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Case Report

A Case Report: High Dose Systemic Corticosteroids as the Therapy for Severe Case Impetigo Herpetiformis

Laila Tsaqilah*, Annisa Febrieza Zulkarnaen, Hartati Purbo Dharmadji, Risa Miliawati Nurul Hidayah, Erda Avriyanti

ABSTRACT

Introduction: Impetigo herpetiformis (IH) is a rare but life-threatening dermatosis of pregnancy. Early recognition and treatment of IH is important because it may cause maternal and fetal morbidity and mortality. Systemic corticosteroids remain the mainstay of treatment for IH and are considered safe for pregnancy. The purpose of this study was to present successful high-dose corticosteroids as a therapy for severe cases of IH. **Case:** We reported a 34-year-old pregnant woman in third trimester of pregnancy with a two-week history of reddish patches and pustules spread almost all over her body. She had a history of the same complaint in her latest pregnancy. The diagnosis of severe IH was made based on clinical, laboratory, and histopathology findings. She was prescribed 80 mg/day of oral prednisolone. The eruption and systemic symptoms gradually improved after 12 weeks of treatment. The dose was maintained until delivery before tapered gradually and stopped. The baby was born healthy, and there were not any new lesions. **Discussion:** Given the possibility of fetal and maternal complications that are potentially life-threatening, IH needs to be detected and treated right away. The mainstay of treatment for IH is systemic corticosteroids. Steroids control the eruption by preventing polymorphonuclear cells from migrating. Due to its limited placental transmission, prednisolone is regarded to be safe for uses during pregnancy. After 12 weeks of treatment of 80 mg daily prednisolone, the eruptions were resolved and there were not any side effects of steroid observed in both the mother and the baby. **Conclusion:** Impetigo herpetiformis not only needs early treatment to prevent maternal and fetal complications but also the safety of the treatment chosen. High-dose oral prednisolone is considered effective and safe to control a severe case of IH as it has low placental transmission.

Keywords: Impetigo herpetiformis, Pustular Psoriasis of Pregnancy, Prednisolone.

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INTRODUCTION:

Impetigo herpetiformis (IH), also known as pustular psoriasis of pregnancy (PPP) is a rare dermatosis of pregnancy, that causes maternal and fetal morbidity and mortality.[1,2] IH occurs generally in the third trimester of pregnancy and recedes after delivery, with a risk of recurrence in subsequent pregnancies. The exact cause of IH is still unknown, but genetic factors are believed to play a role in the development of IH.[2,3] Only 350 cases of IH were described in the American and European literature as of 2000.[4] IH is characterized by erythematous plaques with s of sterile pustules surrounding the margins, which begin in the flexures and spread centrifugally.[2,5,6] Systemic signs such as fever, chills, weakness, diarrhea, nausea, and vomiting can occur.[2,5]

Impetigo Herpetiformis can cause life-threatening complications such as sepsis, hypocalcemia, stillbirth, fetal abnormalities, and intrauterine growth restriction.[3,5] Early recognition and treatment of IH are of utmost importance as maternal and fetal well-being may be compromised.[7] Systemic corticosteroids remain the mainstay of treatment in IH.[2,3,5,8] The initial dose for mild to moderate cases is 15 to 30 mg/day.[2,5] Prednisolone is an option for IH therapy because it carries the least hazard for the fetus.[9] Here, we demonstrate one severe case of IH in an Indonesian pregnant woman treated with high dose of oral prednisolone.

CASE REPORT

A 34-year-old woman at 31–32 weeks of her fourth pregnancy with 47 kg of body weight was referred to the Department of Dermatology and Venereology, Hasan Sadikin Hospital, with a two-week history of itchy, pus-filled pustules and a reddish patch that spreads almost all over her body (Figure 1a, Figure 1b). She also felt fatigued. She has history of the itchy, pus-filled pustules and reddish patch on her buttocks in third trimester of her latest pregnancy. She used neomycin sulfate and fluocinolone acetonide cream to treat the lesion but there wasn't any improvement. The lesions were resolved after delivery. She denied any history of upper respiratory tract infection, reddish patches with thick white scales, swelling and painful joint, consumtion of drugs or herbs, and previous contraceptive use.

The patient was treated with 8 mg of oral methylprednisolone twice a day for five days, but then she was referred to our department because her condition had not improved. Dermatological examination showed a generalized distribution of erythematous patches, with scales, pustules, and crusts. Leukocytosis (16.170/µL), elevated c-reactive protein (CRP) (7.61 mg/dL), hypoalbuminemia (2.90 g/dL), hypocalcemia (4.34 mg/dL), and mild anemia (hemoglobin level was 9,5 g/dL) were found in laboratory exams. The fetus was in good condition. Bacteriologic examination of the pus was negative, which confirmed the sterility of the pustule. The skin

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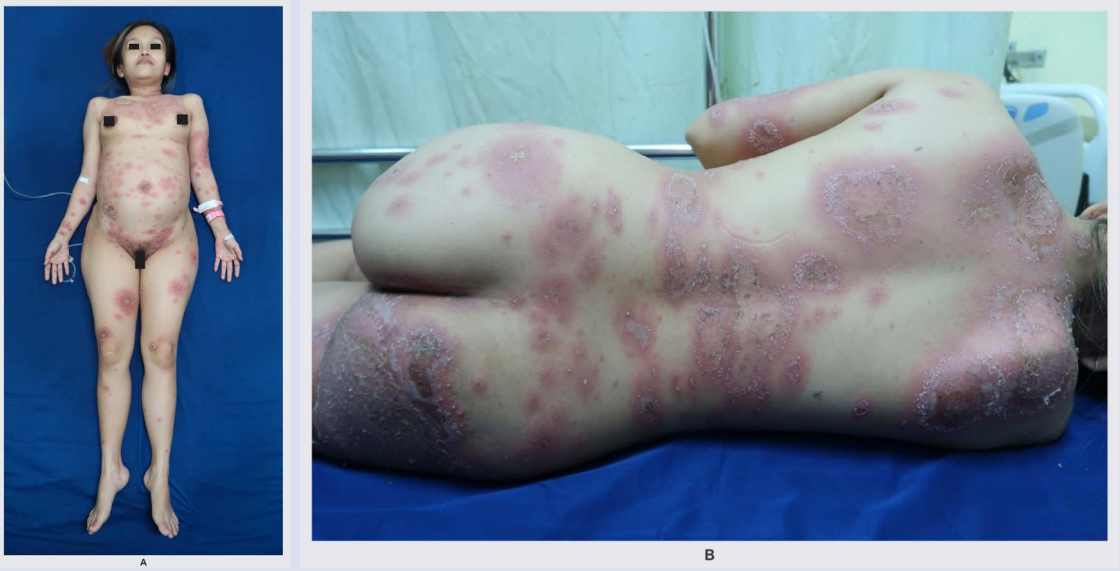

Figure 1: Lesion before treatment (A, B)

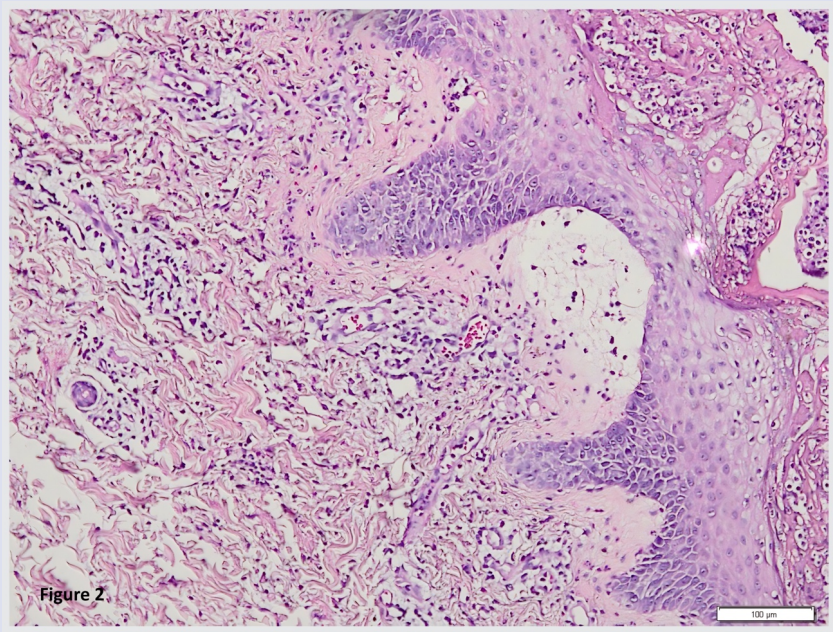

Figure 2: Histopathological result showed pustules contained neutrophils, spongiotic reaction with accumulation of lymphocytes and eutrophils on the epidermis, and very edematous stroma papilla, lightly covered with lymphocytes and neutrophils, mostly at the perivascular

biopsy showed pustules contained neutrophils, spongiotic reaction with accumulation of lymphocytes and eutrophils on the epidermis, and very edematous stroma papilla, lightly covered with lymphocytes and neutrophils, mostly at the perivascular (Figure 2).

The diagnosis of IH was made from clinical and pathological findings. The patient was categorized as severe for a total score of 12 according to the Japanese Dermatological Association Severity Index of GPP (JDA-GPPSI) with a skin severity score of 6 and a systemic and laboratory severity score of 6. For severe cases, the patient was prescribed oral prednisolone 80 mg per day. There was also topical treatment with saline dressing for wet lesions and vaseline for dry lesions. After 12 days of treatment, her condition has improved. Her lesions became dry, and no new lesions appeared (Figure 3a, Figure 3b). At 37 weeks gestation, she gave birth to a healthy female baby weighing 2.5 kilograms. The corticosteroid dose was then tapered and stopped.

DISCUSSION

Impetigo herpetiformis (IH) is a rare, but severe dermatosis that occurs during pregnancy.[1,2,5,10] IH are considered to be subtypes of generalized pustular psoriasis (GPP) exclusively associated with pregnancy.[3] The cause of IH is yet to be understood, but genetic factors such as mutations of interleukin-36 receptor antagonists (IL-36RN) are one of the proposed hypotheses for the development of IH.[2,3,7] Precipitating factors include hypocalcaemia, hypoparathyroidism, hormonal changes, and bacterial infection.[2]

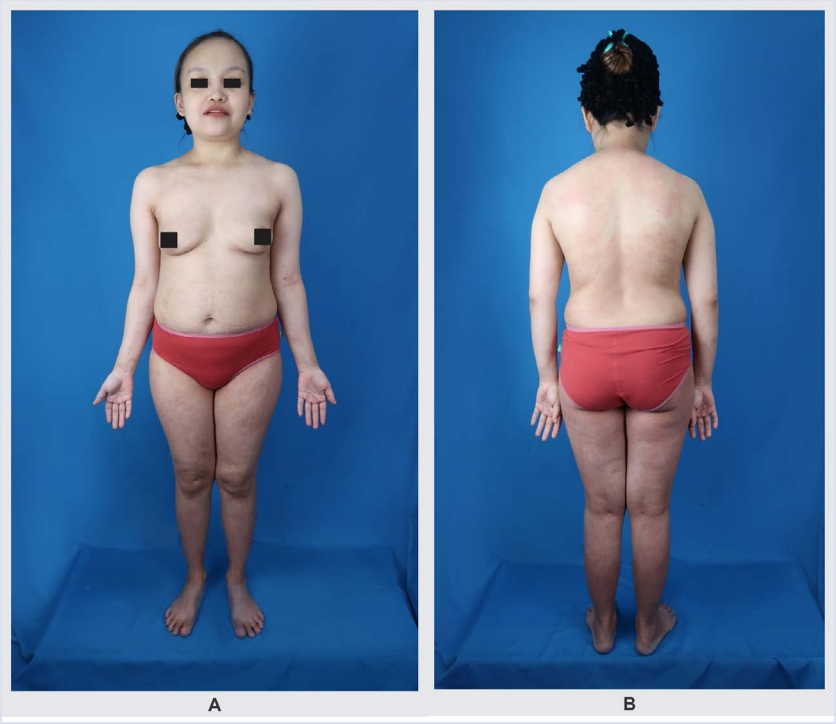

Figure 3: Lesion after treatment (A, B)

Impetigo herpetiformis most commonly occurs typically in the third trimester of pregnancy with the risk of recurrence in the subsequent pregnancy.[3,5,11] The eruption consists of erythematous patches with groups of sterile pustules on the margins, and it begins in the flexural regions before spreading centrifugally to the extremities.[1,2,4,5] They can develop into crusts, erosions, and later impetiginized.[2,5] Systemic symptoms including fever nausea, vomiting, malaise, arthralgia, and diarrhea can also occur.[1,2,5] IH cause maternal and fetal complications such as bacterial sepsis, hypocalcemia, premature delivery, intrauterine growth restriction, and stillbirth.[2,3,5,11] In this case, the patient had the typical clinical features of IH. The eruption appeared in her early third trimester and consisted of erythematous patches with groups of pus-filled pustules, scales, and crusts that began in her chest and buttocks and spread almost to the rest of her body. She also had hypocalcemia. She has had similar complaints in previous pregnancies that resolved after delivery.

Diagnostic criteria that have been proposed for GPP are the presence of sterile pustules, systemic symptoms of inflammation, abnormalities in the laboratory findings, histopathologic findings of spongiform pustules of Kogoj, and recurrence.[10] All five criteria must be met to definitively diagnose GPP.[10] As IH was recently considered a subtype of GPP, we use the proposed diagnostic criteria for IH. The presence of sterile pustules, fatigue, abnormal laboratory findings (leukocytosis, high level of CRP), histological findings of spongiform pustules containing neutrophils (spongiform pustules of Kogoj), and a history of the same complaint in her latest pregnancy were found in our patient. Therefore, we diagnosed the patient with IH.

Laboratory findings of IH are leukocytosis, elevated erythrocyte sedimentation rate, elevated CRP, hypocalcaemia, and a low level of vitamin D secondary to hypoparathyroidism.[1,3,5,12] Histopathological findings from a skin biopsy are spongiform pustules of Kogoj, which contain neutrophils in the epidermis with lymphocytic and neutrophil infiltration in the papillary dermis.[1,3,5,12] Parakeratosis, acanthosis, hyperkeratosis, and capillary dilation of the papillary dermis can also be found.[13,12] Leukocytosis, elevated CRP, and hypocalcemia were found in our patient. Her skin biopsy showed spongiform pustules of Kogoj in the epidermis and infiltration of lymphocytes and neutrophils in the papillary dermis.

Japanese Dermatological Association Severity Index of GPP (JDA-GPPSI) measures the severity of GPP by assessing the skin and clinical and laboratory characteristics.[14,15] The total score ranges from 0 to 17, with the skin severity score ranging from 0 to 9 and the clinical and laboratory severity score ranging from 0 to 8.[14] The disease severity is classified as mild (0–6), moderate (7–10), or severe (11–17).[14,15] Our patient was categorized as severe for a total score of 12 with a skin severity score of 6 and a clinical and laboratory severity score of 6.

IH requires immediate recognition and treatment because of the risk of life-threatening maternal and fetal complications.[3] Systemic corticosteroids remain the mainstay of treatment for IH.[2,3,5,10] In our case, prednisolone was the drug of choice because the patient was pregnant. Prednisolone is considered safe for pregnancy because it has low placental transmission.[8,9,13] Steroids resolve the eruption by suppressing the migration of polymorphonuclear cells.[16] The initial dose to treat IH is a low dose 15-30 mg/day and can be increased up to 60 mg/day even 80mg/day if needed in severe cases.[3,5,10] Lim *et al* reported a case of IH who was treated with systemic corticosteroids at a dose based on body weight; prednisolone 0.5 mg/kg/day.[8] After 5 days of treatment, lesions and clinical symptoms did not show improvement, a low dose of metorexate was added at 7.5 mg per week. Therapeutic response was obtained at the end of the first week of combination therapy.[8]

Bozdag *et al.* used 60 mg/day of prednisolone to treat a 19-year-old pregnant woman with IH.[9] The eruption resolved after six weeks of therapy.[9] Sahin *et al.* show a good treatment response to 30 mg/day prednisolone in patients with recurrent IH.[17] Because our patient had a severe case of IH, we prescribed 80 mg of prednisolone daily. Our patient showed a good response to prednisolone. Her condition improved after 12 weeks of treatment, and there weren't any new

eruptions. We continued at the 80 mg/day dose until delivery before tapering it. After long-term use, the side effects of steroids include osteoporosis, hypothalamic-pituitary-adrenal (HPA) axis suppression, hyperglycemia, an increased risk of infection, weight gain, and skin fragility.[16,18] In our patient, no steroid side effects were observed. The baby was healthy and delivered without any evidence of steroid side effects.

More severe case can be refractory or unresponsive to corticosteroid. Other treatment modalities that have been reported are cyclosporine, anti- tumor necrosis factor (TNF) α, and phototherapy.[9] Patsatsi *et al* reported the use of 4 mg/kg cyclosporine as the additional treatment of an IH case that was unresponsive to systemic corticosteroid.[19] No further eruptive lesions was observed for almost a month before the steroid was tapered until the day of the delivery. Hazarika et.al reported the addition of 3 mg/kg cyclosporine for an IH case that was relapse after the tapering off of the prednisolone.[20] After 10 days of cyclosporine administration, the lesions had compeletely resolved and the baby was born healthily at 38 weeks of pregnancy.[20] However cyclosporine should be used as second line treatment during pregnancy since early rupture of membranes have been noted with the use of cyclosporine.[21]

Anti–TNF α agents such as infliximab and adalimumab (ADA) are classified as pregnancy category B because they did not cause embryotoxicity or teratogenicity in pregnant mice.[2,22] These biologic agents have been used in several IH cases that were resistant to combination therapy.[22] Ogrum *et al* reported the case of IH that was resistant to multple treatment of acitretin 50 mg/day, cyclosporine 5 mg/day, and methylprednisolone 48 mg/day.[23] Infliximab 5mg/kg/day was added at 15 weeks post-partum and clinical improvement was resolved. Becksac *et al* reported the case of IH that was treated with infusion of 5 mg/kg infliximab with 2 mg/kg daily of methylprednisolone.[22] After 2 days of infusion of infliximab, the lesion was resolved. However new eruption was found after 12 days of the first infliximab dose that the second infusion was administered the next day.[22] The lesions were cleared within 48 hours.

Anti-TNF α agents were used in two IH case reported by Fukushima *et al*.[24] In the first case, adalimumab (ADA) was administered in addition to the combination therapy of prednisolone 50 mg/day, cyclosporin 250 mg/day and granulocyte and monocyte adsorption apheresis (GMA) because the lesions were not resolved after fifth weeks of treatment. ADA was given five times two days a week with the dose of 80 mg for the first injection, 40 mg for the second, and 80 mg for the third to fifth injection. The eruption and abnormal laboratory findings were resolved.[24] The second case used certolizumab pegol (CZP) at the dose of 400 mg four times biweekly after three weeks of prednisolone 20 mg/day, cyclosporin 200 mg/day and GMA once a week for 3 weeks combination therapy. Within a few days, the lesions started to regress considerably and the baby was born at 37th weeks of pregnancy without any congenital abnormalities.[24]

Secukinumab also been used to treatment resistant IH. Neema *et al* reported a case of IH that was treated with combination therapy of prednisolone 1 mg/kg and cyclosporine 5 mg/kg.[25] After two weeks of therapy, the response was sub-optimal so secukinumab was administered in the dose of 300 mg subcutaneous at 0, 1, 2, 3, 4 weeks and monthly thereafter. Complete resolution was observed after four weeks of secukinumab administration.[25]

Phototherapy can be used as adjunctional therapy for IH.[2,9] Narrow band-ultraviolet B (Nb-UVB) is a safe option during pregnancy and can be used as adjunctional therapy for corticosteroids resistant case.[2,9] The best phototheraphy for psoriasis is 311 Nb-UVB.[9] Bozdag *et al* reported an IH case that was treated with combination of 60 mg/day of oral prednisolone and NBUVB. NBUVB was commenced as adjunctional therapy because there were new lesions formed even after six weeks of oral prednisolone administration.[9]

There is a risk of recurrence in the following pregnancy, with increased morbidity and mortality from the disease.[11] Therefore, we need to educate the patient about the risk of recurrence and the need for immediate treatment when the symptoms recur. The cooperation between dermatologists and obstetricians attending to the patient is important to ensure the safety of the mother and baby. Safety must be considered in choosing the treatment to avoid the adverse effect of the drugs, especially on the fetus.[2,3]

CONCLUSION

Impetigo herpetiformis is a rare disease that can cause serious maternal and fetal complications; therefore, it needs early diagnosis and treatment. Because it occurs during pregnancy, consideration in choosing the treatment is needed to ensure the safety of the baby. Systemic corticosteroids are still considered the main treatment for IH. High-dose oral prednisolone is considered effective to control a severe case of IH and also safe for the baby as it has low placental transmission.

ETHICAL STATEMENT

The publication of images were included in the patient's consent for publication of the case. Institutional approval from The Research Ethic Committee of Dr. Hasan Sadikin General Hospital Bandung, Indonesia has been obtained to publish the case details (approval number: LB.02.01/X.6.5/472/2023).

CONSENT STATEMENT

The authors certify that they have obtained written informed consent from the patient to the publication of the case details and images.

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CONFLICTS OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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