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Impetigo herpetiformis: A rare pregnancy-specific dermatosis

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Abstract

Impetigo herpetiformis (IH) is a pregnancy-specific dermatosis that is currently considered a form of generalised pustular psoriasis and mainly occurs in late pregnancy during the third trimester. IH presents as erythematous patches and pustules and might have systemic involvement. The disease may be associated with severe maternal, fetal, and neonatal complications. IH treatment is very challenging, however, various therapeutic options are available and effective for disease treatment.

Keywords

pregnancy dermatosis, late pregnancy, erythematous plaques, pustules, fetal growth restriction, placental insufficiency

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Introduction

Impetigo herpetiformis (IH) is a rare form of pustular pregnancy dermatosis, a group of disorders which also includes atopic eruption of pregnancy (AEP), prurigo of pregnancy (patients without atopic predisposition should be labelled prurigo of pregnancy than AEP),[1] polymorphic eruption of pregnancy (PEP), pemphigoid gestationis (PG), and intra-hepatic cholestasis of pregnancy (ICP). IH is classified as a subtype of generalised pustular psoriasis occurring exclusively during pregnancy.[2] The condition most commonly occurs during the last trimester and subsides in the postpartum period; there is a risk of recurrence during subsequent pregnancies.[3] Impetigo herpetiformis is a misnomer because the disease does not have a bacterial or viral origin. The clinical presentation of the disease might, in some cases, involve some systemic manifestations such as nausea, vomiting, fever and diarrhoea. Hypoalbuminemia, hypocalcaemia and low serum vitamin D levels are other severe life-threatening systemic manifestations associated with the disease. Life-threatening maternal problems are attributed to inappropriate disease management, resulting in long-lasting seizures secondary to hypocalcaemia. Fetal adverse effects may include fetal growth restriction or fetal demise, which are mainly attributed to placental failure, the exact reason of which is not clearly known.[4] Systemic and topical corticosteroids are the mainstay for IH treatment, while cyclosporin is reserved for steroid-resistant cases.[5]

Pathogenesis

The exact aetiology of IH is not yet clearly understood. Genetic background is one of the proposed hypotheses for disease development. It was supported by positive IH family history observed for some patients.[6,7] Further genetic analysis of the majority of patients with IH found that they are carriers of homozygous or compound heterozygous interleukin 36 rather (IL36) receptor antagonist (*IL36RN*) mutations, not commonly found in healthy skin.[3] This genetic hypothesis was supported by reports from Japan based on two IH cases with homozygous and heterozygous *IL36NR* mutations[8] and another report from China where a pregnant lady suffering from IH had *IL36RN* mutation.[9] Hypocalcaemia is one of the most common conditions associated with IH; however, its assessment as an underlying cause or sequelae of the disease is yet to be clarified. Probable underlying causes of IH-based hypocalcaemia are hypoparathyroidism,[10] hypoalbuminemia, low serum vitamin D levels, or malabsorption of ionised calcium; hypoparathyroidism is the most probable cause.[11] Several drugs like n-butylscopolammonium bromide[12] and uterine relaxant

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ritodrine hydrochloride[13] are among the drugs that might have a role in IH development.

Clinical presentation of IH

Impetigo herpetiformis (IH) is a rare, potentially life-threatening pregnancy-specific dermatosis that typically occurs during the third trimester. However, few cases of postpartum IH have been reported.[14] Lesions characterising the disease appear as erythematous patches and pustules arranged in marginal groups, first at the periphery then propagating centrally. Erosions, crusts, or impetiginisation may occur. Mucous membranes of the mouth, tongue, or oesophagus might be involved.[15] Nails are affected but less frequently. As mentioned earlier, hypocalcaemia and hypoparathyroidism are known IH-associated conditions.

Adverse maternal effects

Electrolyte imbalance is the primary concern regarding mothers with IH; alterations in serum calcium levels are chief manifestations,[16] causing life-threatening conditions like seizures and hypovolemic shock.[7] Laboratory findings may show hypoalbuminemia, hypocalcaemia, and iron-deficiency anaemia, along with leucocytosis and elevated ESR. IH associated-gestational hypertension has been reported in a patient at 32 weeks of gestation.[17] Disease recurrence is common and has been reported up to nine pregnancies for a young woman. Some recurrences were precipitated by pre-pregnancy use of combined oral contraceptive pills.[18]

Adverse fetal effects

Adverse fetal effects associated with IH include fetal growth restriction (FGR) primarily due to placental insufficiency, fetal demise, premature membrane rupture,[19] and premature delivery.[20] The exact mechanism of IH-associated placental insufficiency is unknown, however, some reports attribute it to an inflammatory process affecting the placenta, resulting in fetal hypoxia.

Diagnosis

The mainstay in IH diagnosis is the characteristic clinical picture of the disease, which consists mainly of erythematous plaques studded with marginal pustules usually starting on the extremities then propagating towards the trunk.[10] Laboratory findings may reveal leucocytosis, elevated ESR and CRP, and in severe cases, hypocalcaemia, hypoalbuminemia or low serum vitamin D levels. Bacteriological sampling of the pustular content is characteristically negative for pathogens (sterile pustules).[21] Histopathology of a skin biopsy may reveal psoriasiform (spongiform) pustules in the epidermis with neutrophil rich subcorneal infiltration in lymphocytes in the dermis.[2] A genetic examination may reveal *IL36RN* mutations encoding IL-36 receptor antagonists.[10]

Differential diagnoses

Differential diagnoses include acute generalised exanthematous pustulosis (AGEP), subcorneal pustular dermatosis, id reaction, and toxin-mediated erythemas. The characteristic clinical picture and histopathological findings help differentiate IH from the three conditions, however, differentiating IH and AGEP is more challenging. Some authors have suggested that AGEP maybe just a form of pustular psoriasis triggered by drugs or infections.[22] Nevertheless, some facts like disease development during the last trimester, unrelated to prior infection or drug intake, absence of fever and eosinophilia, positive history of IH in a previous pregnancy, and dramatic response to steroid therapy all favour IH diagnosis.[14]

Treatment strategies

IH treatment is usually challenging, mainly due to unstable maternal and fetal conditions. Another challenge results from the possible adverse effects of drugs used to treat the disease. Despite several effective IH treatments being reported, there are few evidence-based recommendations specific to efficacy or safety or every treatment intervention. Life-threatening disease complications like fluid and electrolyte imbalance, particularly hypocalcaemia, hypovolemia, and low serum vitamin D levels, should be corrected promptly before starting IH treatment.[20]

Systemic corticosteroids remain the mainstay treatment for IH patients; the starting dose for mild to moderate cases is usually 15–30 mg/day, increasing gradually to a maximum of 80 mg/day.[20] There was historical concern about a correlation between steroid therapy during early pregnancy and the occurrence of fetal cleft palate,[23] however, since IH happens typically during late pregnancy, corticosteroids are considered a safe treatment option.

Cyclosporin has been known as one of the effective therapies for IH treatment. It may be used in combination with systemic corticosteroids, which can be tapered when initiating cyclosporin therapy. It might also be used alone as a second-line drug for steroid-resistant patients. The usual recommended dose of cyclosporin ranges between 2.5–7 mg/kg/day depending on disease severity and treatment response.[24,25] There are safety concerns about cyclosporin use during pregnancy, however, studies on cyclosporin safety, conducted chiefly on renal transplant patients, found no renal impairment associated with drug use. Other studies found no significant association between cyclosporin use and premature rupture of fetal membranes or premature birth.[26] Cyclosporin is a selective immunosuppressive agent that attenuates T-cell-mediated responses by preventing interleukin-2 (IL-2) formation.[26]

The use of anti-TNF-α drugs, such as infliximab and adalimumab, was previously controversial because some researchers consider it among the best IH treatments, however, others advised against using such drugs during pregnancy despite published reports about successful IH treatment and outcome using infliximab.[27] The United States Food and Drug Administration (FDA) historically did not approve the regular use of these therapies during pregnancy but this advice has now been superseded by various international guidelines.[28]

Narrow band ultraviolet B (NBUVB) phototherapy, a safe intervention during pregnancy, can be combined with corticosteroids to treat IH, especially for poor steroid therapy response.[29] Some studies showed a decrease in serum folate levels, but this is not a significant concern since IH is a disease occurring during late pregnancy. Psoralen ultraviolet A (PUVA) photochemotherapy is not recommended as it may cause serious adverse fetal outcomes.[30] Antimicrobial therapy using cephalosporins may partially treat mild IH cases, even though the pustules harbour no organisms.[31,32] Clofazimine, macrolides and ampicillins are other antibiotics with known efficacy to treat IH.

Methotrexate, an antifolate, is not recommended for antenatal use, however, it is effective and safe for postpartum use.[33] Retinoids are also contraindicated during pregnancy because of the associated teratogenicity and can be used postpartum with concomitant use of appropriate contraception.[34]

Conclusion

Impetigo herpetiformis (IH) is a rare pregnancy-specific dermatosis and it may be considered as a subtype of generalised pustular psoriasis. The condition is associated with severe risks to both mother and child due to fluid and electrolyte imbalance and associated placental insufficiency

respectively. Diagnosis is established via the characteristic clinical picture, laboratory findings and histopathological examination of a skin biopsy. Treatment options include corticosteroids as first-line drugs and cyclosporin for severe and resistant cases. Other treatment options may include antimicrobial agents, phototherapy, biologic therapies, while methotrexate and retinoids can be used only postnatally because of the associated teratogenicity.

Further research areas

The exact pathology affecting the placenta in association with all pregnancy dermatoses, including IH, leading to placental failure and adverse fetal outcomes, is not yet clarified, hence, further research in this area may improve fetal outcomes.

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Contributorship

MMAA and KAMA were responsible for conceptualizing the study and reviewing the literature. AME, FK, and FH were involved in secondary data collection, interpretation of studies, and manuscript drafting. DMPB, WWT, and MSJ were critically analyzing literature and expert input in synthesizing knowledge and MNBMD and KXT finalizing the manuscript's content. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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