

Diagnostic testing in gestational bullous pemphigoid: Has enzyme-linked immunosorbent assay replaced direct immunofluorescence as the new gold standard?



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Key words: BP180-NC16a; direct immunofluorescence; enzyme-linked immunosorbent assay; gestational bullous pemphigoid; indirect immunofluorescence.

CASE REPORT

A 42-year-old gravida 2, para 1 woman at 28 weeks' gestation presented with 10 days of a rapidly evolving eczematous eruption involving the extremities and trunk. Her medical history was notable for atopic dermatitis (AD), and she had a maternal history of psoriasis. Her first child was delivered preterm, and the patient did not experience any rash with that pregnancy. She denied new antibiotics or medications. On physical examination, flaccid bullae and circular hyperpigmented, scaly plaques were present on the bilateral upper and lower extremities and abdomen with studded pustules (Fig 1, A and B). The patient had 2+ lower extremity pitting edema. She was normotensive, and bloodwork was within normal limits. Bacterial culture grew heavy *Staphylococcus aureus*. A punch biopsy of the right upper thigh showed a papillary and reticular dermatitis with lymphocytes and eosinophils. A second punch biopsy of the right upper arm found a pustular dermatitis with eosinophils. The microscopic findings suggested either pustular psoriasis of pregnancy or gestational bullous pemphigoid (GBP). Direct immunofluorescence (DIF) testing was negative, but given the presence of bullae, further testing through BP180-NC16a

Abbreviations used:

AD:	atopic dermatitis
BP:	bullous pemphigoid
DIF:	direct immunofluorescence
ELISA:	enzyme-linked immunosorbent assay
GBP:	gestational bullous pemphigoid
IIF:	indirect immunofluorescence

enzyme-linked immunosorbent assay (ELISA) was performed and confirmed the diagnosis of GBP with an antibody level of 66 U/mL (positive ≥ 15).

She was started on prednisone 60 mg, tapered to 50 mg at 31 weeks' gestation, decreased by 5 mg weekly until 20 mg, held at that dose until delivery, and decreased by 2.5 mg weekly postpartum. She was also given fluocinonide ointment, Sarna twice daily, loratadine 10 mg, diphenhydramine 25 mg, and cephalexin 500 mg three times daily. The patient delivered the baby without complication.

DISCUSSION

GBP, previously known as herpes gestationis, is a vesiculobullous autoimmune disease that affects 1 in 50,000 pregnancies.¹ GBP presents in the second or third trimester, and cutaneous involvement includes

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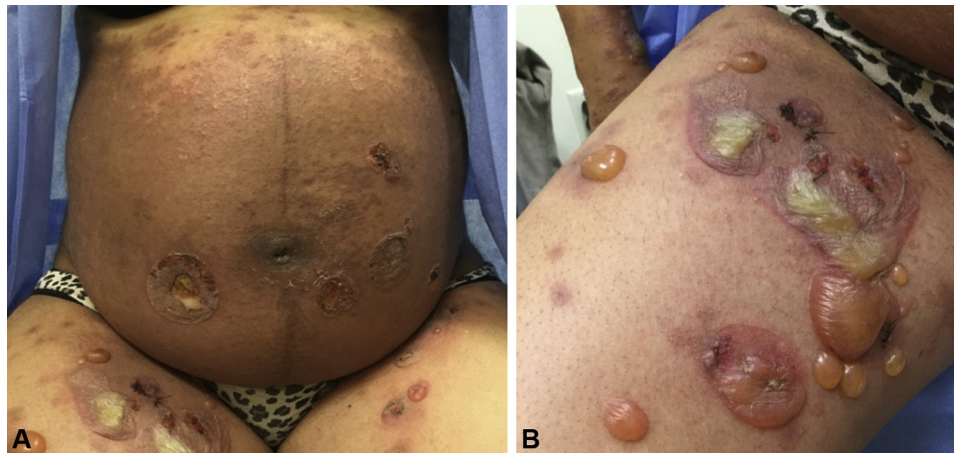


Fig 1. Large eczematous plaques were present on the abdomen (**A**) and back with studded pustules throughout. Vesicles with larger bullae were present on the abdomen, thighs (**B**), and upper extremities.

pruritic urticarial papules, plaques, vesicles, or bullae that start on the umbilicus and spread to the extremities. Often, the condition is exacerbated in the postpartum period and with subsequent pregnancies. GBP is caused by circulating complement-fixing IgG autoantibodies directed against the bullous pemphigoid antigen of 180 kd (BP180 or type XVII collagen), a transmembrane protein found in the epidermal basal membrane zone. This interaction causes separation of the epidermis from the dermis. However, these autoantibodies also bind to the chorionic and amniotic epithelia and cause placental insufficiency, which can result in prematurity and small-for-gestational-age infants. The passive transfer of autoantibodies from mothers with GBP to fetuses can cause skin blistering in the newborn, underscoring the importance of early detection and treatment.²

DIF, the gold standard diagnostic test for GBP, is a staining procedure that measures tissue-bound autoantibodies. Although DIF provides limited information about the tissue antigen, diagnosis can be made based on the immunoglobulin subclass and binding pattern. For GBP, DIF shows a linear deposition of IgG and/or C3 along the dermoepidermal junction. Although the presence of C3 is pathognomonic for GBP, IgG deposits are present only 25% to 30% of the time and are not required for diagnosis.¹ DIF is considered a first-line diagnostic test because it has historically been used to diagnose pemphigoid diseases. Moreover, it is accessible in most laboratories and does not require specialty services. Because of this, DIF is typically recommended for any pregnant patient presenting with urticarial lesions and if GBP is suspected.³ The sensitivity and specificity of DIF in the diagnosis of

GBP are not well reported; however, they have been reported for the diagnosis of bullous pemphigoid (BP), a subtype of bullous skin diseases caused by antibody response toward the hemidesmosome (Table I).

While DIF measures tissue-bound autoantibodies with a skin biopsy, indirect immunofluorescence (IIF) measures anti-C3 and/or anti-IgG autoantibodies circulating within the serum. The substrate is incubated with test serum, washed with phosphate-buffered saline, and incubated with normal human serum as a source of C3 and/or IgG. Microscopy shows deposition of autoantibodies to the upper portion of the lamina lucida beneath the plasma membrane of basal keratinocytes.² IIF requires subjective assessment of reactivity, is time consuming, necessitates specialized personnel and equipment, and does not correlate with disease severity.² Moreover, a wide range of test characteristics for IIF is reported in the literature, with lower sensitivity and specificity compared with DIF (Table I). Thus, IIF is not considered the diagnostic option of choice for GBP.

Finally, BP180-NC16a ELISA testing identifies circulating IgG antibodies directed against the 16th noncollagenous A domain of BP180. NC16a antibodies are detected with indirect ELISA testing, which uses horseradish peroxidase-conjugated antihuman IgG. Tetra-methyl-benzidine is added as the substrate for the horseradish peroxidase, resulting in a color change based on the amount of anti-NC16a antibodies indirectly.⁴ It is considered a highly sensitive and specific test (Table I). Moreover, it does not require skin biopsy, and results are available within 3.5 hours.⁴ Unlike DIF and IIF, the serum levels of autoantibodies detected by the

Table I. Sensitivity and specificity of DIF, IIF, and BP180-NC16A ELISA testing as reported in the literature

	Study	Conditions	Sensitivity (%)	Specificity (%)
Direct immunofluorescence	Sárdy et al, ⁵ 2013	BP	90.8	98
	Meijer et al, ⁶	BP	88.3	99.2
Indirect immunofluorescence	Barnadas et al, ⁷	GBP and BP	74	96
	Powell et al, ⁴	GBP	Combined C3/IgG: 99	NR
	Sárdy et al, ⁵	BP		96.5-97.1
	Meijer et al, ⁶	BP		99
	Barnadas et al, ⁷	GBP and BP	93	96
BP180-NC16A ELISA	Powell et al, ⁴	GBP	96	96
	Sitaru et al, ⁸	GBP	89.9	97.8

NR, Not reported.

ELISA test are found to correlate with disease severity.²

Ultimately, the BP180-NC16a ELISA test accurately provided a diagnosis for our patient. Although DIF may be considered a gold standard given its historical significance, our review finds that BP180-NC16a ELISA may be superior given its high sensitivity and specificity, ease of use, and correlation to disease severity. It is essential that dermatologists and other health care providers know about this diagnostic option for patients with GBP, especially given its influence on fetal development. BP180-NC16a ELISA is especially beneficial for obstetricians who may not perform skin biopsies as frequently or have access to trusted dermatopathologists within their practice. More research is required to establish the sensitivity and specificity for DIF in the diagnosis of GBP and compare DIF and BP180-NC16a ELISA.

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