

## Review Article

# A review of literature of polymorphic eruption of pregnancy

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## ABSTRACT

Polymorphic eruption of pregnancy (PEP), also known as pruritic urticarial papules and plaques of pregnancy [PUPPP] is the most common of all the specific dermatoses of pregnancy. It is a benign, self-resolving, pruritic disorder of pregnancy, usually affecting primigravida during the last trimester of pregnancy or immediately postpartum. Its exact pathogenesis is still unknown, and its clinical presentations are variable. It may mimic many common dermatoses. In PEP, the histological findings are non-contributory and the laboratory results, including direct and indirect immunofluorescence are negative. Diagnosis mainly depends on clinical findings. Significant diagnostic confusion may occur with early lesions of pemphigoid gestationis, which needs to be differentiated from PEP as the former may have a bad fetal outcome. PEP is not associated with any fetal or maternal risk, and symptomatic treatment is all that is usually required. The awareness of this condition helps the physician recognize this entity, reassure the patient, and avoid unnecessary investigations. This review focuses on etiology, various clinical presentations, differential diagnosis, and management of PEP.

**Keywords:** PEP, PUPPP, Pruritus, Dermatoses

## INTRODUCTION

PEP, the most common specific dermatosis of pregnancy, is a benign, pruritic skin condition, usually occurring in primigravida in the last trimester of pregnancy.<sup>1</sup> The exact etiology is still unknown. The skin lesions cause severe itching and usually disappear after delivery without any sequelae.<sup>2</sup> The specific dermatoses of pregnancy have recently been classified into four entities: PEP or PUPPP, atopic eruption of pregnancy (AEP), pemphigoid gestationis (PG) and intrahepatic cholestasis of pregnancy (ICP).<sup>3</sup> The relative rarity of these conditions, the polymorphic clinical presentations, the similarities with the common dermatoses, and the lack of definitive diagnostic tests have led to confusion regarding

the proper diagnosis and management of these specific dermatoses of pregnancy. A review of the literature related to PEP is presented here with variations in clinical presentations, etiopathogenesis, differential diagnosis and management.

## ETIOLOGY

Polymorphic eruption of pregnancy is the most common specific skin dermatosis of pregnancy.<sup>4</sup> It is also known as pruritic urticarial papules and plaques of pregnancy (PUPPP). It was once called as toxemic rash of pregnancy. The term PUPPP was first introduced by Lawley et al in 1979; later, Holmes and Black proposed the term PEP to encompass all the polymorphous skin

eruptions, including urticarial papules, plaques, polycyclic erythematous wheals, vesicles, targetoid lesions, and occasionally bullae.<sup>5</sup> It usually appears in primigravida in the last trimester, and is a self-limiting disease that disappears within 4 to 6 weeks after delivery without scarring.<sup>1</sup> The cause of PEP is still unknown. However, various etiological theories have been proposed, including abdominal distension, hormonal changes, placental factors, fetal DNA in patients skin lesions, and hypersensitivity reaction to unknown antigens.<sup>6</sup>

The exact etiology is obscure, although it is noted in the third trimester of pregnancy and rapidly resolves in the first weeks of postpartum; sometimes, it can appear after delivery.<sup>7-8</sup> There are variations in quoting the incidence of PEP. It is usually about 0.05%.<sup>9</sup> It is more in twin pregnancy [2.9 to 16%] and still increased in triplets.<sup>6</sup> It has also been reported in four women with unusual family relationships suggesting common paternal influence.<sup>10</sup> Excessive abdominal distension resulting in collagen and elastic fiber damage in striae, with subsequent conversion of nonantigenic molecules to antigenic ones, may trigger the inflammatory skin changes.<sup>7</sup> A Mexican study showed an association between high maternal weight and the presence of PEP.<sup>11</sup> Placental or fetal factors (such as the material of paternal origin in maternal circulation or fetal cell migration in women carrying a male fetus), beta-human chorionic gonadotropin or sex hormones levels have been implicated as a cause in various studies. However, its exact pathophysiology is still unknown.<sup>6,12</sup>

As per a study, the most important factor was thought to be due to peripheral chimerism (deposition of fetal DNA) in the third trimester due to increased vascularity and damaged collagen, responsible for affecting immune response.<sup>13</sup> Another hypothesis centers on fibroblast proliferation in the maternal skin, induced by a placental hormonal-type substance.<sup>2</sup> There is no evidence that PEP is an autoimmune entity, and there is no association between PEP and other autoimmune disorders.<sup>6,8</sup> One study that measured circulating immune complexes in 35 patients with PEP suggests that small immune complexes leakage through dilated upper dermal vessels may play a role in the etiology.<sup>14</sup>

## CLINICAL FEATURES

Pruritic urticarial papules and plaques of pregnancy start most often during the last month of pregnancy and are only rarely reported in the postpartum period. The rash consists of pruritic small erythematous and edematous papules and plaques usually surrounded by a narrow and pale halo first start in the abdomen, especially at the stretch marks with characteristic periumbilical sparing. The lesions can coalesce to form larger urticarial abdominal plaques. The eruption extends to the trunks and the extremities over a matter of days but rarely involves the face, palms, soles and mucosa. There are no

excoriations. Sometimes, the lesion becomes papulovesicular.<sup>5,7</sup> In a recent study from 57 patients, the authors tried to classify the clinical findings in PEP in to three types based on the long-term clinical observations.<sup>12</sup> They are type I: mainly urticarial papules and plaques, type II: non-urticarial erythema, papules, or vesicles, type III: combinations of the two forms.

However, there have been several unusual presentations of PEP reported in the literature. PEP developed during the postpartum period have been reported ranging from 2 days to 2 weeks after delivery, including a case of recurrent postpartum PEP.<sup>15-17</sup> A case of postpartum PEP with arm and feet involvement sparing abdomen, one with palmoplantar involvement, and another case with dyshidrosis and acral purpura have been reported.<sup>18-20</sup>

Exclusive involvement of the peripheral limbs was reported in four patients (22%), three of which only had lower extremities involvement, while one case had upper and lower extremity involvement.<sup>7</sup> Some cases with facial involvement were also noted.<sup>5,21</sup>

PEP can present with various morphologies like cutaneous targetoid lesion, annular or polycyclic wheals, which may mimic other common skin diseases.<sup>12,22</sup> A case of postpartum acquired hemophilia-A associated with atypical polymorphic eruption of pregnancy has been reported.<sup>23</sup> Kanj RV report an unusual presentation in a primi gravida with PEP-like skin lesion in her last trimester who later developed skin and gingival ulcers with persistent fever during her post elective cesarean section period proved to be anaplastic large cell lymphoma with lung and brain involvement.<sup>24</sup> There is also a case report of PEP in a photosensitive distribution.<sup>25</sup> A case of frank bullous lesions over both forearms with classical PEP lesion in other areas mimicking pemphigoid gestationis was noted in one case report.<sup>26</sup>

## PROGNOSIS

PEP is self-limited and is not adversely affecting maternal or fetal prognosis even if not treated. There is no scarring of the lesions. It completely disappears without any trace within four weeks after delivery. It rarely recurs in a subsequent pregnancy; when this happens, the condition is much less severe, and it often develops during the first or second trimester and resolves in prepartum.<sup>2,5</sup> Some studies suggest a relationship with a higher incidence of induction of labor and hypertensive disorders.<sup>9</sup> Association of PEP with increased maternal or fetal weight gain is still in debate. One study showed that patients with PEP have an increased maternal birth weight in twin pregnancies compared with controls and the same study also noted an increase in neonatal birth weight while in contrast, two other studies have not reported any significant increase in maternal or neonatal birth weight.<sup>27-29</sup>

## DIFFERENTIAL DIAGNOSIS

Several conditions mimic PEP. The primary differential diagnoses are the other three pruriginous conditions associated with pregnancy: AEP, pemphigoid gestationis (PG, also known as herpes gestationis), and intrahepatic cholestasis of pregnancy (ICP).<sup>30</sup>

AEP is a heterogeneous group of dermatoses with eczematous and/or papular lesions occurring in pregnant patients with an atopic background.<sup>6</sup> It includes eczema of pregnancy, prurigo of pregnancy, and pruritic folliculitis of pregnancy, with considerable clinical overlap among these conditions.<sup>3</sup> AEP usually appears earlier in pregnancy, either with follicular-oriented excoriated papules or eczematous type of rash similar to atopic dermatitis. Furthermore, it often lacks typical urticarial papules and plaques of PEP. It has no specific histopathological or immunofluorescence findings except occasional elevation of serum IgE. It usually persists throughout pregnancy, may recur in subsequent pregnancies.<sup>4,5</sup>

The pre-bullous form of PG resembles PEP, and it is essential to distinguish between these two entities, as the prognosis is different. Developing PG lesions consist of pruritic urticarial papules and polycyclic wheals, resulting later in target lesions and finally large tense bullae. PG usually starts a little early in pregnancy and is not present along the striae. There is also a significant difference in the umbilicus's involvement; PG frequently involves the umbilicus, while the PEP eruption usually spares the umbilicus. The pregnancy complications like IUGR, low birth weight, prematurity are associated with PG but absent in PEP.<sup>5,7</sup> Histologically, PEP and PG (pre-bullous stage) may be difficult to be distinguished because both conditions may show dermal edema and a perivascular lymphohistiocytic infiltrate with eosinophils, though eosinophils are more seen in PG.<sup>5</sup> So it is important to perform direct immunofluorescence (DIF) for PEP cases to avoid any diagnostic confusion with pre-bullous stage of PG. Linear deposits of C3 in the basement membrane zone (BMZ) are the immunopathological hallmarks of patients with PG.<sup>7</sup> Indirect immunofluorescence (IIF) for circulating antibodies to the basement membrane are uniformly negative in cases of PEP.<sup>8</sup> PG 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. Recently few studies showed the usefulness of Enzyme-linked immunosorbent assay (ELISA) against the NC16A portion of BP180 antigen that is highly sensitive and specific in differentiating PG from PUPPP, and it is potentially a valuable tool in the serodiagnosis of PG. Furthermore, Abel MK et al study shows that the BP180-NC16a ELISA test may be superior to DIF given its high sensitivity and specificity, ease of use, and correlation to disease severity.

Since ELISA is a serological test, it is beneficial for obstetricians who may not perform skin biopsies regularly.<sup>31-33</sup> Kwon EJ and co-workers utilized routine IHC for anti-C4d in formalin-fixed paraffin-embedded (FFPE) skin tissue in the specific differential diagnosis of PEP versus PG. They performed C4d IHC on PEP (n is 11), PG (n is 8); none of the PEP cases (0/11) demonstrated C4d positivity at the basement membrane zone. In contrast, 100% of PG cases (8/8) showed linear C4d immunoreactant deposition along the basement membrane zone. The results demonstrate the potential utility of C4d IHC in FFPE tissue for distinguishing PEP from PG.<sup>34</sup> The major differentiating points between PEP and PG are listed in Table 1.

ICP presents in the second or third trimester with the sudden onset of severe pruritus that starts on the palms and soles and quickly becomes more generalized. The absence of primary skin lesion, biochemical evidence of cholestasis, and recurrence with subsequent pregnancies are features that help differentiate from PEP.<sup>3</sup>

Other conditions that mimic PEP are urticaria, contact dermatitis, drug eruption, and viral exanthems. A detailed history with physical examination helps us to diagnose most of these conditions. Urticaria induced by drugs or food does not have a characteristic location and subside when offending agents are withdrawn. Viral exanthems tend to be exanthematous, less pruritic, and of different distribution.<sup>4,5,7</sup> Another cause of itch that can occur in pregnancy (but not exclusive to it) is meralgia paresthetica, which often causes itching over the lateral and anterolateral thigh.<sup>35</sup> Van Kester MS reported an interesting case of drug reaction with eosinophilia and systemic symptoms (DRESS) due to amoxicillin-clavulanate presented as PEP-like lesions in a pregnant lady. The post-delivery patch test was positive for penicillin.<sup>36</sup> An interesting case report of a COVID-19 positive patient presented with postpartum pruritic small erythematous and edematous macules, and papules first started in the trunk stretch marks later coalesced to form larger urticarial plaques often surrounded by blanched halos, with periumbilical sparing. The rashes clinically were PEP and disappeared without any complications on systemic corticosteroid treatment.<sup>37</sup>

## MANAGEMENT

The patient must be reassured that PEP will subside spontaneously within a few weeks after delivery and does not involve any increased risk to the mother or the fetus. The goal of treatment is the relief of symptoms. For mild disease, low to moderate potency, and for severe disease, high potency topical corticosteroids can be used once or twice daily until improvement occurs. Bland emollients and antipruritic formulations containing menthol may also be added with good results.<sup>3</sup> Sedating first-generation antihistamines such as clemastine, hydroxyzine, chlorpheniramine maleate appears to be safe in pregnancy and can be used as an adjunct therapy.

However, the new nonsedating antihistamines are not recommended in pregnancy. For severe disease, intractable pruritus, disturbed sleep leading to exhaustion of the mother can be safely managed with a short course of oral prednisolone (20-30 mg/day) for 7-14 days.<sup>38</sup>

A recalcitrant PEP unresponsive to systemic steroid therapy but improved dramatically within a few hours of delivery by cesarean section has been reported in the

literature.<sup>39</sup> However, PUPPP is generally not considered an indication for early delivery.<sup>3</sup> UVB therapy was also reported to be successful in treating several patients with PEP.<sup>40</sup> Recently, intramuscular injection of autologous whole blood has been suggested as an alternative treatment option in PEP, including postpartum cases, with both subjective and objective improvement of the symptoms.<sup>41</sup>

**Table 1: Features to differentiate between PEP and PG.**

Feature	PEP	PG
<b>Parity</b>	Usually in primi	Any parity
<b>Onset</b>	Third trimester or immediate postpartum	Usually, the second trimester
<b>Gestation</b>	Multiple gestations	No relation
<b>Skin lesion</b>	Urticarial lesions without blisters	Urticarial lesions with blisters
<b>Relation to striae</b>	Start at the striae	No relation to striae
<b>Umbilicus involvement</b>	Spare umbilicus	Involves umbilicus
<b>Fetal effect</b>	No effect	Small-for-gestational age
<b>Recurrence</b>	Rarely recur	Recurrence common
<b>Histopathology</b>	Upper dermal edema, perivascular infiltrate with few eosinophils	Subepidermal bullae containing numerous eosinophils
<b>DIF study</b>	Negative	Positive
<b>IIF study</b>	Negative	Positive
<b>ELISA for BP180 antigen</b>	Negative	Positive
<b>IHC using C4d</b>	Negative	Positive
<b>Treatment</b>	Symptomatically	Needs specific treatment

## CONCLUSION

PEP runs a benign course without any fetal or maternal morbidity; the intense, intractable itching makes the patient uncomfortable and causes sleepless nights and anxiety, requiring attention. It is essential to recognize this entity because of the clinical overlap mainly with early stages of PG, which is related to an increased risk of prematurity and small-for-gestational-age births. Direct immunofluorescence is the key to differentiate from PG and is also crucial in helping the patient plan for future pregnancies. Newer investigation methods like IHC or ELISA can also be utilized in the appropriate settings to differentiate from the early stages of PG. Despite being a well-defined entity, PEP is often underdiagnosed clinically. Sound knowledge of this condition helps the physician detect and treat this benign condition and reassure the patient avoiding unnecessary tests or treatment. More studies are required in the future to delineate the exact etiopathogenesis of this benign condition and to develop a safer approach in managing this condition.

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