Pruritus in Pregnancy

Aleksandra A. Stefaniak1,2 · Manuel P. Pereira1 · Claudia Zeidler1 · Sonja Ständer1

Accepted: 5 December 2021 / Published online: 21 February 2022 © The Author(s) 2022

Abstract
Pruritus in pregnancy is a common and burdensome symptom that may be a first sign of a pregnancy-specific pruritic disease (atopic eruption of pregnancy, polymorphic eruption of pregnancy, pemphigoid gestationis, and intrahepatic cholestasis in pregnancy) or a dermatosis coinciding with pregnancy by chance. Despite its high prevalence, pruritus is often underrated by physicians, and data regarding the safety profiles of drugs for pruritus are very limited. In this review, we illustrate the epidemiology, possible pathophysiology, clinical characteristics, and diagnostic workup of various pregnancy-related diseases and discuss antipruritic treatments. The prevalence of pruritus in pregnancy demonstrates the importance of symptom recognition and the need for an holistic approach, taking into account both the potential benefits for the patient and the potential risks to the fetus.

Key Points

- Chronic pruritus, defined as an unpleasant sensation resulting in a need to scratch that lasts more than 6 weeks, is one of the major complaints during pregnancy.
- Patients presenting with pruritus require an exact workup to establish the proper diagnosis.
- The available treatment options require careful consideration of the potential benefits and risks for both the patient and the fetus in all cases.

1 Introduction

Chronic pruritus (CP), defined as an unpleasant sensation resulting in a need to scratch that lasts more than 6 weeks, is one of the major dermatological complaints during pregnancy. According to recent studies, 18–40% of pregnant patients experience pruritus [1–3]. In addition to being associated with pregnancy-specific conditions (atopic eruption of pregnancy [AEP], polymorphic eruption of pregnancy [PEP], pemphigoid gestationis [PG], and intrahepatic cholestasis in pregnancy [ICP]), pruritus may arise from dermatoses that coincidently develop during pregnancy, exacerbation of preexisting dermatoses, and physiological skin changes in pregnancy. This review aims to provide a comprehensive overview of dermatological and nondermatological conditions leading to CP in pregnancy. Clinical characteristics, diagnostic workup, and treatment options are discussed. When possible, we provide the US FDA letter label indicating pregnancy risk category (Table 1) [4]. The FDA letter grading system was retired and the Pregnancy and Lactation Labeling rule was instituted in 2015 to provide more qualitative information about medications in pregnancy. Therefore, drugs introduced after 2015 do not have letter labeling.

2 Physiological Skin Changes in Pregnancy

Pregnancy is associated with complex endocrinological, immunological, metabolic, and vascular changes that may influence every organ in the body, including the skin. Most of the changes that are important from the dermatological point of view are the result of hormonal alterations during gestation [5]. Almost all pregnant patients notice increased pigmentation (selective hyperpigmentation, secondary areola, linea nigra, and changes in nevi) [6]. Striae gravidarum, also known as stretch marks, occur in many pregnancies as a result of skin stretching combined with genetic and hormonal factors [5] and may be a cause of itch in pregnancy [7]. In addition, eccrine sweat gland and sebaceous gland activity increases and apocrine gland activity decreases in
pregnancy [5], which also may contribute to pruritus in this group of patients. Knowledge of and the ability to distinguish between physiological changes of the skin in pregnancy is necessary for a proper differential diagnosis from pathological symptoms and to avoid unnecessary treatment [5].

3 Pregnancy-Specific Pruritic Diseases

3.1 Atopic Eruption of Pregnancy

3.1.1 Definition and Epidemiology

In 2005, Ambros-Rudolph et al. [8] introduced the term AEP as an umbrella concept for benign pruritic disorders of pregnancy (clinical case 1). AEP covers all patients formerly diagnosed with eczema of pregnancy, prurigo of pregnancy, and pruritic folliculitis of pregnancy and is the most common dermatosis of pregnancy [8]. This term covers both patients with exacerbation of preexisting atopic dermatitis (about 20% of patients) and patients experiencing skin manifestations for the first time during pregnancy [8, 9]. Patients with a family history of atopic dermatitis are at risk of developing AEP [9], but the disease is frequently idiopathic.

Clinical Case 1

Clinical presentation A 40-year-old gravida 2, para 1, presented in the 17th week of gestation with severely pruritic (worst pruritus intensity of the previous 24 h on the numerical rating scale: 10/10) papular skin lesions that first appeared during the first pregnancy, with partial remission after delivery and exacerbation within the first week of the second pregnancy. The pruritus was generalized with additional pinprick sensation causing severe impairment of quality of life (Dermatitis Life Quality Index score: 13, ItchyQoL score: 2.9).

Workup On admission, the patient presented with disseminated inflamed papules, scratch excoriations, and scars sparing the face and scalp areas. Both direct immunofluorescence and ELISA were negative, and no relevant abnormalities were found in routine laboratory blood tests. The patient had a positive medical history of allergic rhinoconjunctivitis, allergies to pollens, and positive family history (sister) of atopic eruption in pregnancy.

Treatment and course Based on the clinical presentation, the diagnosis of atopic eruption of pregnancy was made. Treatment included narrow-band ultraviolet B phototherapy combined with systemic antihistamines (loratadine 10 mg twice daily), topical glucocorticosteroids (diflucortolone valerate 0.1% cream), and sufficient emollient therapy. This treatment regimen brought some relief of the pruritus (20% improvement).
3.1.2 Pathophysiology and Clinical Characteristics

The pathogenesis of atopic exacerbation during pregnancy is not fully understood. As in atopic dermatitis, it is mainly considered to be a T helper type 2 (Th2)-driven disease [10]. In pregnancy, a shift from Th1- to Th2-mediated immunity occurs, which may lead to exacerbation of atopic dermatitis during pregnancy and the manifestation of AEP [8]. AEP usually starts earlier than other pregnancy-specific dermatoses, potentially even at the start of the pregnancy (Fig. 1). Recent studies have reported that patients without an atopic background are more likely to experience onset of the disease in the second or third trimester [11].

Ambros-Rudolph et al. [8] outlined two clinical presentations of AEP.

1. **E-type (eczematous):** classical distribution of lesions, including eczematous eruption on the face, neck, presternal region, and flexure sides.
2. **P-type (prurigo):** the presence of small, pruritic, erythematous, often grouped papules disseminated predominantly on the extensor surfaces of the extremities and the trunk.

E and P types often coexist, and a generalization of the lesions is possible. The secondary lesions include excoriations from scratching and bacterial or viral superinfection (e.g., eczema herpeticum).

3.1.3 Diagnostic Workup

A detailed medical history and comprehensive dermatological examination of the entire skin, including mucosae,

Table 1 US FDA letter labeling assessing pregnancy risk category [4]

| Category | Description |
|----------|-------------|
| A | Adequate and well-controlled studies have failed to demonstrate risk to the fetus |
| B | Animal and reproduction studies have failed to demonstrate risk to the fetus, however, there are no adequate studies in humans |
| C | Animal reproduction studies have shown an adverse effect on the fetus, and there is a lack of studies in humans, but potential benefits may warrant use of the drug in pregnant patients despite potential risks |
| D | There is positive evidence of human fetal risk based on adverse reaction data based on studies in humans, but potential benefits may warrant use of the drug in pregnant patients despite potential risks |
| X | The risks involved in the use of the drug in pregnant patients clearly outweigh potential benefits |

Fig. 1 Onset of pregnancy-specific pruritic dermatoses
are necessary for a diagnosis of AEP. Patients with AEP usually present with early onset of eczematous/prurigo skin lesions (before the third trimester) with involvement of the trunk and limbs and may have atopic family or personal background. Histopathology is nonspecific and varies with the clinical type and stage of the disease. Therefore, skin biopsy is not indicated to make the diagnosis but may be helpful to exclude other causes of pruritus. Direct immunofluorescence (DIF) and indirect immunofluorescence results are negative. Laboratory test results indicate elevated serum immunoglobulin E (IgE) levels in about 30–70% of cases [12]. It is not clear whether IgE levels should be considered a diagnostic criterion as it has not been systematically studied in pregnancy [13]. Prick and patch tests are not recommended during pregnancy [14].

3.1.4 Treatment

Treatment of CP in AEP should focus on patient education and introducing a habit of sufficient emollient therapy, as this constitutes the basic dermatological therapy. Several compounds have been studied for their contribution to skin hydration and subsequent reduction in pruritus (Fig. 2) [15]. The second-line treatment of mild and moderate AEP involves topical glucocorticosteroids and systemic antihistamines. Narrowband ultraviolet B (UVB) is recommended as a second-line treatment in moderate and severe AEP, especially in early pregnancy [16]. For severe AEP manifesting with recalcitrant pruritus, short-term systemic treatment with glucocorticosteroids (prednisolone 0.5–2 mg/kg/day) may be considered.

In severe and very severe cases not responding to phototherapy and requiring prolonged courses of systemic glucocorticosteroids, immunosuppressive agents such as cyclosporine or azathioprine [17] should be introduced with caution and considering all possible risks and benefits. Azathioprine may be used off label in patients with severe uncontrolled AEP in whom other therapy options fail or when cyclosporine is contraindicated.

The anti-interleukin-4 receptor (IL-4R)-α antibody dupilumab may constitute a future further therapy option for AEP. Dupilumab inhibits signaling via IL-4 and IL-13 by inhibiting both IL-4 type 1 and 2 receptors on various immune cells [18, 19]. Data regarding its safety profile in case reports are promising [20, 21] but not yet sufficient. We recommend postponing the use of dupilumab in pregnancy until more experience and evidence becomes available.

3.1.5 Prognosis and Fetal Risks

The patient should be reassured of an excellent prognosis, as AEP is not associated with adverse fetal outcomes [22, 23]. However, depending on the parents’ atopic background, the child might be predisposed to atopic eczema [24], and the disease might recur in subsequent pregnancies.
3.2 Polymorphic Eruption of Pregnancy

3.2.1 Definition and Epidemiology

PEP is also known as pruritic urticarial papules and plaques of pregnancy and is a benign self-limiting pruritic inflammatory disorder with an incidence of 1:120–1:300 pregnancies [25–28]. It usually occurs in the third trimester of pregnancy or immediately postpartum (in about 15% of cases) [8]. The risk factors include first pregnancy (primigravida), excessive maternal weight gain, and multiple pregnancies [29, 30].

3.2.2 Pathophysiology and Clinical Characteristics

Stretching of the skin on the abdomen at the third trimester of pregnancy or over multiple pregnancies may activate dermal nerve endings, leading to pruritus [26, 31]; however, the exact pathogenesis of PEP remains elusive. Another theory suggests that damage to the collagen fibers may induce an allergic-type response, contributing to the development of PEP lesions.

The clinical presentation includes polymorphic skin lesions: highly pruritic urticarial papules that coalesce into plaques, small vesicles 1–2 mm in size (no bullae), widespread non-urticulated erythema, and targetoid and eczematous lesions generally sparing the periumbilical region [8, 26, 32]. The lesions might change in time with the development of the disease [33]. PEP usually starts in the abdominal region, within striae distensae, if they are present. The disease spreads to other body sites such as the thighs, buttocks, and the rest of the trunk; involvement of distal extremities is very rare [34].

3.2.3 Diagnostic Workup

There are no characteristic histological or immunofluorescence findings, and the diagnosis is purely based on the clinical presentation of the disease. As pre-bullous PG is clinically almost indistinguishable from PEP, prolonged follow-up of patients with PEP is recommended. If clinical uncertainty regarding the diagnosis exists, DIF to rule out pre-bullous PG should be performed.

3.2.4 Treatment

Since the disease resolves spontaneously within 4–6 weeks (independently of delivery), the treatment is symptomatic [29] (Fig. 1). Emollients, antihistamines, and topical glucocorticosteroids are considered first-line treatments. If the disease is extensive and pruritus does not resolve, systemic prednisolone may be considered.

3.2.5 Prognosis and Fetal Risks

PEP is a self-limiting disorder that does not affect the prognosis for the fetus or the pregnant patient. Recurrence is rare as it usually occurs only in first pregnancies [29].

3.3 Pemphigoid Gestationis

3.3.1 Definition and Epidemiology

PG, also known as herpes gestationis, is a rare self-limited pregnancy-associated bullous autoimmune disease. Although it usually occurs in the late third trimester, it may develop at any time during pregnancy or in the immediate postpartum [8, 35–39]. The first cases of PG complicating egg donation pregnancy have recently been reported [40, 41]. Beyond pregnancy, it can very rarely occur in association with trophoblastic tumors (choriocarcinoma and hydatidiform mole) [42–48]. The incidence is approximately 1:2000–1:60,000 pregnancies, depending on the prevalence of the human leukocyte antigen (HLA) haplotypes DR3 and DR4 [49, 50]. Relapse of the disease is common (in about 30–50% of patients) in further pregnancies, often occurring at an earlier stage and in a more severe form [26, 37, 38, 51, 52].

3.3.2 Pathophysiology and Clinical Characteristics

Despite the rarity of the disease, the pathogenesis is well-established and is considered to be similar to that of bullous pemphigoid with autoantibodies (immunoglobulin G1 [IgG1] subclass) directed against bullous pemphigoid antigen 180 (BP180) [53, 54]. BP180 is found both in the basement membrane zone of the skin and in placental tissue and fetal membranes. Of interest, the primary site of autoimmunity seems to be the placenta rather than the skin. Proteins presented in the placenta are recognized as foreign, which leads to the production of anti-placental IgG antibodies cross-reacting with BP180-2 proteins in the skin. Binding of these antibodies to the BP180 and BP230 in the hemidesmosomes of the dermoepidermal junction triggers an autoimmune response: complement activation with subsequent deposition of immunocomplexes, consecutive chemoattraction of eosinophil granulocytes, and—finally—degranulation, all of which result in disruption of the basement membrane and blister formation [54].

Clinically, the patient initially presents with severe pruritus and subsequent polymorphic inflammatory skin lesions. At first, erythematous urticarial papules and plaques develop on the abdomen, characteristically involving the periumbilical region, with later spread to other parts of the abdomen and extremities. The disease may involve the entire skin area and mucosal membranes [8, 36, 37, 52]. Later on, lesions...
progress to tense blisters similar to those seen in bullous pemphigoid [36].

3.3.3 Diagnostic Workup

DIF of perilesional skin together with clinical findings remains the gold standard for establishing the diagnosis of PG. DIF shows linear C3 and/or IgG deposits along the dermo-epidermal junction [36, 55]. Histology is not specific and is usually carried out to exclude other potential dermatoses. For biopsy, both lidocaine and epinephrine are considered safe for local anesthesia [16]. If the patient wants to avoid a skin biopsy, detection of circulating autoantibodies can be achieved using complement-binding tests, such as indirect immunofluorescence or enzyme-linked immunosorbent assay (ELISA). ELISA typically reveals circulating IgG antibodies against BP180 with 94–98% specificity and 86–97% sensitivity. ELISA is also useful to monitor the activity of the disease [56–58].

3.3.4 Treatment

The natural course of PG includes remissions and exacerbations during pregnancy, with characteristic flares during delivery or immediately postpartum resolving spontaneously within 4 weeks [9, 59]. The disease may also flare after abortion. Rarely, the disease recurs during menstruation or with use of oral contraceptives [60]. As the disease may cause fetal complications (such as preterm labor and intrauterine growth retardation), patients should undergo strict dermatological and gynecological follow-up during the entire pregnancy.

Treatment of PG mainly focuses on reducing pruritus and preventing the formation of new blisters. The treatment of choice is high-potency topical glucocorticosteroids and antihistamines. In patients with blistering disorders, non-fluorinated topical glucocorticosteroids are preferable, as the disrupted skin barrier may induce systemic absorption, and non-fluorinated topical glucocorticosteroids are known to cause fewer side effects [61, 62]. If topical glucocorticosteroids are contraindicated or the patient refuses treatment, therapy with calcineurin inhibitors may be introduced on small areas with caution (no more than 5 g/day for 2–3 weeks) [16, 63]. As a second-line treatment, short courses of prednisolone up to 0.5 mg/kg/day (preferably < 20 mg/day) should be introduced [16, 64]. If response to treatment is adequate (no new blister formation for 2 weeks), topical and systemic glucocorticosteroids should be slowly tapered to prevent fetus-related side effects [65, 66]. If PG remains refractory to treatment, or prolonged courses of steroids are required, other agents such as intravenous immunoglobulins, dapsone, and azathioprine < 2 mg/kg/day should be considered as steroid-sparing agents [65]. Intravenous immunoglobulins (FDA pregnancy category C) have a good safety profile for the patient and fetus and should be used either in monotherapy or as adjuvant treatment [66–74]. Dapsone (FDA pregnancy category C) is also considered safe during gestation. Glucose-6-phosphate dehydrogenase levels should be measured before initiation. Close blood monitoring with a special emphasis on methemoglobin because of the risk of maternal or neonatal anemia is of utmost significance [64]. Vitamin E 800 U/daily and C 1 g/daily should be supplemented to decrease the risk of potential side effects [75]. More information about the use of azathioprine and its safety profile may be found in Sect. 5.2.4.

Rituximab administered before conception may help to prevent the recurrence of PG in subsequent pregnancies, but rituximab has a long half-life, and patients are advised to avoid pregnancy 12 months after the last infusion [76, 77]. After delivery or abortion, the full spectrum of immunosuppressive agents should be considered.

3.3.5 Prognosis and Fetal Risks

Fetal prognosis is relatively good. The risks include preterm labor and intrauterine growth retardation and are most probably linked to the severity of the disease itself rather than the treatment [78]. PG is associated with an increased risk of other autoimmune disorders in the pregnant patient, especially Graves disease, which may be explained by the presence of HLA-DR3 and DR4 [36]. The disease tends to recur in subsequent pregnancies.

3.4 Intrahepatic Cholestasis in Pregnancy

3.4.1 Definition and Epidemiology

ICP is a liver disorder unique to pregnancy and has a reported incidence of 0.3–5.6% and ethnic, geographic, and seasonal variations [2, 79–85] (clinical case 2). A striking geographic variation is noted, with an incidence as high as 28% especially in patients with overt Araucanian Indian descent [86]. Mutations of ABCB4 (MDR3) involved in the biliary secretion of phospholipids have been studied in ICP and may play an important role, at least in some patients [87]. Diseases associated with ICP include gallstones [88, 89], hepatitis C infection [90, 91], preeclampsia, and gestational diabetes [92–94]. ICP is characterized by an inability to excrete bile salts from the liver, which increases serum bile acid concentration, causing pruritus (possibly because of the increased availability of brain opiate receptors [95]) and negatively influences the fetal prognosis. It is a reversible cholestasis that occurs in the second and third trimesters of pregnancy (> 30th week). Earlier onset has been sporadically reported [96, 97].
3.4.3 Diagnostic Workup

Diagnostic workup should focus on the exclusion of other clinical entities included in the differential diagnosis of pruritus in pregnancy. This includes seasonal variability and diet, and environmental factors such as atopic conditions and other dermatological disorders. The serum bile acid level was 12.2 μmol/l (reference value 0–6 μmol/l), with only marginally elevated aspartate aminotransferase (37 U/l; reference value 10–35 U/l), serum amylase (107 U/l; reference value 28–100 U/l), and triglycerides (236 mg/dl; reference value < 150 mg/dl).

Treatment and course

Based on the clinical picture and laboratory findings, the diagnosis of intrahepatic cholestasis in pregnancy was made. Therapy with ursodeoxycholic acid 500 mg twice daily and loratadine 10 mg twice daily was initiated. Emollients with polidocanol, urea, and menthol were recommended. The patient was lost to follow-up.

3.4.2 Pathophysiology and Clinical Characteristics

Potential etiopathogenetic factors include genetic (altered expression of hepatobiliary transport proteins), hormonal (especially estrogen levels), and environmental factors such as seasonal variability and diet [87, 98]. Recent studies have explored the role of alterations in gut microbiota and long-term therapy with vaginal progesterone preparations as potential risk factors for ICP [99, 100].

Clinical triad characteristics for this disease include severe pruritus, jaundice starting 2–4 weeks after the onset of pruritus, and elevated bile acids [82]. The disease is characterized by elevated serum bile acids in maternal blood (> 10 μmol/l) and abnormal liver function results (mainly serum transaminases) [101]. Although the disease is historically linked to jaundice [102], more recent data have indicated that yellowish or greenish pigmentation of the skin and whites of the eyes is reported in only about 10% of patients [103]. Pruritus classically begins on the palms and soles but may become generalized. Patients present without skin alterations apart from secondary scratch lesions. Pruritus might worsen with the development of the pregnancy. Other symptoms include steatorrhea and dark urine.

3.4.4 Treatment

ICP usually resolves spontaneously within 6 weeks after delivery [104]. The primary goal in the management of ICP is to reduce serum bile acid levels, which is proven to reduce pruritus, prolong pregnancy, and decrease fetal risks. The first-line treatment is the administration of ursodeoxycholic acid (UDCA) 15 mg/kg/day (not assigned an FDA pregnancy category) [105]. Although the PITCH study published in 2019 in The Lancet [106] suggested that UDCA may not be effective in preventing stillbirth, the newly published guidelines (2021) [107] highlighted weaknesses of the PITCH study (the administered dose of UDCA was not taken into consideration) and advocated for the use of UDCA in this group of patients. The role of the synergistic effect of rifampicin 300–1200 mg (FDA pregnancy category C) on bile acid clearance in severe ICP (bile acids > 100 μmol/l) is still being discussed [108–111] and should be considered when there is no improvement with UDCA alone. Early-term induction should be discussed with patients, especially after gestation week 37 (or sooner with documented pulmonary maturity) and if bile acid concentrations are > 100 mmol/l [79].

3.4.5 Prognosis and Fetal Risks

ICP has been associated with increased rates of fetal complications, perinatal mortality rates, stillbirths, low birth weight, preterm birth, and fetal distress during labor [102, 112–115].

4 Other Pruritic Conditions in Pregnancy

Pruritic dermatoses that are known to flare during pregnancy include psoriasis (especially pustular psoriasis), atopic dermatitis, dyshidrotic eczema, dermatomyositis, urticaria, mastocytosis, and lichen planus [116, 117]. Infections and infestations such as scabies and bacterial, mycological, and viral infections (including pityriasis rosea, HIV/AIDS, Zika, and coronavirus disease 2019 [COVID-19]) should also be part of the differential diagnosis of pruritus in the pregnant patient [118–120]. It is important for clinicians to keep these conditions in mind, as their management may
differ in pregnant patients. Some 20% of pregnancies are complicated with pruritus due to skin diseases, such as vulvar lichen sclerosus or irritant contact dermatitis, coinciding with pregnancy [8, 121, 122].

Pruritus may also result from physiological changes during pregnancy. Pregnancy alters glucose metabolism and predisposes patients to gestational diabetes. Although the exact pathogenesis of pruritus in diabetes is not known, it is likely that altered insulin levels in short-lasting diabetes mellitus cause skin dryness and subsequently pruritus [123–126]. According to a recent study, pruritus due to diabetes may complicate 0.68% of all pregnancies [2]. Abdominal stretching and leg edema together with increased sweat gland activity might also predispose to skin xerosis. Other possible causes of CP of non-lesional skin in pregnancy include hypothyroidism (1.02%) and chronic hepatitis B and C virus infection (0.34%) [2, 127].

Clinicians should be aware that pruritus without skin lesions may occur before the presentation of other symptoms, which is typical in the course of PG and ICP. Therefore, careful examination and prolonged follow-up should be considered in all pregnant patients with pruritus without skin lesions to avoid missing diseases that may impair fetal health.

5 Therapeutic Considerations

Treating pruritus in pregnancy remains a challenge requiring prudent consideration of the potential benefits to the pregnant patient as well as the possible negative effects on the fetus. If possible, specific topical and systemic treatments for the underlying etiology should be initiated (Table 2). Additionally, general pruritus-relieving measures, which include avoidance of factors that foster dryness of the skin, use of mild detergents, and sufficient emollient therapy should be taken into consideration [15] (Fig. 2).

5.1 Topical Treatment

5.1.1 Glucocorticosteroids

Topical glucocorticosteroids are usually considered as first-line treatment of CP if inflammatory skin lesions are present. According to a Cochrane review update [128], there are no causal associations between maternal exposure to low- or moderate-potency topical glucocorticosteroids (i.e., methylprednisolone aceponate) (Table 3) and pregnancy outcomes, including mode of delivery, congenital abnormalities, preterm delivery, and fetal death. However, caution is warranted with excessive use of potent or very potent topical glucocorticosteroids because a risk of low birth weight seems to correlate with the quantity of topical corticosteroid exposure (total dosage > 300 g during the entire pregnancy) [129].

5.1.2 Calcineurin Inhibitors

If usage of topical steroids is contraindicated or the patient refuses treatment, topical calcineurin inhibitors may be introduced with caution. They should be applied only on small areas and with no more than 5 g/day for 2–3 weeks or when needed [16, 63].

5.2 Systemic Treatment

5.2.1 Antihistamine Drugs

Several studies have evaluated the safety of antihistaminers during pregnancy [130–134]. The first-generation H1 antihistamine (sedative) chlorpheniramine (4 mg every 4–6 h; FDA pregnancy category B) can be administered in early pregnancy as first-line therapy. It is widely available and inexpensive and can be useful on an as-needed basis and/or before bed. Second-generation antihistamines (nonsedative) have a less sedating effect and fewer cholinergic side effects than first-generation agents. They should be introduced from the second semester on as they may incur a higher risk of malformations (neural tube defects, hypoplastic left heart syndrome, and tetralogy of Fallot) [134] when used in early pregnancy. Loratadine 10 mg once daily and cetirizine 10 mg once daily are considered second-generation antihistamines of choice in pregnancy [131, 133]. Data regarding the use of levocetirizine (FDA pregnancy category B) and fexofenadine (FDA pregnancy category C) are also reassuring [135, 136].

5.2.2 Phototherapy

Narrowband UVB is considered safe in pregnancy and is recommended as a second-line treatment, especially in early pregnancy, when other medications are contraindicated [16]. Although patients who have been exposed to high levels of UVB radiation do not have an increased risk of abnormal delivery outcomes, it is worth remembering that there is a paucity of studies regarding ultraviolet A (UVA) or UVB light therapy and pregnancy-related complications or long-term effects on the fetus. The use of UVB therapy was linked with low levels of serum folate, and folate supplementation (0.8 mg/day) should be recommended to reduce the risk of neural tube defects [137–139]. Patients are also at risk of developing melasma after UV exposure [140], so facial covering is advised.

5.2.3 Glucocorticosteroids

For severe cases of recalcitrant pruritus, short-term systemic treatment with glucocorticosteroids may be considered. Prednisolone 0.5–2 mg/kg/day is the corticosteroid of choice in pregnancy. Oral steroids should be used with caution in the first trimester of pregnancy because of the unclear association
### Table 2: Diagnostic features of, treatments for, and outcomes with pregnancy-specific dermatoses

| Disease | Clinical and diagnostic features | Treatment | Prognosis | Fetal risk |
|---------|---------------------------------|-----------|-----------|------------|
| **AEP** | Eczematous, papular and prurigo skin lesions | First line: emollient therapy<br>Second line: topical GCS and systemic antihistamines<br>Third line: narrowband UVB therapy<br>Fourth line: prednisolone, cyclosporine, azathioprine | Possible recurrence in subsequent pregnancies | Fetal prognosis is unaffected |
| **PEP** | Polymorphic skin lesions (urticarial papules that coalesce into plaques, vesicles, widespread erythema, targetoid and eczematous lesions); periumbilical region generally unaffected; never bullae | First line: emollient therapy, topical GCS and systemic antihistamines<br>Second line: systemic prednisolone | Rash usually resolves in 4–6 weeks independent of delivery; disease tends not to recur | Fetal prognosis is unaffected |
| **PG**  | Begins with pruritus, followed by skin lesions (urticarial papule and bullae); periumbilical region affected<br>DIF: linear IgG/C3 deposition at the basal membrane<br>ELISA: IgG antibodies against BP180 | First line: emollient therapy, topical potent GCS and systemic antihistamines<br>Second line: systemic prednisolone<br>Third line: azathioprine, intravenous immunoglobulins, dapson | Recurrences in subsequent pregnancies are common; long-term increased risk of Graves’s disease | Preterm birth, low birthweight |
| **ICP** | Classical triad: (1) pruritus; (2) jaundice (1–4 weeks after pruritus); (3) bile acids elevated (> 10 μmol/l) | Ursodeoxycholic acid (15 mg/kg/day); induced preterm delivery | Resolves spontaneously within 6 weeks after birth | High risk of preterm birth/stillbirth (up to 60%) |

*AEP* atopic eruption of pregnancy, *BP180* bullous pemphigoid antigen 180, *DIF* direct immunofluorescence, *ELISA* enzyme-linked immunosorbent assay, *GCS* glucocorticosteroids, *ICP* intrahepatic cholestasis in pregnancy, *IgG* immunoglobulin G, *PEP* polymorphic eruption of pregnancy, *PG* pemphigoid gestationis, *UVB* ultraviolet B
with orofacial clefts [141, 142]. Although some studies suggested that the use of glucocorticosteroids in pregnancy might be associated with lower birth body weight [143], single treatments of medium to high doses of glucocorticosteroids in the third trimester did not affect body size or cardiovascular risk factors of the offspring in long-term follow-up [144]. During pregnancy, long-term use of glucocorticosteroids may also increase the risk of gestational diabetes, preeclampsia, and even membrane rupture and preterm delivery.

5.2.4 Other Immunosuppressive Agents

In cases not responding to phototherapy and requiring prolonged courses of systemic glucocorticosteroids, steroid-sparing agents, such as cyclosporine (FDA pregnancy category C) or azathioprine (FDA pregnancy category D) [17] should be considered. When initiating cyclosporine A, the minimal possible dose should be used, and maternal blood pressure and renal function should be monitored closely. Data on the use of cyclosporine in dermatological conditions in pregnancy are sparse and are primarily derived from organ transplant recipients. The teratogenic risk among the offspring appears to be low, even though lower body weight in infants and premature labor have been reported. However, all these events might be associated with the patients’ medical conditions rather than with the drug itself [145, 146]. Azathioprine is considered relatively safe in pregnancy and has not been linked with teratogenicity [145, 147]. Data on the usage of azathioprine in pregnancy come mostly from studies of transplant recipients and patients with Crohn disease. In these groups, higher rates of pregnancy complications (low birth weight, prematurity, and jaundice) have been reported [148]. Analysis of the Swedish Medical Birth Register has indicated a possibility of a moderately increased risk of congenital malformations, specifically ventricular/atrial septal defects, and a higher risk of growth restriction and preterm delivery in infants exposed to azathioprine during early pregnancy [149].

5.2.5 Biologics and Small Molecules

Monoclonal antibodies targeting components of the immune system, such as cytokines or chemokines, are included in biological therapy. They were developed to treat primary autoimmune disorders, but a growing number of clinical

| Potency group | Corticosteroid |
|---------------|---------------|
| Medium potency (group 4) | Betamethasone dipropionate (spray 0.05%) |
|  | Clofertolone pivalate (cream 0.1%) |
|  | Flucinolone acetonide (ointment 0.025%) |
|  | Flurandrenolide (ointment 0.05%) |
|  | Fluticasone propionate (cream 0.05%) |
|  | Hydrocortisone valerate (ointment 0.2%) |
|  | Mometasone furoate (cream, lotion, solution 0.1%) |
|  | Triamcinolone acetonide (cream 0.1%; ointment 0.05% or 0.1%; aerosol 0.2 mg/2 second spray, dental paste 0.1%) |
| Lower-mid potency (group 5) | Betamethasone dipropionate (lotions 0.05%) |
|  | Betamethasone valerate (cream 0.1%) |
|  | Desonide (ointment, gel 0.05%) |
|  | Flucinolone acetonide (cream 0.025%) |
|  | Flurandrenolide (cream, lotion 0.05%) |
|  | Fluticasone propionate (lotions 0.05%) |
|  | Hydrocortisone butyrate (cream, lotion, ointment, solution 0.1%) |
|  | Hydrocortisone valerate (cream 0.2%) |
|  | Prednicarbace (cream, ointment 0.1%) |
|  | Triamcinolone acetonide (lotions 0.1%, ointment 0.025%) |
| Low potency (group 6) | Alclometasone dipropionate (cream, ointment 0.05%) |
|  | Betamethasone valerate (lotions 0.1%) |
|  | Desonide (cream, lotion, foam 0.05%) |
|  | Flucinolone acetonide (cream, lotions, oil 0.01%) |
|  | Triamcinolone acetonide (cream, ointment 0.025%) |
| Least potent (group 7) | Hydrocortisone acetate (cream 1%, 2.5%, lotion 2%) |

Table 3 Low to medium potency (groups 4–7) topical corticosteroid preparations (classified according to the US system) [154, 155]
studies are investigating biologics and small molecules as new treatments for pruritic dermatoses. They are considered a treatment option in moderate to severe disease phenotypes when conventional treatment is not tolerated or efficiency is limited. Unfortunately, data regarding the safety profile in pregnancy remain limited.

The humanized recombinant monoclonal antibody omalizumab (FDA pregnancy category B) binds specifically to the Ce3 domain of the IgE heavy chain and is used in the treatment of chronic spontaneous urticaria [150]. It is considered a safe and effective therapeutic option in pregnant patients refractory to antihistamines [151–153].

The anti-IL-4R-α antibody dupilumab is considered an effective option in the treatment of refractory atopic dermatitis. To date, only two case reports of treatment with dupilumab in pregnancy with good fetus and pregnancy outcomes have been published [20, 21]. We recommend postponing the use of dupilumab in pregnancy until more data regarding the safety profile are available.

To date, data regarding safety and efficacy are insufficient to recommend small molecules (such as neurokinin 1 and Janus kinase inhibitors) in the treatment of CP in pregnant patients.

6 Conclusion

In pregnancy, pruritus is the main dermatological symptom and should never be neglected. Patients presenting with pruritus need an exact workup to establish a proper diagnosis, which is not only essential for the wellbeing of the expectant patient but also to prevent negative outcomes for the fetus. Pruritus is the main symptom of pregnancy-specific dermatological diseases such as PEP, PG, AEP, and ICP but may also coincide by chance with other diseases or even physiological changes in pregnancy. In the algorithmic approach, the first step is to rule out other possible causes of pruritus; in the second step, the four specific dermatoses of pregnancy need to be differentiated [26]. Careful medical history with an emphasis on the location and temporal course of the pruritus often reveals important clues that, together with laboratory findings, may facilitate diagnosis and efficacious treatment. Treatment of pruritus in pregnancy requires prudent consideration of the benefits and risks of the available therapeutic regimens for the patient and fetus. All specialists involved (dermatologist, gynecologist, general practitioner, midwife) should cooperate closely to improve the management of pruritus in pregnancy.

Declarations

Funding No sources of funding were used to conduct this study or prepare this manuscript.

Conflict of interest AAS has no conflicts of interest that are directly relevant to the content of this article. MPP has served as an investigator for Trevi Therapeutics, is a consultant and/or member of an advisory board for AbbVie, Menlo Therapeutics, Novartis, P. G. Unna Academy, and Trevi Therapeutics. CZ has served as an investigator in clinical trials for Novartis, Janssen, Pfizer, UCB, Lilly, AbbVie, Boehringer Ingelheim, Sanofi, Regeneron, Leo, and Galderma; has received speaker honoraria from Dermalense, Beiersdorf, and Leo; and has received author honoraria from AbbVie. SS has served as an investigator in clinical trials for Dermalense, Galderma, Kiniksa, Menlo Therapeutics, Novartis, Sanofi, Trevi Therapeutics, and Vanda Therapeutics and as a consultant and/or member of an advisory board for AbbVie, Almirall, Beiersdorf, Bellus, Bionorica, Cara Therapeutics, Celgene, Clexio, DS Biopharma, Escent, Galderma, Leo, Lilly, Kiniksa, Menlo, Novartis, Pfizer, Sanofi, Trevi Therapeutics, and Vifor.

Ethics approval Not applicable.

Consent for participation/publication Consent was obtained for publication of patient photographs included in this manuscript.

Availability of data and material Not applicable.

Code availability Not applicable.

Author contributions All authors contributed significantly to the concept and planning, drafting, and revision of the manuscript. All authors approved the final submitted version of the manuscript.

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