Gineco.eu[11] 138-140 [2015]
DOI: 10.18643/gieu.2015.138

Pemphigoid gestationis - a rare disease encountered in pregnancy

Mircea Tampa[1,2], Madalina Mitran[2], Cristina Mitran[2], Isabela Sarbu[2], Clara Matei[1], Vasile Benea[2], Tony Hangan[3], Diana Badiu[3], Dan Navolan[4], Simona-Roxana Georgescu[1,2]

1. "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania, 2. "Victor Babes" Hospital for Infectious and Tropical Diseases, Bucharest, Romania, 3. Faculty of Medicine, "Ovidius" University of Constanta, Romania, 4. Department of Obstetrics-Gynecology and Neonatology, "Victor Babes" University of Medicine and Pharmacy Timisoara, City Emergency Clinical Hospital Timisoara, Timisoara, Romania,

Correspondence: Mircea Tampa e-mail: tampa_mircea@yahoo.com

**All authors have equally contributed to this work.*

Acknowledgement: This paper is partly supported by the Sectorial Operational Programme Human Resources Development (SOPHRD), financed by the European Social Fund and the Romanian Government under the contract number POSDRU 141531.

Received: *June 19, 2015*
Revised: *July 03, 2015*
Accepted: *August 21, 2015*

Abstract

Pemphigoid gestationis is a specific autoimmune disease of pregnancy. The onset occurs most commonly in the second or third trimester of pregnancy. Initially, the clinical picture is difficult to distinguish from polymorphic urticarial papules and plaques of pregnancy, urticarial plaques being present in both. Afterwards, the lesions form tense vesicles and bullae on an erythematous base. Direct immunofluorescence reveals C3 linear deposits, with or without IgG deposits along the basement membrane zone. Circulating antibodies are directed primarily against type XVII collagen (BP 180). The main fetal risks are preterm birth and fetal growth restriction. The treatment may be harmful for the fetus. Mild and moderate topical corticosteroids should be used. Systemic corticotherapy, azathioprine or dapsone should be administered in severe cases. Disease activity and treatment efficacy may be evaluated by measuring antibodies titer.
Keywords: *pemphigoid gestationis, pregnancy, autoimmune disease*

Introduction

Pregnancy is a period characterized by metabolic, endocrinological and immunological changes that have an impact on the skin[1]. The immunosuppressant during pregnancy, needed for the tolerance of the fetus by the mother's immune system, plays a role in the occurrence of the autoimmune diseases in pregnant women[2]. Pemphigoid gestationis (PG), was the first specific dermatosis of pregnancy ever described. PG can be differentiated from the other dermatoses since 1973, when immunofluorescence microscopy was developed. The first classification of specific dermatoses of pregnancy was accomplished in 1982 by Holmes et al. and included pemphigoid gestationis, polymorphic urticarial papules and plaques of pregnancy (PUPPP) and prurigo of pregnancy[3].

PG is an autoimmune skin disorder, occurring more frequently during the second and third trimester, but the onset may be at any stage of the pregnancy[4,5]. PG has also been reported in puerperium period in 14-20% of cases. It is a rare disease with an incidence of 1 in 50.000. However, Zurn and contributors have estimated an incidence of 1 in 7000, in their study[6]. An association between PG and the presence of human leukocyte antigen (HLA) DR3 and HLA DR4 has been observed[7]. PG is more common in caucasian people. This could be explained by the fact that HLA DR3 and HLA DR4 are found in a greater proportion in these individuals[6,8]. Furthermore, PG was originally termed herpes gestationis by John Laws Milton, in 1872, given the herpetiform appearance of the lesions. Subsequently, further studies have shown that there is no connection between PG and herpetic infection[9].

Clinical manifestations

If PG is not timely recognized, the treatment may be inappropriate. Pruritus is a common symptom in pregnant women and is frequently attributed to other diseases that occur during pregnancy. The absence of an early diagnosis can lead to neonatal complications and preterm birth[10]. The main differential diagnosis is associated with PUPPP and could be achieved using immunoblotting or enzyme-linked immunosorbent assay (ELISA), tools based on the identification of anti-basement membrane zone autoantibodies[11].

Usually the onset of lesions is periumbilical and the eruption extends to the abdomen and legs, involving the palms and soles[12]. In a recent study, it was found that the lesions started on the legs in the majority of patients[13]. The face and mucous membranes are rarely involved[9]. However, the study conducted by Rassai and contributors including 13 pregnant women with PG, revealed the frequent involvement of the face, as well as the fact that the majority of the patients were primiparous[4]. In contrast, other studies have showed that PG commonly occurs in multiparous women[14,15]. A study performed by Tani el al. has revealed that multiparous women develop PG during an earlier stage of pregnancy than primiparous[16]. Oral mucous membrane is involved in 20% of cases[17]. A case of PG that initially involved the oral mucous membrane has also been reported[18].

PG is characterized by urticaria-like lesions consisting in itchy edematous plaques. Sometimes the lesions have a target-like or polycyclic aspect. Intense itching is a constant complaint. Pruritus may precede the onset of the lesions[12,19,20]. Afterwards, the lesions form tense

vesicles and bullae on an erythematous base. The patient may develop a generalized eruption. The lesions improve just before the delivery but worsen at the time of delivery[9]. Sometimes the lesions are reminiscent of erythema multiform lesions. Several cases of PG without blisters have been reported[6]. The rash may be painful. The blisters may break and small ulcers may occur. The healing is without scarring[21]. In the prebullous stage, the clinical differentiation between PUPPP and PG may be difficult[1].

Pathogenesis

The pathogenic mechanism of PG remains unclear. It is based on the formation of antibodies against placental proteins, which are also found in the skin. The immune process starts in the placenta. Antibodies are particularly directed against type XVII collagen (BP180), a transmembrane hemidesmosomal protein which is found in both placenta and skin (i.e. the amniotic epithelium of the placenta and umbilical cordon, and basement membrane zone of the skin)[22,23]. A smaller amount of antibodies are directed against BP 230. The immune process is based on an abnormal expression of major histocompatibility complex class II molecules in the placenta, which act as a trigger for the inflammatory pathway[23]. Recent studies have emphasized a possible role of T helper 2 lymphocytes subset, in the production of the antibodies[24].

Circulating antibodies, found in the serum of the patients, belong to immunoglobulin G class (subclass G1)[7]. These antibodies bind to the extracellular NC 16A domain of the carboxyl terminus of the 180 kDA bullous pemphigoid antigen. It seems that NC 16A contains epitopes that represent the main target of the circulating autoantibodies. Then the classical complement pathway activates, attracting eosinophils and lymphocytes. An inflammatory infiltrate develops in the basement membrane zone and cellular mediators are released resulting in the dermal-epidermal junction damage and blisters formation[8,11,12]. Antibodies against BP 180 have also been identified in other diseases such as bullous pemphigoid and linear IgA disease[11].

The first case of PG with antibodies to type VII collagen, the main antigen found in epidermolysis bullosa acquisita has recently been described. Cases of patients with PG, which progressed to bullous pemphigoid have been described in the medical literature[25]. PG may be associated with autoimmune diseases, trophoblastic tumors, hydatiform mole and choriocarcinoma[10,26]. In addition patients with PG have a higher risk of developing Grave's disease[5].

Diagnosis

Histopathological findings reveal subepidermal blisters that are located in the lamina lucida, necrosis of basal cells at the tip of the dermal papillae and a dermal inflammatory infiltrate consisting of lymphocytes, eosinophils and histiocytes. Histopathological changes depend on the stage and severity of the disease. In the prebullous stage, edema of the dermis and perivascular inflammatory infiltrate may be observed[3,17].

Physical examination, direct immunofluorescence and serology are the main steps in making the diagnosis. Direct immunofluorescence of perilesional skin represents the key in the diagnosis of PG and reveals linear deposition of C3 along the basement membrane zone, with or without IgG deposits[6,23,25]. Immunoelectonomicroscopy identifies immunoreactants deposits in the lamina lucida, in its upper layer[27]. Circulating autoantibodies may be found by indirect immunofluorescence, in 20-60% of cases. By using complement fixation technique IgG antibodies are detected in 90% of cases[5,8].

Biopsy is not always accepted by the patient, therefore additional tests are needed. Immunoblotting and ELISA seem to be useful alternatives. These tests detect antibodies against BP 180[27]. These antibodies are not found in PUPPP, thus NC16A ELISA may be useful in the differential diagnosis. NC16A ELISA has a high sensitivity and specificity[8,11,12]. Furthermore, ELISA is faster and less costly than immunoblotting[28-30].

Differential diagnosis

The differential diagnosis of pruritic cutaneous lesions in pregnant women should include PUPPP, atopic eruption of pregnancy and intrahepatic cholestasis of pregnancy. PUPPP is the most common specific dermatosis of pregnancy. PUPPP mainly affect primiparous women in the last trimester of pregnancy or immediately postpartum[31,32]. The diagnosis is based on clinical findings. Urticarial papules and plaques are seen on the limbs and abdomen[21]. As in PG, lesions begin on the abdomen but the umbilical region is not involved. Direct immunofluorescence is negative in PUPPP[5].

Treatment

PG is a rare disease, thus there are not many studies about the most appropriate therapeutic options. In mild cases, topical corticosteroids and oral antihistamines are recommended. The use of potent topical corticosteroids is more effective in some cases, than systemic administration of corticosteroids. Potent corticosteroids should be used carefully for a short period of time due to the risk of fetal growth restriction[5]. There is a lack of data regarding the use of topical corticosteroids in pregnant women[30].

In severe cases systemic corticotherapy should be administered in a dose of 0.5 mg/kg prednisolone[24]. According to some authors, systemic corticosteroids do not increase fetal risk and play a role in decreasing the placental inflammatory process[31]. The main objectives of the treatment are the improvement of the pruritus and preventing the emergence of new blisters. Plasmapheresis and intravenous immunoglobulin administration may be useful in refractory PG[9,25]. In some cases, symptoms last for months or years after delivery and cyclophosphamide, azathioprine or dapsone are needed.

The titre of antibodies correlates with the stage of the disease and treatment effectiveness[2].

Prognosis and fetal risk

In most cases PG regresses within three months after delivery. Chronic PG has been reported in a few cases (i.e. lasting longer than six months). It has been described in older multiparous women with PG in previous pregnancies. In these cases the eruption was extensive involving the mucous membranes[28]. A patient who developed PG during pregnancy, presents a high risk of developing PG in a subsequent pregnancy. Studies have shown that the onset of PG will be earlier and the injuries will be more severe[10]. Only 8% of pregnant women will not develop PG in a subsequent pregnancy[21]. The main conditions that may generate an episode of PG in the postpartum period are menstruation and the use of oral contraceptives[6,9,29].

The major fetal complications are preterm labor and low birth weight. These complications are correlated with placental insufficiency observed in these pregnant women. The risk of passive transplacental transmission of antibodies is higher in premature babies[1,20]. However, there is not an increased risk of fetal death. Approximately 5% to 10% of newborns may develop bullous cutaneous lesions, erythema or small ulcers. The prognosis is favorable, the lesions heal without scarring[6,20,23]. Fetal complications are correlated with the earlier onset of PG. The level of antibodies is not related to the fetal health[23].

Conclusions

PG is a rare autoimmune disorder, which frequently starts in the second or third trimester of pregnancy. The pruritus diagnosed in a pregnant woman should raise the suspicion of PG. It is important that PG be treated on time and properly to avoid the main maternal and fetal complications. The patients should be aware of the increased risk of developing PG in subsequent pregnancies. They should also be informed of the potential triggers such as menstruation and oral contraceptives. In most cases, the disease regresses postpartum. ■

References

1. Vora RV, Gupta R, Mehta MJ. et al. Pregnancy and Skin. J Family Med Prim Care 2014, 3(4), 318-24.
2. White S, Philips R, Neill MM, Kelly E. Pregnancy-specific skin disorders. Skin Therapy Lett 2014, 19(5), 7-9.
3. Ambros-Rudolph CM. Dermatoses of pregnancy - clues to diagnosis, fetal risk and therapy. Ann Dermatol 2011, 23(3), 265-75.
4. Rassai S, Pazyar N, Alavi SM, et al. Pemphigoid gestationis: a retrospective study in southwest Iran. Acta Med Iran 2013, 51(6), 408-10.
5. Huilaja L, Mäkikallio K, Tasanen K. Gestational pemphigoid. Orphanet J Rare Dis 2014, 9, 136. doi: 10.1186/s13023-014-0136-2.
6. Campbell SM, Balazs K, Conroy M. Pemphigoid gestationis: a case report and review of the literature. Cutis 2011, 88(1), 21-6.
7. Rodrigues Cdos S, Filipe P, Solana Mdel M. et al. Persistent herpes gestationis treated with high-dose intravenous immunoglobulin. Acta Derm Venereol 2007, 87(2), 184-6.
8. Sentürk S, Dilek N, Tekin YB. et al. Pemphigoid gestationis in a third trimester pregnancy. Case Rep Obstet Gynecol 2014, 2014, 127628.
9. Stevenson ML, Marmon S, Tsou H. et al. Pemphigoid gestationis. Dermatol Online J. 2013, 19(12), 20715.
10. Lardenoije CM, van de Water M, Mertens HJ, Gondrie ET. Pemphigoid gestationis. BMJ Case Rep 2011, 2011. pii: bcr0120102623. doi: 10.1136/bcr.01.2010.2623.
11. Powell AM, Sakuma-Oyama Y, Oyama N. et al. Usefulness of BP180 NC16a enzyme-linked immunosorbent assay in the serodiagnosis of pemphigoid gestationis and in differentiating between pemphigoid gestationis and pruritic urticarial papules and plaques of pregnancy. Arch Dermatol 2005, 141(6), 705-10.
12. Cobo MF, Santi CG, Maruta CW, Aoki V. Pemphigoid gestationis: clinical and laboratory evaluation. Clinics (Sao Paulo) 2009, 64, (11), 1043-7.
13. Castro LA, Lundell RB, Krause PK, Gibson LE. Clinical experience in pemphigoid gestationis: report of 10 cases. J Am Acad Dermatol 2006, 55(5), 823-8.
14. Boudaya S, Turki H, Meziou TJ. et al. Pemphigoid gestationis: a study of 15 cases . J Gynecol Obstet Biol Reprod (Paris) 2003, 32(1), 30-4.
15. Huilaja L, Mäkikallio K, Sormunen R. et al. Gestational pemphigoid: placental morphology and function. Acta Derm Venereol 2013, 93(1), 33-8.
16. Tani N, Kimura Y, Koga H. et al. Clinical and immunological profiles of 25 patients with pemphigoid gestationis. Br J Dermatol 2015, 172(1):120-9.
17. Kar S, Krishnan A, Varma P Shivkumar. Pregnancy and Skin. J Obstet Gynaecol India 2012, 62(3), 268-75.
18. Shimanovich I, Skrobek C, Rose C, et al. Pemphigoid gestationis with predominant involvement of oral mucous membranes and IgA autoantibodies targeting the C-terminus of BP180. J Am Acad Dermatol 2002, 47(5), 780-4.
19. Podolec-Rubiś M, Wołek M, Brzewski P, Wojas-Pelc A. Suspicion of pulmonary embolism during treatment of pemphigoid gestationis. Postepy Dermatol Alergol 2013, 30(1), 59-61.
20. Bergman H, Melamed N, Koren G. Pruritus in pregnancy. CFP 2013, 59(12), 1290-4.
21. Bremmer M, Driscoll MS, Colgan R. The skin disorders of pregnancy: A family physician's guide. J Fam Pract 2010, 59(2), 89-96.
22. Semkova K, Black M. Pemphigoid gestationis: current insights into pathogenesis and treatment. Eur J Obstet Gynecol Reprod Biol 2009, 145(2), 138-44.
23. Henry S. Recognizing presentations of pemphigoid gestationis: a case study. Case Rep Obstet Gynecol 2014, 2014, 415163.
24. Thomas S, Rajan U, George S, George M. Postpartum Pemphigoid Gestationis. Indian J Dermatol 2012, 57(2), 146-8.
25. Yang B1, Wang C, Wu M, et al. A case of pemphigoid gestationis with concurrent IgG antibodies to BP180, BP230 and type VII collagen. Australas J Dermatol 2014, 55(1), e15-8.
26. Matsumoto N, Osada M, Kaneko K, et al. Pemphigoid gestationis after spontaneous expulsion of a massive complete hydatidiform mole. Case Rep Obstet Gynecol 2013, 2013, 267268.
27. Sitaru C, Powell J, Messer G, et al. Immunoblotting and enzyme-linked immunosorbent assay for the diagnosis of pemphigoid gestationis. Obstet Gynecol 2004, 103(4), 773-63.
28. Boulinguez S1, Bédane C, Prost C, et al. Chronic pemphigoid gestationis: comparative clinical and immunopathological study of 10 patients. Dermatology 2003, 206(2), 113-9.
29. Tunzi M, Gray GR. Common skin conditions during pregnancy. Am Fam Physician 2007, 75(2), 211-8.
30. Chi CC, Wang SH, Mayon-White R. Pregnancy outcomes after maternal exposure to topical corticosteroids: a UK population-based cohort study. JAMA Dermatol 2013, 149(11), 1274-80.
31. Chi CC, Wang SH, Charles-Holmes R. et al. Pemphigoid gestationis: early onset and blister formation are associated with adverse pregnancy outcomes. Br J Dermatol 2009, 160(6), 1222-8.
32. De Gaetano JS, De Caetano HM. Pruritic urticarial papules and plaques of pregnancy: an unusual case. J Am Osteopath Assoc 2002, 102(1), 44-6.