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Dermatological Disorders Associated with Pregnancy

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ABSTRACT

Introduction and purpose: Pregnancy is a remarkable and delicate period in a woman's life, marked by significant physiological adaptations to accommodate the growing fetus. These changes affect every organ system, including the skin. The aim of this review paper is to raise awareness and assist clinicians in recognizing, diagnosing, and effectively managing these distinct skin conditions associated with pregnancy.

Material and methods: An extensive examination of articles published in scientific journals was carried out through online research platforms PubMed and Google Scholar. We searched articles by entering keywords in appropriate configuration: "pregnancy dermatoses", "pemphigoid gestationis", "polymorphic eruption of pregnancy", "intrahepatic cholestasis of pregnancy", "pustular psoriasis of pregnancy", "atopic eruption of pregnancy".

Description of the state of knowledge: This diverse set of pregnancy-related skin conditions includes pemphigoid gestationis, polymorphic eruption of pregnancy, intrahepatic cholestasis of pregnancy, atopic eruption of pregnancy, and pustular psoriasis of pregnancy.

Summary: Early diagnosis and treatment are crucial to mitigate maternal and fetal complications, and in some conditions, prevent fatalities. Improving clinicians' in-depth understanding of these disease processes can enhance patient safety and quality of life during and after pregnancy.

Keywords: "pregnancy dermatoses", "pemphigoid gestationis", "polymorphic eruption of pregnancy", "intrahepatic cholestasis of pregnancy", "pustular psoriasis of pregnancy", "atopic eruption of pregnancy"

INTRODUCTION

Pregnancy-related skin conditions constitute a diverse and distinct set of dermatological disorders that are unique to the gestational and postpartum stages. These skin conditions develop due to the interplay of multiple factors within the body and skin during pregnancy. The main factors driving common skin changes during pregnancy are elevated hormone levels, increased intravascular volume, and physical skin compression from the growing uterus [1]. Proper understanding and recognition of these physiologic changes is essential for all clinicians caring for pregnant women, as many of these changes can mimic or predispose to pathologic skin conditions [2]. Misdiagnosis or failure to recognize these benign changes can lead to unnecessary stress, interventions, and potential harm for the mother and fetus [3]. The skin conditions unique to pregnancy comprise:

- pemphigoid gestationis,
- polymorphic eruption of pregnancy,
- intrahepatic cholestasis of pregnancy,
- pustular psoriasis of pregnancy
- atopic eruption of pregnancy [4].

This article presents a comprehensive review of the literature on each of the conditions mentioned above. This article aims to increase awareness of these pregnancy-related skin conditions and equip physicians with the knowledge needed to identify and manage them effectively.

Pemphigoid gestationis (PG)

Epidemiology and pathogenesis

Pemphigoid gestationis, previously known as herpes gestationis, is a rare and potentially severe subepidermal bullous autoimmune disease that arises specifically during pregnancy or the immediate postpartum period. The incidence of pemphigoid gestationis is 1 in 50,000 to 1 in 60,000 pregnancies. [5]. The most significant risk factor for PG is having it in a previous pregnancy. Based on various studies, pemphigoid gestationis typically manifests in the second or third trimester of pregnancy. Approximately 18% of the 117 PG patients first experienced

symptoms in the first trimester, 34% in the second trimester, another 34% in the third trimester, and 14% in the postpartum period [6]. In pemphigoid gestationis, the initial immune response is believed to originate in the placenta. The abnormal expression of human leukocyte antigen class II molecules in the placenta triggers the production of antibodies in the mother's immune system [7]. Class G antibodies (IgG) bind to the BP180 antigen found in the placenta, and cross-react with the same antigen found in the basement membrane of the skin, leading to the activation of the complement system cascade, resulting in the separation of the epidermis from the dermis, clinically manifested by the formation of blisters with a tight lid - a characteristic feature of PG [8].Pemphigoid gestationis is an autoimmune disease that occurs more often in individuals with the expression of certain HLA class II genes, specifically HLA-DR3 and HLA-DR4. The greatest risk to the mother is recurrence of PG in subsequent pregnancies, described in 30-50% of patients. There is also a higher risk of preterm birth (PTB) and having a baby too small for gestational age [9].

Clinical presentation and diagnosis

Pregnancy pemphigoid manifests clinically in the form of sudden onset of itchy papules and edematous erythematous lesions with subsequent formation of a cluster of vesicles, with which may or may not coexist tense blisters formed on an erythematous base. From the onset of itchy papules and plaques to the formation of large, tense blisters takes several days to 4 weeks [10]. The eruption typically starts on the umbilical region and can spread to involve the extremities, including palms and soles, in severe cases [11]. Mostly, they do not occupy the face or mucous membranes. The skin lesions usually resolve spontaneously in the last weeks of pregnancy. The diagnosis of pemphigoid gestationis can be confirmed by taking two skin samples: one for histological analysis and another for direct immunofluorescence testing (DIF). Histological examination of the early stage of pemphigoid gestationis reveals skin edema with perivascular infiltration of lymphocytes, histiocytes, and eosinophils. The blistering stage is characterized by the separation of the epidermis from the underlying dermis, resulting in blister formation. The DIF test makes it possible to detect deposits of antibodies and complement system proteins in skin sections. All patients have a pathognomonic linear deposition of the C3 component of the complement system along the basement membrane of the skin around the lesions [12]. The diagnosis of PG is also established by indirect immunofluorescence (IIF) and enzyme-linked immunosorbent assay (ELISA). ELISA has been found to have similar

specificity to IIF, but greater sensitivity [13]. The test finds application in the diagnosis and follow-up of disease activity, as well as in the evaluation of treatment efficacy [14].

Treatment

The primary objectives of treatment are to prevent the formation of new blisters and alleviate the associated itching. The initial therapeutic approach to prevent additional blisters is the topical application of potent corticosteroids [15]. When pemphigoid gestationis persists, systemic corticosteroid therapy is recommended. For pregnant women who do not respond to oral corticosteroids, intravenous immunoglobulins, azathioprine, and dapsone have been shown to be effective treatments. Antihistamines are the primary medication used to manage the associated itching. Pregnant women typically receive second-generation antihistamines, which carry a lower risk of sedation and anticholinergic side effects [16].

Polymorphic eruption of pregnancy (PEP)

Epidemiology and pathogenesis

Polymorphic eruption of pregnancy occurs in approximately 1 out of every 200 pregnancies, typically manifesting in the third trimester and being more common among first-time mothers. Polymorphic eruption of pregnancy is a self-resolving skin condition that can also occur after childbirth [5]. The exact cause of polymorphic eruption of pregnancy remains unclear. However, it is believed that the expansion of the abdomen during pregnancy can lead to stretching and damage of the connective tissue. This may expose certain skin antigens, triggering an inflammatory response and a cross-reaction against collagen found in the skin in other areas of the body [17]. Another hypothesis suggests that polymorphic eruption of pregnancy is an immune system response to fetal antigens circulating in the mother's bloodstream. The presence of fetal cells in the mother's bloodstream is believed to trigger an immune reaction analogous to a "graft versus host" response [18].

Clinical presentations and diagnosis

Polymorphic eruption of pregnancy typically presents as an intensely pruritic, erythematous, and edematous rash that first appears on the abdomen, often sparing the umbilical

region, and may spread to the thighs and buttocks [19]. The rash typically spreads to involve the limbs, chest, and back within a few days. However, the face, palms, and soles of the feet are usually spared. Over time, the lesions evolve from urticarial papules and plaques to more polymorphic papules, vesicles, and plaques [17]. The diagnosis of polymorphic eruption of pregnancy is primarily clinical, based on the characteristic morphology and distribution of the skin lesions, as well as the timing of their appearance during pregnancy. PEP has non-specific histopathology findings. In about 30-50% of cases, the epidermal lesions may involve edema between epidermal cells, thickening of the outermost epidermal layer, as well as excessive and abnormal keratinization.The dermis frequently exhibits non-specific changes, including perivascular and interstitial accumulations of lymphocytes, as well as the presence of edema, neutrophils, and eosinophils [17].

Treatment

The main objective of treatment is to alleviate the intense itching. The skin lesions often clear up on their own within 4 to 6 weeks. The initial treatment approach involves the use of topical corticosteroids with mild to moderate potency, along with emollient products and oral antihistamines. Topical corticosteroids of varying potencies, such as hydrocortisone 2.5% ointment or cream, desonide 0.05% ointment or cream, triamcinolone acetonide 0.1% ointment or cream, mometasone furoate 0.1% cream, or fluocinolone acetonide 0.025% ointment, may be used to manage the skin lesions. For cases of pruritus that do not respond to previous treatments, short-term administration of systemic glucocorticoids may be a safe and effective approach [13] [5]

Intrahepatic cholestasis of pregnancy (ICP)

Epidemiology and pathogenesis

The prevalence of ICP varies by geographic region, likely due to differences in genetic predisposition, susceptibility in ethnic groups, environmental factors and the number of reported cases. The overall incidence is approximately 0.1-2% of all pregnancies, with higher rates reported in countries like Chile, Bolivia, and Scandinavian countries. In Europe, the incidence is 1.5% or less. In the United States, the incidence is as low as 0.32% in white

populations to as high as 5.6% in Hispanic groups [5].Factors associated with an increased risk of developing intrahepatic cholestasis of pregnancy include personal or family history of the condition, underlying hepatobiliary diseases, and older maternal age. Factors linked to more severe cases of ICP include smoking, a prior cholecystectomy, a history of ICP in a previous pregnancy, and pre-existing diabetes [20]. Furthermore, research has identified that variations in genes responsible for bile transport proteins, the bile acid receptor, and the bile acid salt export pump may contribute to an individual's predisposition to intrahepatic cholestasis of pregnancy. Elevated levels of reproductive hormones, such as estrogen and progesterone, have also been linked to the development of intrahepatic cholestasis of pregnancy [21]. Other environmental factors, maternal characteristics, and liver diseases have been linked to increased rates of ICP. For instance, selenium deficiency and low vitamin D levels are associated with higher ICP incidence. Intrahepatic cholestasis of pregnancy is more common among women with multiple pregnancies, older maternal age, and a family history of cholestasis during pregnancy. Underlying liver conditions, including hepatitis C, progressive liver fibrosis, and nonalcoholic cirrhosis, have been linked to an increased risk of developing intrahepatic cholestasis of pregnancy [22].

Clinical presentation and diagnosis

ICP typically manifests in the late second or third trimester, with the majority of patients, around 80-86%, experiencing symptoms after the 30th week of pregnancy [23]. Intrahepatic cholestasis of pregnancy is characterized by the sudden development of severe, widespread itching, often affecting the palms of the hands and soles of the feet. The itching associated with intrahepatic cholestasis of pregnancy is typically more severe at night, but it gradually subsides as the pregnancy progresses. While there are no distinctive skin lesions associated with intrahepatic cholestasis of pregnancy, patients often develop secondary skin changes, such as excoriations and prurigo nodules, due to the intense itching [22]. Jaundice develops in 14-25% of patients, typically within 2-4 weeks of experiencing pruritus [24]. Patients with intrahepatic cholestasis of pregnancy may also experience systemic consequences of the condition, including light-colored stools, dark-colored urine, fatty diarrhea, impaired absorption of fat-soluble vitamins, and an increased tendency for bleeding [13]. The diagnosis of intrahepatic cholestasis of pregnancy is primarily based on the clinical presentation, including the characteristic sudden-onset, intense pruritus and elevated serum bile acids. According to a systematic review of 11 studies, elevated serum bile acid levels demonstrated a sensitivity of

91% and a specificity of 93% in the diagnosis of intrahepatic cholestasis of pregnancy [25]. Patients with intrahepatic cholestasis of pregnancy often exhibit elevated levels of liver enzymes, such as aminotransferases, alkaline phosphatase, and bilirubin (both total and direct) [25]. Hepatic imaging techniques, like ultrasonography, can be helpful in identifying and eliminating other potential causes of cholestasis that may occur during pregnancy.

Treatment

The main objective of treatment is to lower serum bile acid levels, thereby reducing maternal and fetal complications. Oral administration of ursodeoxycholic acid continues to be the preferred therapeutic approach. A randomized trial involving 125 patients found that UDCA significantly relieved pruritus compared to the placebo group [26]. Ursodeoxycholic acid has demonstrated the ability to lower maternal serum bile acid levels, restrict their transfer to the fetus and placenta, and enhance the function of bile acid transport mechanisms [27]. The Society for Maternal-Fetal Medicine (SMFM) 2021 guidelines recommend a starting dose of 10–15 mg/kg per day, which can be divided into two or three daily doses [28]. Early delivery is also recommended as a treatment approach for women with ICP. Currently, the SMFM recommends timing of delivery based on the level of total bile acids.

Atopic eruption of pregnancy (AEP)

Epidemiology and pathogenesis

Atopic eruption of pregnancy is the most common dermatosis of pregnancy, affecting approximately 1 in 300 pregnant women [29]. AEP is the most common pregnancy skin disorder, accounting for 50% of all pregnancy dermatoses [30]. The majority of patients with atopic eruption of pregnancy, around 75%, experience the condition during the first trimester of pregnancy. Additionally, a study examining 72 individuals with AEP revealed that over half (51%) of the women who experienced atopic lesions for the first time during pregnancy had a personal or family history of atopy [31]. The cause of this condition is unclear, and there are no recognized adverse effects for the mother or fetus. However, it often recurs in subsequent pregnancies [24].

Clinical presentation and diagnosis

Atopic eruption of pregnancy is characterized by severe itchiness accompanied by either patchy eczema-like lesions, known as the E-type, or papular eruptions, known as the P-type. The intense pruritus can lead to secondary effects like excoriations from scratching and superimposed bacterial or viral infections in both subtypes. [32] The diagnosis of atopic eruption of pregnancy is based on a clinical assessment, which involves ruling out other pregnancy-associated skin conditions. The diagnosis is determined by the characteristic pattern of skin lesions, the timing of their appearance early in the pregnancy, a personal or family history of atopic conditions, or elevated levels of IgE antibodies. Histopathology is generally nonspecific, with the epidermis revealing spongiosis, acanthosis, hyperkeratosis, or parakeratosis. The dermis is composed of perivascular lymphocytic infiltrate.

Treatment

Treatment of atopic eruption of pregnancy is primarily symptomatic. Atopic eruption of pregnancy typically responds rapidly to low-to mid-potency topical steroids [24]. Topical urea, 1–2% menthol and oral glucocorticoids may also provide relief [31].

Pustular psoriasis of pregnancy (PPP)

Epidemiology and pathogenesis

Pustular psoriasis of pregnancy is an infrequent skin condition that emerges during the latter half of pregnancy. The question of whether pustular psoriasis of pregnancy is unique to pregnancy or is merely aggravated by it remains a subject of debate [29].Pustular psoriasis that manifests during pregnancy is an uncommon variant of this skin disorder. Genetic factors appear to play a role in the development of pustular psoriasis of pregnancy, as cases have been reported in twins, siblings, and women with IL36RN gene mutations [33]. Some researchers propose that the hormonal changes and mineral imbalances common in late pregnancy, such as hypocalcemia, low vitamin D, and hypoparathyroidism, may contribute to the development of pustular psoriasis during this period [34].

Clinical presentation and diagnosis

The lesions typically manifest as symmetrical erythematous plaques in flexural areas, with circumferential rings of sterile pustules along the periphery. Pustular psoriasis of pregnancy most often arises during the final trimester of pregnancy [35]. The plaques then spread to involve the trunk and limbs, often sparing the hands, feet, and face. Over time, the plaques may develop erosions and crusting in the center. The appearance of these lesions is often sudden, and they may be accompanied by fever, chills, malaise, lymphadenopathy and sometimes nausea and vomiting [33]. Pustular psoriasis of pregnancy is distinct from other pregnancy-related skin conditions as it typically presents without the characteristic severe itching [36]. Diagnosis is primarily based on the clinical presentation, however histopathological examination and laboratory studies can aid in ruling out other conditions. The histopathological findings in pustular psoriasis of pregnancy resemble those observed in pustular psoriasis in non-pregnant individuals, showing spongiform pustules containing neutrophils, epidermal hyperplasia, and parakeratosis. Common laboratory findings associated with pustular psoriasis of pregnancy include elevated white blood cell count with increased neutrophils, low calcium levels, low albumin, reduced parathyroid hormone, decreased vitamin D, and an elevated sedimentation rate [13].

Treatment

Due to the potential for serious maternal and fetal complications, prompt treatment of pustular psoriasis of pregnancy is critical. Early initiation of comprehensive laboratory monitoring and management of fluid/electrolyte imbalances is critical in all cases, due to the risks of maternal infections, substantial fluid depletion, and electrolyte disturbances. The mainstay of treatment for pustular psoriasis of pregnancy is systemic glucocorticoids, given their ability to induce rapid improvement in skin lesions and prevent disease progression. Narrowband UVB phototherapy may also be used as an adjunct therapy in some cases. Acitretin, methotrexate, and cyclosporine have been utilized, but their use during pregnancy remains controversial due to the potential for teratogenicity. Biological agents, such as anti-IL-17 or anti-TNF-alpha therapies, have been reported to be effective in some case reports, but their safety in pregnancy requires further evaluation [37]. Pustular psoriasis of pregnancy commonly resolves on its own following childbirth. Inducing labor has also been reported as a potential treatment approach for patients with severe or treatment-resistant pustular psoriasis of

pregnancy who are close to their due date or at full term [38].

Summary

In summary, the specific dermatoses of pregnancy represent a diverse group of skin conditions that can arise during the gestational period. The majority of skin conditions associated with pregnancy resolve following delivery and only necessitate symptomatic management. However, there are specific treatments for some conditions (e.g. intrahepatic cholestasis of pregnancy, pustular psoriasis of pregnancy). This article provides a comprehensive review of the literature to help clinicians recognize, diagnose, manage, and treat these rare conditions.

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Aleksandra Kiełczewska: Conceptualization, Writing-rough preparation

Grzegorz Szcześniak: Methodology, Investigation Resources

Anna Kiełczewska: Formal analysis, Visualisation, Writing-review and editing

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