate), and, unlike benign PUPPP, IH-associated hypocalcemia or hypoparathyroidism may lead to tetany, delirium, convulsions, stillbirth, and perinatal deaths.



Figure 4. Impetigo herpetiformis. Diffuse erythroderma with innumerable overlying sterile pustules that have desquamated, leaving serpiginous plaques of hyperpigmentation and micaceous scale.

Treatment consists of monitoring fetal status, maternal serum calcium, and maternal fluid balance. Prednisone 1 mg/kg/d or ultraviolet radiation B (UVB) phototherapy may help. In severe cases, therapeutic abortion, induction of labor, or cesarean section may be required. IH usually remits post partum but can recur in subsequent pregnancies. The infant has a 5% to 10% chance of developing lesions.²⁹

Pemphigoid gestationis (PG) (herpes gestationis) is a rare (1:60,000) autoimmune condition caused by complement-fixing autoantibody attacking the epidermal basement membrane zone. Placental antigen cross-reacts with skin and triggers the immune response. Despite the synonym "herpes," PG is **not** related to herpetic infection.

PG usually occurs during the third trimester. Pruritic urticarial plaques, characteristically periumbilical, rapidly evolve to vesicles and bullae on the trunk and then spread to extremities, palms, and soles (Fig. 5). Fever, nausea, and malaise can occur.

Histology shows a subepidermal split of the skin with superficial and deep lymphohistiocytic perivascular infiltrate with eosinophils, suggestive but not diagnostic of PG. Direct immunofluorescence of skin biopsy, when positive, is specific in the clinical setting of pregnancy with urticarial plaques and constitutional symptoms: complement 3 (C3) deposited in the basement membrane zone, with or without IgG.

Treatment consists of antihistamines, potent topical steroids, or oral steroids. Occasionally, additional immunosuppression with azathioprine, intravenous immune globulin, or cyclosporine is required.²⁶



Figure 5. Pemphigoid gestationis. A, Erythematous papules and coalescing plaques on the abdomen and upper thighs with raised red borders. Note characteristic periumbilical distribution. B, Advanced case showing tense bullae on widely margined erythematous bases.

HEREDITARY ANGIOEDEMA IN PREGNANCY

General

Hereditary angioedema (HAE) is a rare but potentially fatal disorder, with an incidence of 1:50,000 and an onset usually by adolescence. Also referred to as *angioneurotic edema*, it is an autosomal dominant systemic disorder caused by mutations in the complement 1-inhibitor (C1-INH) gene on chromosome 11 leading to plasma deficiency of C1-INH. C1-INH is a protein synthesized by hepatic fibroblasts, monocytes, megakaryocytes, and placenta. Up to 20% of affected kindreds may be new mutations.

There are two phenotypes of HAE. Type I (85% of patients) has both low antigenic and functional levels of normal C1-INH and has 30 distinct mutations. Type II (15%) patients show normal or elevated levels of dysfunctional mutant protein and lower levels of functional protein with 10 distinctive mutations.

C1-INH deficiency yields unregulated proteolytic activation of the complement and kallikrein systems that can cause potentially life-threat-

ening consequences. Complement 1 (C1) activation is uncontrolled, yielding complement 2 (C2) and complement 4 (C4) consumption. The resulting formation of kinin-like fragments and other pharmacologically active mediators trigger the clinical signs and symptoms of HAE.

Diagnosis

Unlike common urticaria/angioedema, HAE lesions are nonpruritic and pale. Instead of resolving in 24 hours, they persist for 2 to 5 days. Attacks may occur every few days to yearly. Most commonly, attacks are spontaneous and unprovoked, but well-described provocative stimuli include dental work, intubation, menses, pregnancy, and delivery.

While pregnant, 23 of 25 women with HAE had a marked decrease or absence of attacks from months 4 to 9. Ten women, with a total of 25 pregnancies, did not experience vaginal edema during delivery⁸; however, in 2 kindreds of 271 members, with 36 reported term pregnancies, some patients had worsening of symptoms with pregnancy or oral contraceptives. These patients were treated with fresh frozen plasma C1-INH concentrate.³⁰ Some deaths have occurred during childbirth in subjects with HAE,⁷ and recurrent worsening has occurred during multiple pregnancies.²⁸ Thus, symptoms may unpredictably wax or wane during pregnancy. Although the majority of attacks have been spontaneous, HAE has been associated with localized perineal swelling postdelivery, leading to irreversible shock and death.²² A primary attack of HAE has occurred on the third postpartum day.⁶

The edema of HAE is commonly localized to three major sites, with potential for morbidity at each site. Swelling of subcutaneous tissues and submucosa of the extremities may prevent walking and eating. Bowel wall edema produces abdominal pain, vomiting, and guarding. Differentiation of HAE acute abdomen from surgical or obstetrical emergencies is essential to prevent fruitless surgery and can be accomplished with ultrasound examination. Bowel wall edema can be seen and the baby's status quickly assessed. Maternal upper airway (i.e., lips, face, larynx) edema produces hoarseness, dysphagia, and sometimes life-threatening upper airway obstruction. Laryngeal edema responding poorly to antianaphylaxis therapy is typical of HAE.

C4 levels are decreased between attacks and near absent during active episodes for both types I and II. The diagnosis is confirmed by determining low levels of functional C1-INH levels.

HAE rarely can produce cutaneous necrosis. A temporary hypercoagulable state caused by activated protein C resistance in a pregnant woman with HAE caused a coumarin-like necrosis.²¹ She was originally treated at 22 weeks' gestation for superficial thrombophlebitis with antibiotics. A month later, extensive cutaneous necrosis was treated with heparin, C1-INH concentrate, systemic steroids, and surgical débridement. Laboratory evaluation showed normal protein C, antithrombin III, total protein S, and free protein S, but decreased functional protein S

activity and activated protein C resistance.²¹ Therefore, protein S deficiency secondary to HAE during pregnancy should be considered in the setting of severe cutaneous necrosis.

There may be variations in the HAE spectrum, such as a report of two sisters with severe angioedema and some urticaria only with oral contraception ingestion and during pregnancy.²⁸ Both had laryngeal edema, abdominal colic, nausea, exacerbation by trauma, and resistance to antihistamine and corticosteroid therapy, but C1-INH and complement levels were normal.²⁸

Prevention and Treatment

Prevention of HAE Attacks

HAE attack prevention demands avoidance of the typical triggers, including trauma, surgery, dental procedures, and stress. Angiotensin-converting enzyme inhibitors are contraindicated in HAE, as they may potentiate the increased kinin-like activity noted in HAE. Preventive pharmacotherapy must be individualized during pregnancy as is done in the nonpregnant woman. Stimulation of C1-INH synthesis by the one normal gene with attenuated androgen prophylaxis (based on dose titration of danazol or stanozolol to the minimum level necessary to prevent HAE attacks) represents the treatment of choice in the nonpregnant woman experiencing life-threatening HAE attacks. During pregnancy, androgen prophylaxis generally is not required or warranted, as the potential for drug-related fetal damage, including female masculinization, pseudohermaphroditism, and spontaneous abortion, are common. To prevent these adverse fetal effects from occurring during early pregnancy before confirmation of pregnancy, effective contraception during androgen therapy is mandatory by women of childbearing potential. Oral contraceptives generally are tolerated by women with HAE, although estrogens may adversely affect some. The hormonal contraceptives of choice in women with HAE are progestational agents, as they may help raise C1-INH levels. Planning of conception should be attempted only after successful discontinuation of androgen prophylaxis.

Prevention of HAE attacks following elective surgeries is accomplished by pretreatment with the following regimen: (1) C1-INH concentrate, if available (discussed later in article), (2) attenuated androgens (danazol 600 mg daily or stanozolol 6 mg daily for 6 days before and 3 days after surgery), or (3) 2 units of fresh frozen plasma 24 hours before the procedure. Vaginal deliveries appear safe for HAE patients; epidural anesthesia has been effective and is not likely to induce HAE. Cesarean section, on the other hand, requires preoperative transfusion of two units of fresh frozen plasma or C1-INH concentrate, if available, to prevent attacks. Regional anesthesia is preferred to general anesthesia in order to avoid endotracheal intubation, which could trigger laryngeal edema.

Treatment of Acute Attacks

Life-threatening laryngeal edema during pregnancy caused by HAE requires rapid and aggressive therapy, including emergent airway management with intubation or tracheostomy. Large volumes of intravenous fluids may be needed to reverse hypovolemia induced by abdominal crises. Severe pain is treated with narcotics.

The best acute pharmacotherapy for HAE and the future drug of choice in pregnant women with HAE rests with purified C1-INH (or recombinant human C1-INH, in the future), but it presently is an investigational drug. C1-INH is available in the United States through compassionate use (Immuno Clinical Research Corp, New York, NY) or research centers. Administration of 1000 to 1500 U of C1-INH concentrate (with 1 U corresponding to the amount of C1-INH found in 1 mL of normal human plasma) has been effective in reversing severe laryngeal edema and abdominal attacks from 30 to 60 minutes and 60 to 120 minutes, respectively, in 82 of 83 infusions of HAE patients.¹ Before 1986, non-A, non-B hepatitis occurred in some patients receiving C1-INH concentrates in Europe. Improved preparations of C1-INH concentrate have undergone vapor heating and viral polymerase chain reaction (PCR) identification to eliminate HIV and hepatitis B and C contamination. Fresh frozen plasma infusion should be avoided during acute episodes, as it may provide proportionally greater amounts of substrate (which could potentiate the attack). Antifibrinolytic agents, such as epsilon aminocaproic acid (Amicar, Immunex Corporation, Seattle, WA) and tranexamic acid, should be avoided during pregnancy because of their potential thrombogenic properties. The usual therapies for angioedema (epinephrine, antihistamines, corticosteroids) typically are ineffective in HAE attacks, although they should be tried in high dose at the start of an episode if C1-INH is not available. Prompt recognition of postpartum episodes of HAE and institution of aggressive therapy with large volumes of fluid and reinstitution of androgenic therapy may be necessary.²⁹

SUMMARY

Not only is the pregnant patient "eating for two," the physician of the pregnant patient with atopic dermatitis, urticaria, or other pregnancy-related dermatosis is "treating for two." Consideration of the mother and fetus' unique responses to various treatment regimens helps achieve the goal of a term pregnancy and healthy baby and mother.

RESOURCES FOR PATIENTS AND PHYSICIANS

American Academy of Dermatology

Peer-reviewed information for patients on urticaria and atopic dermatitis

1-888-462-3376

<http://www.aad.org>

American Academy of Allergy, Asthma, and Immunology
Peer-reviewed information for patients and physicians on allergic diseases, including atopic dermatitis, urticaria, and HAE
<http://www.aaaai.org>

American College of Asthma, Allergy, and Immunology
Peer-reviewed information for patients and physicians on allergies and urticaria
<http://allergy.mcg.edu/advice>

National Eczema Association for Science and Education
1-800-818-7546
<http://www.eczema-assn.org>

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