




First-Trimester Impetigo Herpetiformis Leads to Stillbirth: A Case Report

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ABSTRACT

Introduction: Pustular psoriasis of pregnancy (PPP), also known as impetigo herpetiformis (IH), is a rare variant of generalized pustular psoriasis (GPP) in pregnancy. It typically occurs in the third trimester and is a life-threatening condition for both the pregnant mother and the fetus if not diagnosed and treated promptly. Drug-induced PPP has been reported in sporadic case reports. Here we present a case of first-trimester PPP occurring after applying drugs including chloroquine, which we consider a possible culprit triggering the disease.

Case report: A 29-year-old female was admitted to our department at 45 days gestation with sudden onset of fever and widespread

erythematous pustules for 9 days. She had been on medications including hydroxychloroquine before onset. The eruptions and systemic symptoms were controlled with high-dose systemic steroids; however, she was detected to have a stillbirth, and underwent dilation and curettage of the uterine. At the latest follow-up about 2 years after her admission, she reported to have delivered a healthy baby about 1 month previously.

Conclusions: Chloroquine has potential to lead to PPP in the first trimester of pregnancy. Further studies are warranted to investigate the etiology and treatment of PPP to facilitate early recognition and optimal management of this relatively rare dermatosis in pregnancy.

Keywords: Pustular psoriasis of pregnancy; Impetigo herpetiformis; Pregnancy; Chloroquine; Stillbirth

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Key Summary Points

A case report of first-trimester pustular psoriasis of pregnancy (PPP) leading to stillbirth is described.

PPP in the first trimester is rare. To the best of our knowledge, there are only four case reports published in the PubMed database. It indicates that early-onset and fast progression in the first trimester might indicate poor fetus outcomes.

The PPP case occurred after chloroquine initiation, which we consider a possible culprit triggering the disease.

Further studies are required to investigate the etiology and treatment of PPP to facilitate early recognition and optimal management.

BACKGROUND

Impetigo herpetiformis (IH) was first described and named by von Hebra in a case published in 1872 [1]. In a 3-year longitudinal study, impetigo herpetiformis accounted for 4.25% among all 47 pregnancy-related dermatoses seen in a dermatology department [2]. IH clinically and histologically resembles pustular psoriasis, but with particular onset during pregnancy and resolving after miscarriage or labor. Thus, it has been argued for decades whether it is a distinct disease entity [3]. However, current opinion and data suggest that it is a variant of generalized pustular psoriasis (GPP) [4]. Therefore, it is named pustular psoriasis of pregnancy (PPP). PPP typically occurs in the third trimester and can be life-threatening for both pregnant women and fetuses. Risks include tetany, seizures, delirium, stillbirth, and placental insufficiency [5]. Here, we present a case of first-trimester PPP occurring after initiation of drugs, including chloroquine, which we consider a possible culprit triggering the disease.

CASE PRESENTATION

A 29-year-old female, gravida 1 para 0, at 45 days of gestation, was admitted to our department with sudden onset of fever and widespread erythematous pustules for 9 days. The erythematous rash initially appeared under bilateral breasts, with subsequent extension to the torso and extremities. Pin-sized pustules formed at the margin of the annular erythematous rash and gradually merged into pustular lakes. The skin eruptions were accompanied by chills, fever, and vaginal bleeding. The patient had severe pain and burning sensation in areas affected by the eruption, interfering with her sleep.

Before pregnancy, she was suspected of antiphospholipid antibody syndrome at the local hospital. She was prescribed oral aspirin enteric-coated tablets 25 mg three times daily initially. Two weeks later, after initiation of the treatment, she was found pregnant. Then the regimen was augmented with hydroxychloroquine 100 mg three times daily, cyclosporine 50 mg three times daily, and prednisone 7.5 mg once daily. At onset of symptoms, she was given hydrogesterone tablets 10 mg three times daily due to vaginal bleeding. Two days prior to admission, she received empiric treatment of three doses of cefoperazone and sulbactam sodium injection 2 g per dose, and the prednisone dosage was augmented to 10 mg twice daily on that and 20 mg twice daily the next day. Her rash continued to progress despite the above treatments. There was no personal or family history of skin diseases. She denied any history of infectious diseases or blood transfusion.

On admission, the patient was febrile at 38.7 °C and tachycardic, with widespread confluent erythematous plaques studded with tiny peripheral pustules, worse in the intertriginous areas. Some pustules had merged into larger pus-filled bullae (Fig. 1). Her palms, soles, nails, and oral mucosa were spared. The laboratory findings at admission showed significantly elevated inflammatory markers, including erythrocyte sedimentation rate (49 mm/h), C-reactive protein (99 mg/L), leukocytosis



Fig. 1 **a** Erythema, pustules, and pus-filled bullae on admission. **b** Erythematous pustules and pustule lakes over the limbs on day 3. **c, d** Pustules on the trunk dried up and

become desquamative with large scales on day 3. **e** Generalized swollen erythema covered with plenty of scales on day 5. **f** Rash largely alleviated on day 20

($21.3 \times 10^9/L$), and neutrophilia. Repeated blood cultures and swabs from the pustules were sterile. Other significant laboratory parameters were hypoalbuminemia, elevated fibrinogen (6.4 g/L), D-dimer (3750 $\mu\text{g/L}$), and CA125. The rest of her blood tests results, including serum calcium level, were within normal limits.

Initial differential diagnosis of acute generalized exanthematous pustulosis (AGEP) with PPP was considered; thus, hydroxychloroquine and cyclosporine were discontinued as they were added a week prior to the eruption and were suspected as possible culprit drugs. Oral prednisone 20 mg twice a day was given. Aspirin enteric-coated tablets and dydrogesterone tablets were continued with the same dose at admission. Additional therapy was

implemented with intravenous gamma globulin 20 g daily, azithromycin injection 0.5 g daily to prevent infection, enoxaparine 4000 u subcutaneous injection daily to correct coagulation status, and nonsteroidal antiinflammatory drug (acetaminophen). The lesions showed rapid exacerbation in the first five days, with more erythematous pustules developing over the neck, face, and limbs. Older lesions dried up and become desquamative with large scales (Fig. 1). Then she had generalized swollen erythema covered with plenty of scales (Fig. 1). The patient experienced severe pain and persistent fever. We replaced oral prednisone with intravenous methylprednisolone 30 mg twice daily because of rapid exacerbation on the sixth day.

Moreover, intravenous human albumin was infused as she had severe hypoalbuminemia

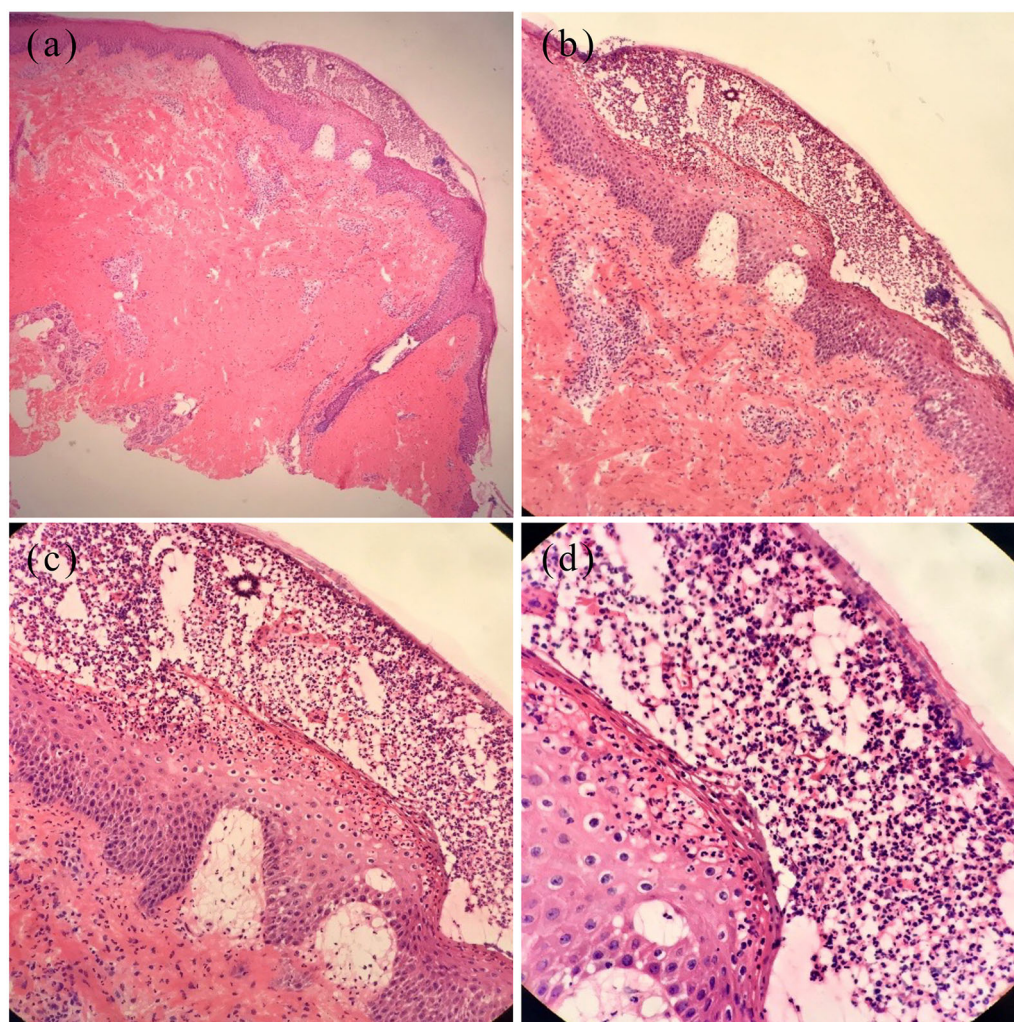


Fig. 2 Pathology of skin biopsy from the lesions on the right shin showed focal acantholysis subcorneal pustules with aggregation of abundant neutrophils.

a Magnification $\times 40$, **b** magnification $\times 100$, **c** magnification $\times 200$, **d** magnification $\times 400$

(22 g/L). A diagnosis of pustular psoriasis of pregnancy was supported by histopathological investigation of the lesions on the right shin, which showed focal acantholysis subcorneal pustules with aggregation of abundant neutrophils. The papillary dermis was edematous with perivascular lymphocytes infiltration (Fig. 2). Direct immunofluorescence of the perilesional skin IgG, IgA, IgM, Fp, and C3 were all negative. As her skin rash gradually relieved and her general condition improved, the dosage of intravenous methylprednisolone was gradually tapered. Transvaginal sonography and β -hCG levels were checked repeatedly to monitor the

fetus. Her β -hCG levels on the 4th, 6th, 11th, and 18th day of hospitalization were 26,045.0 IU/L, 31,618.0 IU/L, 50,854.0 IU/L, and 70,787.0 IU/L, respectively. On the 8th day of hospitalization, transvaginal sonography showed an intrauterine pregnancy sac with size of about $2.2 \times 1.7 \times 1.7 \text{ cm}^3$, the embryo length was about 0.28 cm, and the original heartbeat was noticeable. On the 17th day of hospitalization (gestational age of 8 weeks), sonography confirmed stillbirth by reporting an intrauterine pregnancy sac size of about $3.1 \times 2.3 \times 2.4 \text{ cm}^3$, the embryo length was about 0.5 cm, and the original heartbeat could not be observed. As her

rash largely alleviated and general condition was stable, after consulting the gynecology and obstetrician department, she was transferred to the OBGYN department for dilation and curettage of the uterine. She was discharged one day after the procedure.

After discharge, her skin lesions gradually subsided completely. There were no new eruptions or any signs of relapse. Methylprednisolone was gradually tapered off. The latest follow-up was about 2 years after her admission. She reported delivering a healthy baby about 1 month prior. During her second pregnancy, she only received heparin injection, and there was

no rebound of the skin lesions as she had during her first pregnancy.

DISCUSSION

Pustular psoriasis in pregnancy is life-threatening for the pregnant mother and the fetus. PPP typically presents during the third trimester, though cases of first-trimester PPP have been reported [6]. To the best of our knowledge, only four cases of PPP were reported during the first trimester in the PubMed database. Details of all reports of first-trimester PPP to date, including our case, are described in Table 1. Two cases

Table 1 First-trimester PPP cases reported to date

First author (year of publication)	Age of patient (years)	Ob/gyn history, gestational weeks at onset	Psoriasis history	Treatment	Fetus outcome	Maternal outcome
Shaw (2011) [7]	25	G2P1 previously uncomplicated pregnancy, Week 7, aggravated at week 31	No	High-dose oral steroids unresponsive, cyclosporine used	Healthy male infant spontaneous labored at 41(+ 2) weeks	Symptoms were controlled
Saito-Sasaki (2017) [8]	30	G4 10 weeks	No	Granulocyte and monocyte apheresis (GCAP)	Delivered a healthy female baby with normal birth weight (1764 g, 35 weeks' gestation)	Skin eruptions improved dramatically
Mohaghegh, (2021) [10]	35	G1P0 Week 5	No	Prednisolone, cyclosporine	Miscarriage at 10 weeks' gestation	Skin lesions recovered
Gligora (1982) [9]	22	First month	NA	Hormonal treatment	Abortion	Marked improvement was seen
Our case (2022)	29	G1P0 Week 4	No	Prednisolone	Stillbirth at 8 weeks gestation	Skin lesions recovered Delivered a healthy baby 2 years later

Ob/gyn obstetrician-gynecologist; *G2P1* gravida 2, para 1; *G1P0* gravida 1, para 0; *NA* not applicable

delivered healthy infants; the other three cases had unfavorable results, including miscarriage, abortion, and stillbirth. The first patient with a good fetus outcome had a painful periumbilical rash at week 7, which was nonresponsive to topical steroid preparations, aggravated at week 31 with a feverish widespread erythematous rash [7]. The second patient had rash onset at week 10 and finally delivered a healthy female baby [8]. With the latest onset at week 5, the other three cases all had severe progression during the first trimester [9, 10]. It seems that early onset and fast progression in the first trimester might indicate poor fetus outcomes. Thus, early diagnosis and treatment are essential to avoid complications.

The exact mechanism of PPP is still largely unknown. A genetic study showed PPP patients with interleukin 36 receptor antagonist (IL36RN) mutations, which is identical to generalized pustular psoriasis (GPP) [11]. No known environmental factors have been solely implicated in the pathogenesis of PPP [4]. Hypoparathyroidism is widely considered to have a possible role [12]. Drug-induced PPP has been reported in sporadic case reports. In Guerriero's case, after 5 days of *N*-butyl-scopolammonium bromide therapy, a woman developed PPP at 34 weeks' gestation [13]. PPPs caused by ritodrine hydrochloride in a nulligravida woman at 31 weeks' gestation has also been reported [14]. Our patient did not have family or personal history of psoriasis, nor did her second pregnancy have psoriasis relapse. We noticed her different medication history between the two pregnancies. Synthetic anti-malarial drugs (SADs) can exacerbate or induce psoriasis [15]. Recent case reports have also reported exacerbation of psoriasis following hydroxychloroquine in patients with suspected or diagnosed coronavirus disease 2019 (COVID-19) [16, 17]. Thus, it is sensible to consider hydroxychloroquine as a possible psoriasis trigger during her first pregnancy.

A systematic review summarized existing literature and reported 18 cases of psoriasis-related complications after HCQ use; 50% ($n = 9$) of patients experienced de novo psoriasis with a latency period of 1 week to 1 month [18]. Our patient had de novo pustular psoriasis onset

1 week after initiation of hydroxychloroquine, which is consistent with the latency period summarized in the review. The exact mechanism for why hydroxychloroquine could trigger psoriatic flares is still not fully understood. Wolf et al. studied the in vitro effect of HCQS on uninvolved skin of psoriatic patients and demonstrated enhanced and irregular keratinization and dermo-epidermal detachment and cleft formation [19]. A study conducted by Said proved that chloroquine (CHQ) maintains a pathological IL23/IL-6/Th17 axis in inflammatory skin conditions with elevated levels of IL-1 cytokines [20]. Reports of psoriasis triggered by hydroxychloroquine in pregnant women are quite rare. Agoritsa et al. reported rapid exacerbation and pustular transformation of mild psoriasis vulgaris in a primigravida (25th week of gestation) [21]. To our best knowledge, this is the first case of possible hydroxychloroquine-triggered generalized pustular psoriasis during pregnancy without prior psoriasis history.

Our initial consideration was the differential diagnosis of AGEP with PPP. It is challenging to distinguish AGEP from pustular psoriasis as they share similar clinical and histopathologic findings [22, 23]. Several cases of AGEP induced by hydroxychloroquine have been reported in literature [24, 25]. This makes the differential of our case even more challenging. In our case, the clinical presentation showed small pustules on the edges of multiple annular erythematous patches, comparable to the morphology of PPP previously described in literature, and considered a characteristic of PPP [3, 26–28]. Meanwhile, AGEP usually has a distinctive appearance of pin-sized monomorphic pustules overlying edematous and erythematous skin. The cutaneous symptoms of AGEP typically resolve within 15 days of discontinuation of the causative agent [29]. However, our patient took longer to achieve resolution. Moreover, the laboratory and histopathologic findings did not reveal any signs of blood eosinophilia, necrotic keratinocytes, eosinophilic spongiosis, or dermal eosinophilia, which are common in AGEP [30, 31]. All the above-discussed features are concluded as hints favoring PPP over AGEP.

The treatment of PPP may be challenging. As PPP is a rare disease, treatment recommendations are given based on cases and reviews. The National Psoriasis Foundation recommends corticosteroids, cyclosporine, and infliximab as first-line treatments and phototherapy as second-line treatment, considering their teratogenic potential [32]. As a pregnancy category X medication, postpartum methotrexate has been used successfully to treat recalcitrant cases of PPP [33]. Besides tumor necrosis factor (TNF) alpha blockers such as infliximab and adalimumab, interleukin-12/23(IL-12/23) antagonist ustekinumab and interleukin-17A(IL-17A) antagonist secukinumab have also been used to treat recalcitrant cases, with favorable results [34, 35]. PPP usually resolves after delivery; in cases not responding to drug therapy, induction of labor in the third trimester and termination of pregnancy in the second trimester have been proven effective [36, 37]. A minimal number of patients have been treated for PPP that started during the first trimester. Both our case and case 4 in Table 1 had a detrimental outcome for the fetus; in contrast, in case 2, where granulocyte and monocyte apheresis (GCAP) was applied, both skin eruption and intrauterine growth were improved with a healthy baby delivered [8].

CONCLUSIONS

Our study suggests that chloroquine might trigger PPP. As a rare disease, especially when occurring during the first trimester, more cases are warranted to investigate further the etiology and treatment of PPP to facilitate early recognition and optimal management.

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Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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