Herpes Gestationis

Donald P. Lookingbill, MD, and Ronald A. Chez, MD

Milton S. Hershey Medical Center
Pennsylvania State University
Hershey, Pennsylvania

Herpes gestationis (HG) is not a viral disease. Classically, the term "herpes," as defined by Galen, was used to describe any skin disease characterized by the formation of small vesicles, often in clusters. It was in this context that, over a century ago, the blistering disease specifically associated with pregnancy was given the name "herpes gestationis."[1]

A variety of skin reactions may occur with pregnancy[2-4] including pustular,[5] papular,[6] blistering, and urticarial[7,8] eruptions. HG is the only pregnancy-associated skin condition characterized by vesicles *and* bullae. There are other blistering diseases, and those listed in Table 1 (in approximate descending order of frequency) should be considered for any patient, whether pregnant or not, who presents with a blistering skin eruption.

TABLE 1. Acquired Blistering Diseases

Intraepidermal	Subepidermal
Contact dermatitis	Erythema multiforme
Viral	Dermatitis herpetiformis
Herpes simplex	Bullous pemphigoid
Herpes zoster varicellosus	Herpes gestationis
Bullous impetigo	Lupus erythematosus*
Pemphigus	Lichen planus*

*Blisters may occur in these disorders but are uncommon.

The differential diagnosis for blisters is contingent upon whether the blister location is intraepidermal or subepidermal—a determination that in some cases may only be established by a skin biopsy. A skin biopsy is usually not necessary for the more common intraepidermal processes, which tend to have characteristic clinical pictures. For example, acute vesicular contact dermatitis is characterized by its sudden onset, the distribution of lesions on exposed areas, and short duration. Skin eruptions caused by herpes virus infection usually also have characteristic presentations. If desired, this diagnosis can be confirmed by performing a Tzanck preparation in which multinucleated giant cells are found in a Wright's-stained smear of the contents of one of the vesicles. Bullous impetigo is both uncommon and often missed. Although the blisters usually contain very clear fluid, gram-positive cocci are seen on Gram's stain, and a culture will grow *Staphylococcus aureus.* Pemphigus is the only intraepidermal blistering process that would require a biopsy for confirmation of the diagnosis. This disease is extremely rare, though in one recent series of eight women with bullous dermatoses that developed during pregnancy, one was found to have pemphigus.[9]

Subepidermal diseases are much less common than the first three intraepidermal

Clinical Obstetrics and Gynecology, Vol. 26, No. 3, September 1983

blistering diseases discussed above. HG is the only one that is peculiar to pregnancy. Erythema multiforme,[10] as the name suggests, usually presents with multiform lesions, including erythematous plaques, target lesions, blisters, and, in the severe form, Stevens-Johnson syndrome, extensive mucous membrane involvement. Often a precipitating cause is not uncovered; but when one is found, it is usually either a drug or an infection—often herpes simplex.[11] Dermatitis herpetiformis usually presents as a widespread, posteriorly located, symmetric eruption of vesicles. Because the primary skin lesions in this disease are extremely pruritic, excoriations may be the only lesions detected.[12] It is a chronic disease, often associated with a gluten enteropathy.[13] Bullous pemphigoid[14] affects patients who are 60-80 years old most commonly—a group unlikely to be seeking obstetric care. But, as will be further discussed, bullous pemphigoid and HG share many common immunopathologic features.[15,16]

For one to establish a correct diagnosis in a subepidermal blistering disease, a skin biopsy is mandatory. A routine histologic examination will be helpful in discriminating between the diseases listed, but immunofluorescence staining provides further valuable diagnostic information. The immunofluorescent findings in these subepidermal blistering diseases are listed in Table 2. The implication of these findings for HG will be discussed further.

Clinical Features

Since HG is rare, exact incidence figures are not known. An early report estimated that its occurrence was as frequent as 1 in 3000-4000 deliveries[17] is widely repeated[2-4] but may no longer be true. In two more recent surveys there were 1) only two cases found in 112,769 deliveries at two university hospitals[18] and 2) only two cases diagnosed in 84,000 consecutive deliveries.[19]

The onset of the disease is usually in the second trimester of pregnancy but may occur earlier (especially in women affected by the disease in a previous pregnancy).[20] It can also occur later—occasionally even beginning in the immediate postpartum period. However, it is rare for the disease to begin later than 3 days postpartum. In only 3 of 93 episodes of HG was the onset on the 4th postpartum day or beyond.[18]

Pruritus is a constant feature. It may precede the eruption, which is usually polymorphous in nature; that is, papules, erythematous and urticarial plaques, vesicles, and bullae may all occur. The papules often precede the bullae by as long as a month, and in this stage, the diagnosis may be confused

TABLE 2. Immunofluorescent Findings in Subepidermal Blistering Diseases

Disease	Usual Findings
Erythema multiforme	Negative
Dermatitis herpetiformis	IgA
Bullous pemphigoid	Complement (C_3) ± IgG
Herpes gestationis	Complement (C_3) ± IgG

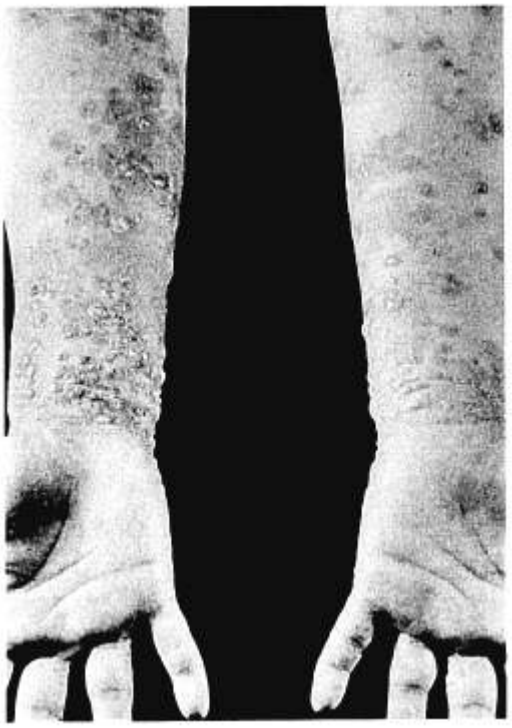

FIG. 1. *Bullae in HG, some of which are on clinically noninflammed skin. (Courtesy O. Fred Miller, MD.)*

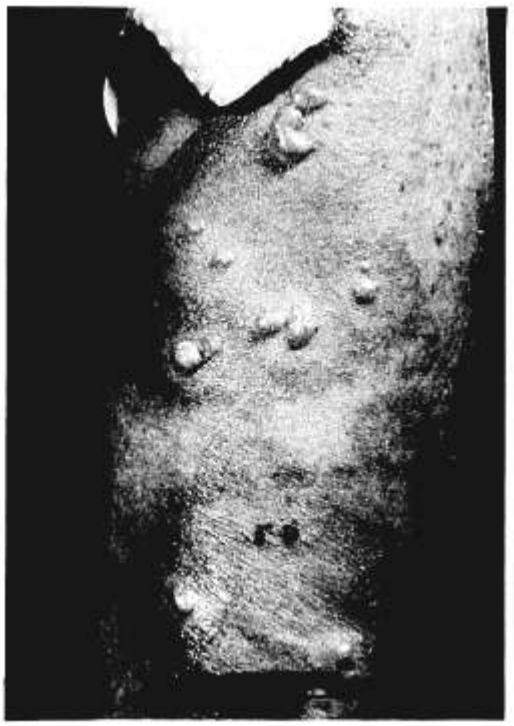

FIG. 2. *Bullae arising from erythematous plaques. (Courtesy O. Fred Miller, MD.)*

with other papular disorders of pregnancy.[19] The bullae occur either on clinically noninflammed skin (Fig. 1); or more commonly, they are superimposed on erythematous plaques (Fig. 2). The erythematous plaques often become quite large and may assume geographic shapes (Fig. 3). When fresh bullae are present, they are usually tense; this is a clinical characteristic of subepidermal blisters. With age, the bullae become more flaccid and, after rupturing, leave denuded areas covered with crusts. Barring significant secondary infection, the lesions usually heal without scar, though marked postinflammatory hyperpigmentation may occur. Usually, this pigmentation fades slowly with time.

Skin lesions often start in the periumbilical area; and the distribution of the lesions frequently remains proximal, the abdomen (Fig. 4) and proximal extremities usually being most affected. However, any body area can be involved, including the face, palms, and soles. Mucous membrane involvement is rare.

The pruritus associated with HG is usually intense, a quantitative feature distinguishing it from bullous pemphigoid. In the latter, pruritus, when present, is usually only mild to moderate in degree. In HG, other symptoms that may accompany the pruritus include fever, malaise, nausea, and headache.

Histology

Skin biopsy is important in confirming the diagnosis of HG. The preferred biopsy site is the edge of a fresh vesicle or bulla and should include the margin of the blister as well as surrounding nonblistered skin. Routine histologic processing will reveal a subepidermal bulla associated with areas of basal cell necrosis and underlying edema in the

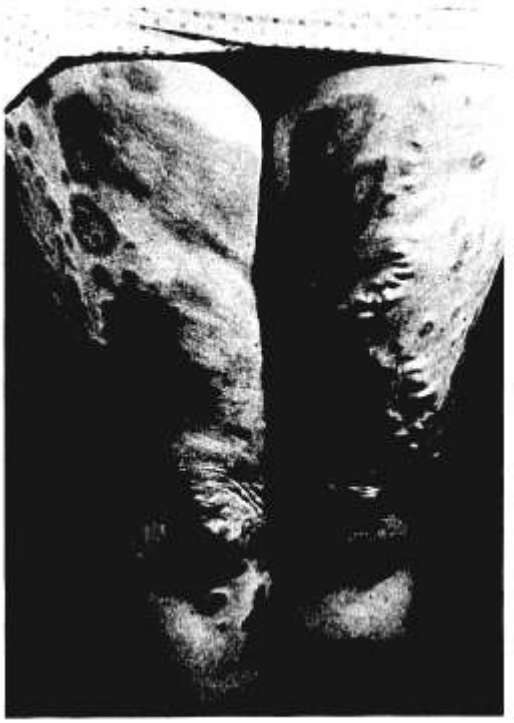

FIG. 3. *Erythematous plaques in geographic patterns. (Courtesy O. Fred Miller, MD.)*

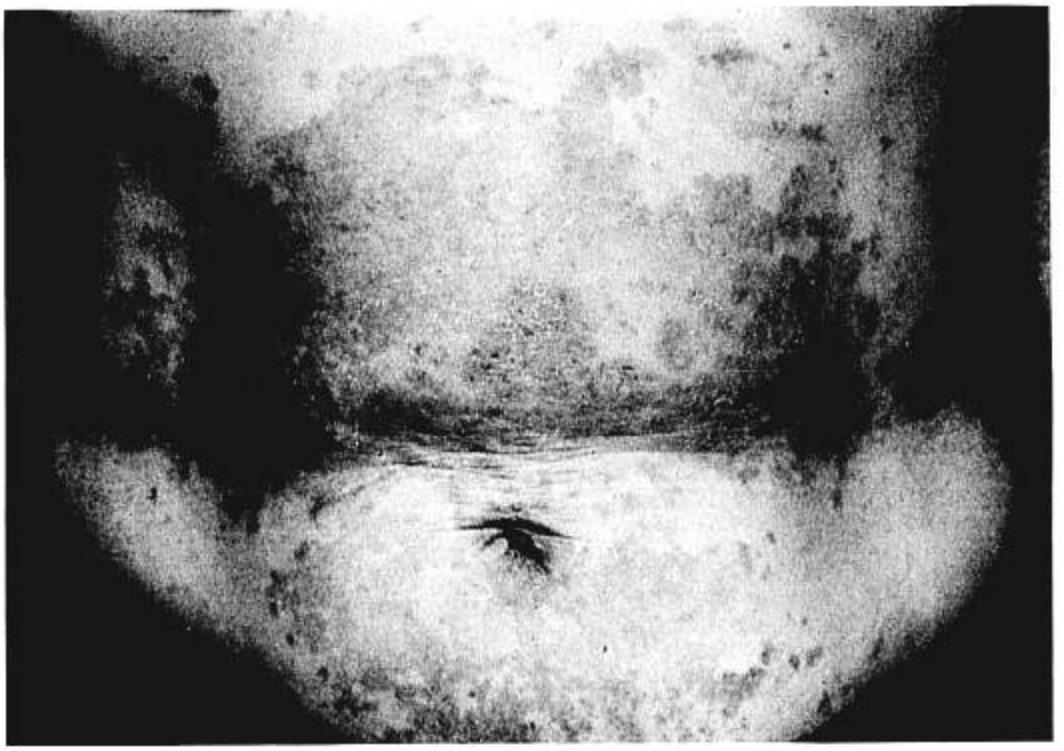

FIG. 4. *Erythematous plaques in a typical periumbilical location. (Courtesy O. Fred Miller, MD.)*

papillary dermis. In addition, in both bullous and nonbullous lesions, there is a mixed inflammatory infiltrate composed of lymphocytes, histiocytes, and eosinophils dispersed about both the superficial and deep dermal vascular plexuses.[21] A peripheral blood eosinophilia is often also present.

Ultrastructural studies show necrosis of basal cells with blister formation occurring above the basal lamina in the region of the lamina lucida.[22,23] Immunoelectron microscopic findings reveal IgG and complement deposition at the basal cell plasma membrane.[23,24]

Direct immunofluorescence light microscopy techniques, which are more widely available than ultrastructural studies, provide the usual laboratory confirmation of the disease. Best results are obtained if biopsies are taken from either peribullous skin or erythematous/urticarial plaques. The most diagnostic (and most common) finding is the deposition of the third component of complement (C3) which is found along the basement membrane zone[19,23,25-27] (Fig. 5). Deposition of IgG occurs as well, although less frequently, and is found in only 20-30% of the cases.[19,23]

Other components of both the classical and alternate complement pathways are also sometimes found in involved skin, and C3 deposition has been described in uninvolved skin as well. Complement deposits may persist for up to a year after the skin lesions have resolved.[28]

Pathogenesis: Mechanism of Lesion Production

HG is mediated by circulating humoral factor initially designated as the "HG factor" when first reported by Provost and Tomasi in 1973.[25] Subsequently, this factor was identified as an IgG immunoglobulin that had the propensity to localize at the basement membrane zone of the skin,[26,27] in

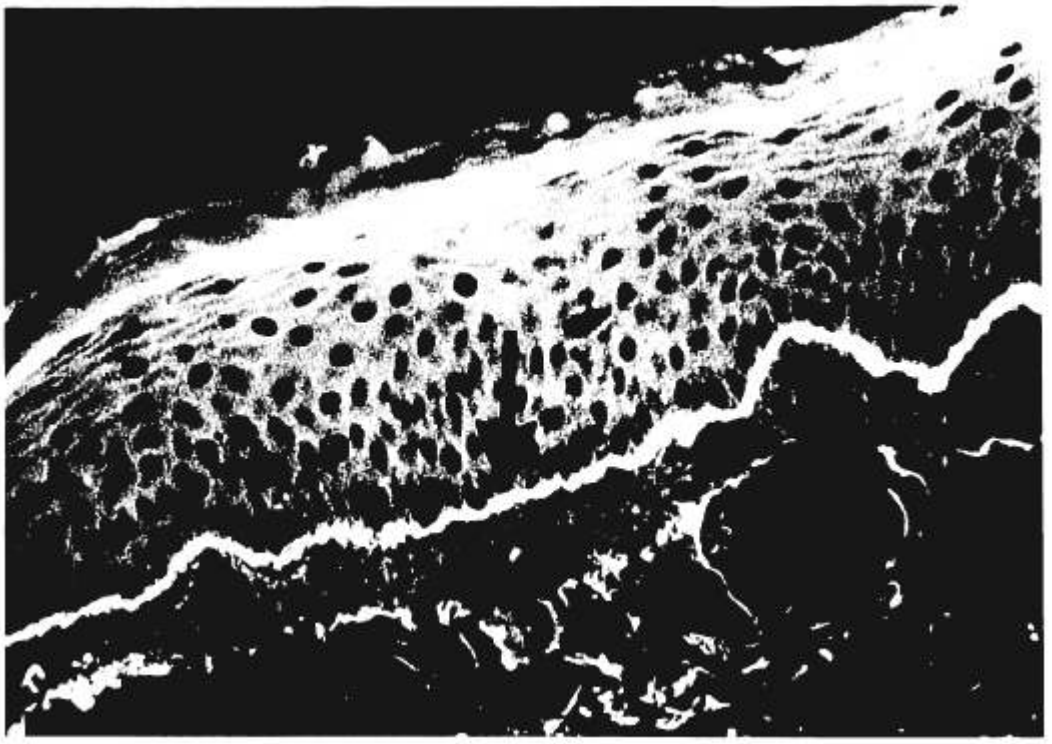

FIG. 5. *Complement deposition at the basement membrane zone.*

a manner and location similar, if not identical, to the IgG found in bullous pemphigoid.[23,29] The IgG in bullous pemphigoid circulates in sufficiently high titers, and thus it can be identified by a readily available "indirect" immunofluorescence technique in which the serum of a patient with bullous pemphigoid is incubated with normal skin or a suitable epithelial alternative, washed, and counterstained with fluorescein-labeled-anti-IgG antibody. In HG, probably because of its low titer, the IgG responsible for the disease is usually not detected by this method.[23] Rather, an indirect complement immunofluorescence technique is usually required. In this procedure, which is less readily available than the above-described IgG method, the serum of a patient with HG is incubated with an epithelial substrate, rinsed, covered with complement (C3), rinsed again, and finally stained with fluorescein-conjugated-anti-C3 antibody. This technique is more sensitive in detecting basement-membrane-localizing IgG and has been the one most frequently employed in the diagnostic evaluation of serum from patients with HG.

Once the IgG is localized to the basement membrane zone of the skin, the stage is set for the ensuing inflammatory reaction, which ultimately results in blister formation. The inflammatory reaction is mediated by a complement activation—either via the alternate pathway,[25,30] the classical pathway, or both.[26,27]

Ultrastructural studies further define the exact localization of the IgG deposition in HG. In a pattern nearly identical to that seen in bullous pemphigoid, the IgG is deposited on the basal cell plasma membrane and the upper part of the lamina lucida region of the basement membrane[23,29] (Fig. 6). A recent in vitro study has substantiated the close similarity of IgG localization in bullous pemphigoid and HG, though very subtle differences may exist.[31] As expected, localization of C3 is also found at the basal cell plasma membrane and throughout the lamina

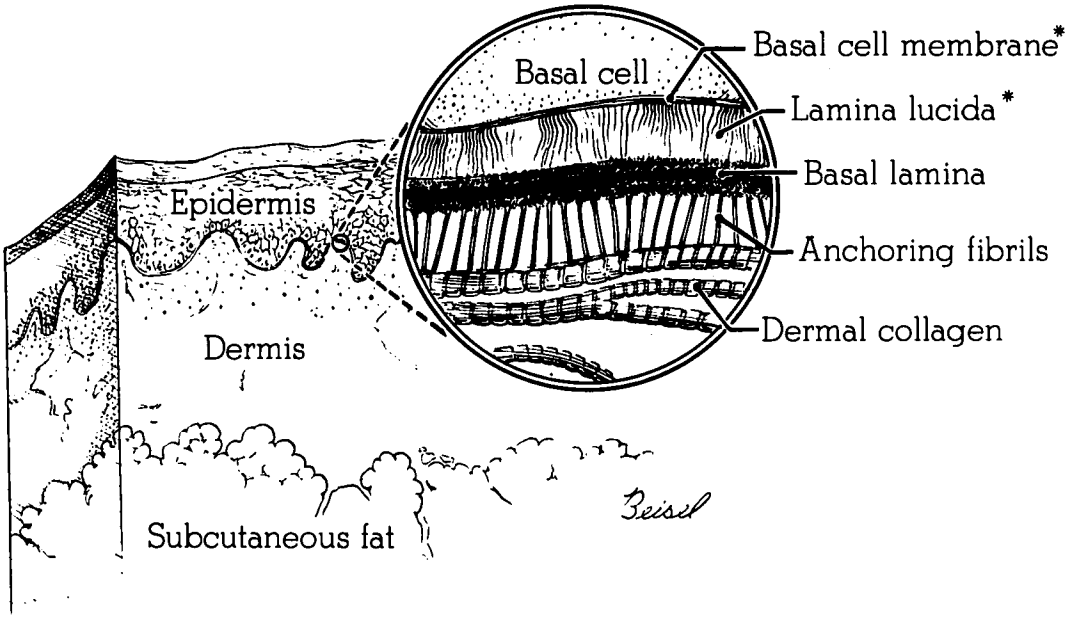

FIG. 6. *Anatomic details of the basal cell plasma membrane area. *Sites of Ig[6] and complement deposition in H6.*

lucida.[23,24] Complement activation is then thought to initiate the inflammatory response, which ultimately results in necrosis of the basal cells and ultimately blister formation. As previously mentioned, histologically the inflammatory infiltrate in the skin is composed mainly of lymphocytes and histiocytes, although eosinophils are found in various numbers. The latter may play an important role mediating tissue destruction in both bullous pemphigoid and HG via release of their lysosomal enzymes, which results in degradation of the basement membrane structures.[15]

Etiology

The precise cause of HG remains unknown. Both hormonal and autoimmune processes have been implicated.

Hormonal Factors

Hormonal factors have long been suspected as being important in the pathogenesis of this disease. The reports of exacerbations of HG with menstruation[20,32] and following administration of oral contraceptives[32-35] lend support to the suspicion of the role of hormones in this disease. Importantly, there have been no reports of the precipitation of HG by hormonal therapy in patients without a prior history of HG.

HG has also been reported in association with hydatidiform moles[26,36,37] and choriocarcinoma.[38,39,40] In the most recent report concerning choriocarcinoma, the skin lesions cleared concurrently with successful treatment of the choriocarcinoma with methotrexate.[40] Although, hormonal factors might be implicated in the responsibility for these associations, it has also been suggested that an autoimmune reaction may be precipitated by the presence of abnormal placental or malignant tissue.[37]

Autoimmune Factors

Recently, HG has been reported in association with other autoimmune disorders. Holmes and Black were the first to report HG in 3 patients with Graves' disease.[41] One of these patients also had alopecia totalis and ulcerative colitis. These 3 patients are

included in a larger series of 24 patients with HG, in which 5 were found to have autoimmune thyrotoxicosis, 2 had alopecia areata, 1 had vitiligo, and 1 had ulcerative colitis.[19]

Recently attention has been focused on a possible genetic predisposition of patients with HG. An increased incidence of HLA-B8 (79%) and HLA-DR3 (80%) were reported in one series.[19] Shornick et al.[42] reported an incidence of HLA-DR3 of 61% in 23 patients with a history of HG, as compared with an incidence of 22% in control subjects ($P < 0.00001$). The same P value for the concurrent presence of these two HLA antigens was recently found also by Holmes and his group.[32] One theory suggests that the immunologic abnormalities (for example, involvement of the complement system control mechanisms) in HG may be under the control of genes located in the HLA-D/DR region.[42]

Investigative efforts are also being focused on the possible role of anti-HLA antibodies in HG. Finding that only 10% of primipara develop such antibodies (usually in low titer), Reunala et al. suggested that the presence of high titers of anti-HLA antibodies in their patient with HG may have played a role in the pathogenesis of the disease.[43] Support for this theory comes from more recent work, in which increased antibodies to both maternal and paternal HLA antigens were found in the serum of patients with HG.[44,45] Also, in one series, patients with high titers of antibasement membrane antibodies or peripheral blood eosinophilia, or both, tended to have more severe disease.[46]

In summary, although the precise cause of HG remains unclear and hormonal factors may play an important role, increasing evidence points to the importance of an autoimmune mechanism, possibly in genetically predisposed women, as an agent in this disease. Whatever the stimulus, an IgG antibody is subsequently formed that is deposited in the lamina lucida area of the basement membrane of the skin, where it activates complement, resulting in an inflammatory process and clinical skin lesions.

Clinical Course

HG is a disease of varying severity. Even in the same patient, the disease often waxes and wanes in activity over its time course. Patients whose disease begins in the second trimester may experience a relative remission in the last 6-8 weeks of pregnancy.[19] Exacerbations, sometimes severe, often develop immediately postpartum, occurring in as many as 50-75% of the cases.[19,46] The disease then usually gradually regresses over a period of weeks to several months. In one review, in only 15 of 70 cases did disease activity persist beyond 2 postpartum months,[18] and in two other series the mean time for disease remission was 7.5 weeks[17] and 13 weeks.[20] In a more recent series, of 39 affected pregnancies, the average postpartum duration of disease was reported to be 60 weeks![19] Rarely, has the disease been reported to persist for years.[19,20] Women once affected have a high rate of recurrence of the disease in subsequent pregnancies, in which it often has an earlier onset.[18,20] Recurrences may also be precipitated by menstruation[17,20,46] and oral contraceptives.[29,30,32-35,42]

Fetal Involvement

Although there are no reports of the disease being associated with increased maternal mortality, the fetal risk is less well established. In 1969, in a report of several cases with a literature review, Kolodny found no evidence for increased fetal morbidity or mortality.[18] More recently, Lawley et al., in a series of 39 cases, found a 7.7% incidence of stillbirth and a 23% incidence of premature deliveries—incidence rates higher than expected.[46] These authors suggested a possible increased risk of fetal complications in the presence of high levels of maternal anti-basement membrane antibodies. Holmes et al. found no stillbirths or neonatal deaths in their series of 39 deliveries, although 7 of the babies weighed less than 2.5 kilograms. Postnatal development was described as normal.[19]

The incidence of clinical skin lesions developing in the newborn is low. The highest incidence of such involvement was reported by Lawley et al.[46] Four of the 35 live births in this series had cutaneous lesions. HG in the newborn has only recently been immunologically documented to be due to the identical process found in the mother.[48] Passive transfer of the anti-basement membrane antibodies to the fetus has been well documented. However, Foidart et al. were unable to demonstrate binding of such maternal antibodies to placental or fetal membranes.[47] These antibodies have been found in cord blood[27] as well as the blood of the newborns, those both with[46] and without[43] skin lesions. Complement (C3) deposition has also been found in the basement membrane zone of affected[46,48,49] and unaffected[27,43] infants born to mothers with HG.

Vesicles and blisters have been described in affected infants, but the time course is short and does not require specific treatment. Clearing of these conditions normally occurs within several weeks.[48,49]

Treatment

For women with mild cases of HG, symptomatic treatment with antihistamines and topical steroids may suffice. But for the majority of the affected women, the disease is severe enough to require systemic steroid therapy.[4,46,47] Prednisone, in a divided daily dose of 20-40 mg, usually is adequate. Symptomatic improvement is usually prompt, often occurring within 48 hours. Uncommonly, higher doses of prednisone are required. Doses of up to 180 mg daily have been administered.[46] Postpartum azathioprine therapy has also been reported as an effective treatment, in two patients with particularly severe disease.[46] In another report, plasma exchange was employed in one patient to provide temporary remission both during her pregnancy and her postpartum exacerbations.[50]

In prednisone-treated patients whose disease comes under control during pregnancy, attempts at tapering the steroid dosage can be made.[51] After delivery and treatment of any postpartum exacerbation, the prednisone dosage is gradually reduced as the disease spontaneously subsides.

References

1. Milton JL. The pathology and treatment of diseases of the skin. London: Robert Hardwicke, 1872:205.
2. Sasseville D, Wilkinson RD, Schnader JY. Dermatoses of pregnancy. Int J Dermatol 1981;20:223.
3. Winton, GB, Lewis CW. Dermatoses of pregnancy. J Am Acad Dermatol 1982;6:977.
4. Wade TW, Wade SL, Jones HE. Skin changes and diseases associated with pregnancy. Obstet Gynecol 1978;52:233.
5. Oumeish OY, Farraj SE, Bataineh AS. Some aspects of impetigo herpetiformis. Arch Dermatol 1982;118:103.
6. Spangler AS, Reddy W, Bardawil WA, Roby CC, Emerson K. Papular dermatitis of pregnancy. JAMA 1962;181:577.
7. Lawley TJ, Hertz KC, Wade TR, Ackerman AB, Katz SI. Pruritic urticarial papules and plaques of pregnancy. JAMA 1979;241:1696.
8. Callen JP, Hanno R. Pruritic urticarial papules and plaques of pregnancy (PUPPP): a clinicopathologic study. J Am Acad Dermatol 1981;5:401.
9. Honeyman JF, Eguiguren G, Pinto A, Honeyman AR, Parra MA, Navarrete W. Bullous dermatoses of pregnancy. Arch Dermatol 1981;117:264.
10. Tonnesen MG, Soter NA. Erythema multiforme. J Am Acad Dermatol 1979;1:357.
11. Kazmierowski JA, Peizner DS, Wuepper KD. Herpes simplex antigen in immune complexes of patients with erythema multiforme: presence following recurrent herpes simplex infection. JAMA 1982;247:2547.
12. Katz SI, Strober W. The pathogenesis of dermatitis herpetiformis. J Invest Dermatol 1978;70:63.
13. Katz SI, Hall RP, Lawley TJ, Strober W. Dermatitis herpetiformis: the skin and the gut. Ann Intern Med 1980;93:857.
14. Person JR, Rogers RS. Bullous and cicatricial pemphigoid: clinical, histopathologic,

and immunopathologic correlations. Mayo Clin Proc 1977;52:54.

15. Sams WM, Gammon WR. Mechanism of lesion production in pemphigus and pemphigoid. J Am Acad Dermatol 1982;6:431.
16. Holmes R, Black MM, Williamson DM, Scutt RW. Herpes gestationis and bullous pemphigoid: a disease spectrum. Br J Dermatol 1980;103:535.
17. Russell B, Thorne NA. Herpes gestationis. Br J Dermatol 1957;69:339.
18. Kolodny RC. Herpes gestationis: a new assessment of incidence, diagnosis, and fetal prognosis. Am J Obstet Gynecol 1969;104:39.
19. Holmes RC, Black MM, Dann J, James DCO, Bhogal B. A comparative study of toxic erythema of pregnancy and herpes gestationis. Br J Dermatol 1982;106:499.
20. Carruthers JA. Herpes gestationis: clinical features of immunologically proved cases. Am J Obstet Gynecol 1978;131:865.
21. Hertz KC, Katz SI, Maize J, Ackerman AB. Herpes gestationis. Arch Dermatol 1976;112: 1543.
22. Schaumburg-Level G, Saffold OE, Orfanos CE, Lever WF. Herpes gestationis. Arch Dermatol 1973;107:888.
23. Harrington CI, Bleehen SS. Herpes gestationis: immunopathological and ultrastructural studies. Br J Dermatol 1979;100:389.
24. Yaoita H, Gullino M, Katz SI. Herpes gestationis: ultrastructure and ultrastructural localization of in vivo-bound complement. J Invest Dermatol 1976;66:383.
25. Provost TT, Tomasi TR Jr. Complement activation via the alternate pathway in skin diseases. I. herpes gestationis, systemic lupus erythematosus, and bullous pemphigoid. J Clin Invest 1973;52:1779.
26. Bushkell LL, Jordon RE, Goltz RW. Herpes gestationis: new immunologic findings. Arch Dermatol 1974;110:65.
27. Katz SI, Hertz KC, Yaoita H. Herpes gestationis: immunopathology and characterization of the HG factor. J Clin Invest 1976;57: 1434.
28. Katz SI, Provost TT. Herpes gestationis. In: Fitzpatrick TB, et al, eds. Dermatology in general medicine. 2nd ed. New York: McGraw-Hill, 1979:324.
29. Honigsmann H, Stingl G, Holubar K, Wolff K. Herpes gestationis: fine structural pattern of immunoglobulin deposits in the skin in vivo. J Invest Dermatol 1976;66:389.
30. Grimwood R, Arroyave CM, Weston WL, Aeling JL. Herpes gestationis associated with the C_3 nephritic factor. Arch Dermatol 1980;116:1045.
31. Pehamberger H, Gschnait F, et al. Bullous pemphigoid, herpes gestationis and linear dermatitis herpetiformis: circulating antibasement membrane zone antibodies; in vitro studies. J Invest Dermatol 1980;74:105.
32. Holmes RC, Black MM, Jurecka W, Dann J, James DCO. Clues to the aetiology of herpes gestationis. Br J Dermatol 1982;107:9.
33. Lynch FW, Albrecht RJ. Hormonal factors in herpes gestationis. Arch Dermatol 1966;93: 446.
34. Mitchell DM. Herpes gestationis and the "pill." Br Med J 1966;2:1324.
35. Gordon B. Herpes gestationis and the "pill." Br Med J 1967;1:51.
36. Dupont C. Herpes gestationis with hydatidiform mole. Trans St. Johns Hosp Derm Soc 1974;60:103.
37. Tindall JG, Rea TH, Shulman I, Quismorio FP. Herpes gestationis in association with a hydatidiform mole: immunopathologic studies. Arch Dermatol 1981;117:510.
38. Whitfield JM, Smith L, Manson RC. Chorioepithelioma with herpes gestationis. Va Med 1946;73:257.
39. Tillman WG. Herpes gestationis with hydatiform mole and chorion epithelioma. Br Med J 1950;1:1471.
40. Slazinski L, Degefu S. Herpes gestationis associated with choriocarcinoma. Arch Dermatol 1982;118:425.
41. Holmes RC, Black MM. Herpes gestationis. A possible association with autoimmune thyrotoxicosis (Grave's disease). J Am Acad Dermatol 1980;3:474.
42. Shornick JK, Stastny P, Gilliam JN. High frequency of histocompatibility antigens HLA-DR3 and DR4 in herpes gestationis. J Clin Invest 1981;68:553.
43. Reunala T, Karvonen J, Tiilikainen A, Salo OP. Herpes gestationis: a high titre of anti-HLA-B8 antibody in the mother and pemphigoid-like immunohistological findings in the mother and the child. Br J Dermatol 1977;96:563.

44. Eberst E, Tongio MM, Eberst B, Mayer S, Basset A. Herpes gestationis and anti-HLA immunization. Br J Dermatol 1981;104: 553-559.

45. Shornick JK, Stastny P, Gilliam JN. Anti-HLA antibodies and paternal HLA typing in herpes gestationis. J Invest Dermatol 1982; 78:340.

46. Lawley TJ, Stingl G, Katz SI. Fetal and maternal risk factors in herpes gestationis. Arch Dermatol 1978;114:552.

47. Foidart JM, Yaar M, Hall R, Gaspard U, Katz SI. Immunopathological and clinical studies in herpes gestationis. Br J Obstet Gynaecol 1981;88:153.

48. Chorzelski TP, Jablonska S, Beutner EH, Maciejowska E, Jarzabek-Chorzelska M. Herpes gestationis with identical lesions in the newborn. Passive transfer of the disease? Arch Dermatol 1976;112:1129.

49. Katz A, Minta JO, Toole JWP, Medwidsky W. Immunopathologic study of herpes gestationis in mother and infant. Arch Dermatol 1977;113:1069.

50. Van de Wiel A, Hart H, Flinterman J, Kerckhaert JAM, Du Boeuff JA, Wimhof JW. Plasma exchange in herpes gestationis. Br Med J 1980;281:1041.

51. Hertz KC, Crawford PS, Chez RA, Katz SI. Herpes gestationis: an update. Obstet Gynecol 1977;49:733.