Atopic Eczema and Itch in Pregnancy: Therapeutic Considerations

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Abstract With an estimated prevalence of 3 % in adults, atopic eczema is probably the most common cause for itch in pregnancy. Differential diagnoses of an itchy skin condition in a pregnant patient have to be considered carefully, because specific treatment is important to minimize risks for the mother and the child. Treatment is challenging, because safety data are limited for many drugs currently used to treat inflammatory dermatoses, such as topical steroids, calcineurin inhibitors, antihistamines, and systemic steroids in pregnancy. On the other hand, undertreatment of severely affected patients may lead to complications, such as superinfection.

Keywords Pregnancy · Atopic eczema · Atopic dermatitis · Eczema · Atopic eruption of pregnancy · Pemphigoid gestationis, intrahepatic cholestasis of pregnancy · Polymorphic eruption of pregnancy · Safety

Introduction

Although itch in pregnancy is relatively common, many dermatologists are not familiar with the differential diagnoses and for obvious reasons some are afraid to initiate adequate treatment for these women. Itch causes substantial distress in pregnant women, especially by aggravating pregnancy-related sleeping difficulties.

With a prevalence of approximately 3 % in the adult population [1], atopic eczema accounts for a significant proportion of itchy dermatoses in pregnancy, but almost any other pruritic skin condition can coincide with pregnancy. Nevertheless, the most important differential diagnoses are pregnancy-specific disorders: polymorphic eruption of pregnancy (PEP), pemphigoid gestationis (PG), intrahepatic cholestasis of pregnancy (ICP), and atopic eruption of pregnancy (AEP). Of note, pemphigoid gestationis and intrahepatic cholestasis of pregnancy are associated with impaired fetal outcome.

Because clinical trials in pregnant women are very difficult, almost any treatment available is off-label in pregnancy, leaving the risk to the prescribing doctor and the patient. As a result, pregnant patients very often are treated inadequately and left with substantial pruritus, disfigurement, and other symptoms of their disease, which leads to considerable distress.

Itchy Skin Conditions Unrelated to Pregnancy

Pregnant women are more likely to present with an itchy skin condition unrelated to pregnancy than with a specific dermatosis of pregnancy (Table 1). Apart from preexisting skin diseases, which may worsen in pregnancy (e.g., atopic eczema, lupus erythematoses, acne), common diagnoses to be considered in this age group include urticaria, insect bites, infestations, contact dermatitis, or polymorphic light eruption.

Whereas insect bites, contact dermatitis, or polymorphic light eruption are usually self-limiting during a period of 1–2 weeks, a substantial number of patients with urticaria need treatment for extensive swelling or severe pruritus. Simple measures, such as wet compresses, cool emollients, wet wrap dressings, or lotio alba aquosa, are helpful to alleviate

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Table 1 Pruritic dermatoses in pregnancy

Coinciding/preexisting disease	Pregnancy-specific dermatoses
Atopic eczema	Polymorphic eruption of pregnancy
Urticaria	Pemphigoid gestationis
Infestations	Intrahepatic cholestasis of pregnancy
...	Atopic eruption of pregnancy

pruritus in mild and self-limiting conditions. In more severe or prolonged cases, antihistamines or even systemic administration of corticosteroids may be needed; the choice of a specific drug depends on severity and gestational age.

If scabies is suspected, careful examination should be performed to identify *Sarcoptes scabiei* by dermatoscopy or microscopy of skin scrapings. In Europe, permethrin 5 % is recommended for treatment of pregnant women with scabies. Obviously, it is very important to look for potential carriers and to treat them accordingly to avoid the need for repeated courses of a neurotoxic drug.

Atopic Eczema

Atopic eczema is probably the most common itchy skin condition to persist or worsen in pregnancy. In our personal experience, a majority of patients present with worsening of their eczema during pregnancy, some get better, and some show no change. This is in line with some smaller studies [2, 3]. Looking into changes in severity of atopic eczema, it has to be considered that a lot of women reduce treatment by the time they get pregnant or even when they are planning to get pregnant. Of note, the clinical type of atopic eczema usually remains the same in pregnancy, e.g., there is no switch to a prurigoform type or manifestation in different body areas.

In contrast to other skin conditions (e.g., urticaria, psoriasis), undertreatment of atopic eczema increases the risk for complications, such as bacterial superinfection with *Staphylococcus aureus* or eczema herpeticum. Both are potentially harmful, especially when occurring close to delivery with a serious risk of transmission to the newborn. Furthermore, severe atopic eczema of the hands is of major impact in daily life, even more in the situation with a newborn and the need for regular hand washing. Visible disfigurement may cause additional psychological stress.

General guidelines for the treatment of atopic eczema also apply in pregnancy [4, 5]. Optimal basic therapy to restore barrier function is of particular importance to reduce the need for specific therapy to a minimum. From personal experience, women in the second and third trimesters of pregnancy usually need slightly richer emollients, preferably with moisturizers (urea, glycerol) compared with the nonpregnant state. Regular application of wet-wrap dressings with emollients is very helpful and safe. If colonization

with *Staphylococcus aureus* is massive or signs of superinfection are present, dressings can be soaked with antiseptics to reduce staphylococcal burden.

In moderate to severe atopic eczema, topical corticosteroids are necessary to stabilize the disease. A recent study with a large number of patients found no increased risk for fetal malformation, fetal death, or preterm delivery but found dose-dependent fetal growth restriction in women who were prescribed potent or very potent topical corticosteroids shortly before or during pregnancy. In contrast, mild to moderate topical steroids were not associated with any negative outcomes and were considered to be safe [6•].

In conclusion, if avoiding trigger factors, optimal basic therapy and other measures, such as relaxation techniques, are not sufficient to control atopic eczema in pregnancy, mild or moderate topical steroids can be used safely to ensure stable disease, reduce itch, and minimize the risk of superinfection.

Specific Dermatoses of Pregnancy

The specific dermatoses of pregnancy occur exclusively in pregnancy and the postpartum period; all are associated with pruritus. They were reclassified in 2006 by Ambros-Rudolph and coworkers [7] and now include polymorphic eruption of pregnancy (PEP), also known as pruritic papules and plaques of pregnancy, intrahepatic cholestasis of pregnancy (ICP), atopic eruption of pregnancy (AEP), and pemphigoid gestationis (PG), formerly named herpes gestationis (Fig 1). PEP and AEP are treated symptomatically with topical corticosteroids and antihistamines, whereas systemic steroids are usually needed to control PG. Patients with ICP may benefit from ursodeoxycholic acid. Because polymorphic eruption of pregnancy and pemphigoid gestationis are discussed elsewhere in this section, we will focus on intrahepatic cholestasis of pregnancy and atopic eruption of pregnancy.

Fig. 1 Detail showing tense vesicles on urticarial plaques in a patient with pemphigoid gestationis

Intrahepatic Cholestasis of Pregnancy (obstetric cholestasis)

Intrahepatic cholestasis of pregnancy results from hormone-induced cholestasis mostly in the third trimester. Prevalence in Europe is 1 in 50 to 1 in 500 pregnancies. Bile salts are insufficiently excreted and accumulate in serum. ICP is associated with severe pruritus; any skin changes are secondary to scratching. Mutations in biliary transporter proteins have been identified as predisposing genetic factors. In addition, hormones and exogenous factors are discussed as trigger factors. ICP is more common in multiple pregnancies and women older than age 35 years. ICP is associated with adverse fetal outcomes, because excessive bile salts in the serum of the mother may cause placental hypoxia and cardiac depression with an increased risk for preterm labor, intrapartum fetal distress, neonatal respiratory distress syndrome, and stillbirth.

Pruritus in ICP typically starts on the palms and soles and generalizes quickly. Any skin changes originate from extensive scratching and present as excoriations, prurigoform skin lesions, crusted erosions, and lichenification. Jaundice may be an additional sign in patients with severe cholestasis and extrahepatic involvement. Pruritus typically subsides quickly after delivery and laboratory abnormalities return to normal within a few weeks.

Laboratory investigations should include serum bile acid levels, because routine liver function tests often are within normal limits. Bilirubin is elevated in 10–20 % of patients. A recent study from Cork, Ireland investigated normal serum bile acid levels throughout pregnancy in 219 women excluding women with liver problems, alcohol intake, or excessive obesity body mass index (BMI) >40 [8]. Serum bile acid levels ranged in all but 3 of 219 pregnant women between 0.3 to 9.8 $\mu\text{mol/l}$ without any significant changes throughout pregnancy but a decrease after delivery. These results confirm current reference ranges with a cutoff at 11 $\mu\text{mol/l}$ for serum bile acids in pregnancy, which is slightly higher than the normal range of 0–6 $\mu\text{mol/l}$ in normal population. Levels >40 $\mu\text{mol/l}$ are considered as extensively elevated associated with adverse fetal outcome.

The mechanisms mediating cholestatic pruritus are only partially understood. Until recently, mainly bile salts and opioids have been implicated as pruritogens in cholestatic pruritus [9], but levels of bile salts and opioids do not correlate with intensity of pruritus. Antihistamines have little effect on cholestatic pruritus, ruling out histamine as relevant mediator.

Recently, lysophosphatidic acid has been identified as possible pruritogen in cholestatic pruritus based on an *in vitro* assay. A neuroblastoma cell line (SH-SY5Y cells) was stimulated with sera from cholestatic patients with and without pruritus and from healthy controls to identify pruritogenic substances. Subsequent intradermal injection of lysophosphatidic acid in a rodent animal model induced

dose-dependent itch as reflected by scratching of the animals [10•]. In addition, autotaxin, an enzyme responsible for conversion of lysophosphatidylcholine to lysophosphatidic acid, is increased in patients with ICP, further pointing toward a potential role of lysophosphatidic acid as pruritogen in cholestatic pruritus and a potential target for therapy [10•]. Furthermore, progesterone metabolites are discussed as possible mediators of cholestatic pruritus and of particular interest in cholestasis of pregnancy. Treatment of ICP with ursodeoxycholic acid not only lowers levels of serum bile acids but also of steroid disulfated progesterone metabolites through increased hepatobiliary secretion, which is paralleled by improving pruritic symptoms [11].

Ursodeoxycholic acid is used worldwide to treat ICP although this is not strictly evidence-based. Experimental data point toward a protective role of ursodeoxycholic acid on syncytial clot formation and villous edema associated with placental hypoxia in ICP [12, 13]. In addition, *in vitro* and animal studies have shown a protective effect of ursodeoxycholic acid on cardiomyocytes causing fetal arrhythmias [14, 15].

In small clinical studies, ursodeoxycholic acid in a dose of 750 mg/day has been found to decrease elevated liver enzymes and bile acids in patients with ICP as well as ameliorate pruritus [11, 16]. A recent larger trial from Great Britain [17•] included 111 women with ICP randomized to ursodeoxycholic acid (2×500 mg/day up to 2 g/day) versus placebo showed a significant reduction of pruritus (–16 mm on Visual Analog Scale [VAS] scale) in the treatment group, but this was below the –30 mm difference thought to be clinically significant; 32 % in the treatment group compared with 16 % in the placebo group had a reduction of at least 30 mm on pruritus VAS. Elevated liver enzymes and bilirubin levels were significantly reduced by ursodeoxycholic acid treatment, whereas the effect on bile acid levels was less pronounced and failed to reach statistical significance.

Looking at fetal outcome, babies born to mothers taking the placebo were significantly more likely to have meconium-stained amniotic fluid (a sign of fetal distress) compared with mothers taking ursodeoxycholic acid treatment. There was a trend to reduced gestational age at the time of delivery in the placebo group, but this was due to a higher number of twin pregnancies in this group. Looking at singleton pregnancies only, there was no difference in time of delivery. All other fetal parameters were not different between the groups as were adverse events.

In conclusion, ursodeoxycholic acid is a promising therapeutic option for the treatment of ICP with potential positive effects on fetal outcome and proven effect on maternal pruritus and laboratory values, although it remains “off-label use.” Cholestyramine and other bile acid exchange resins should be avoided, because they cause vitamin K malabsorption and increase the risk of hemorrhage.

Atopic Eruption of Pregnancy (prurigo gestationis, pruritus folliculitis in pregnancy)

Atopic eruption of pregnancy (AEP) summarizes a spectrum of pruritic disease in pregnancy, including prurigo of pregnancy Besnier and pruritic folliculitis of pregnancy. The term has widely been accepted in Europe, but some authors argue that the old classification was more specific and patients with true atopic eczema might be wrongly classified as AEP [18, 19].

AEP usually presents during the first or second trimester with pruritic eczematous or papular skin lesions. Eczematous lesions (so-called E-type AEP) present most frequently on face, neck, and flexural surfaces, whereas papular lesions (so-called P-type AEP) are mainly located on trunk or as prurigoform nodules on shins and extensor surfaces of the arms. Most women have a history of atopic disease or show typical minor signs of atopy [20]. An enhanced Th2 immune response in pregnancy is thought to trigger flare-ups of preexisting atopic eczema and AEP. Sometimes it is impossible to differentiate between atopic eruption of pregnancy and a flare up of preexisting atopic eczema with long remission or minimal symptoms in the past. Prognosis is good for mother and child, and recurrence in subsequent pregnancies is common.

Treatment of AEP is similar to atopic dermatitis with intensive basic therapy, topical corticosteroids and sometimes antihistamines. UVB phototherapy may be used in severe cases.

Antipruritic Treatment in Pregnancy

Basic Therapy

Emollients with urea, polidocanol, or menthol as mildly antipruritic agents should be used extensively. Wet-wrap dressing can substantially help to alleviate pruritus, especially when arms and legs are affected. General rules of avoiding trigger factors, especially irritants (soaps, detergents) and adequate clothing, are important issues to explain to the patient.

Topical Corticosteroids

Corticosteroid use in pregnancy has raised concerns about orofacial clefts, fetal growth restriction, and fetal adrenal insufficiency depending on timing and duration of corticosteroid exposure.

A recent Danish study looking at any corticosteroid use during pregnancy and its association with orofacial clefts found an association for dermatological corticosteroid use in the first trimester of pregnancy with cleft lip with or without

cleft palate (odds ratio [OR] 1.45; 95 % confidence interval [CI] 1.03–2.05). Of note, in the same study no association with orofacial clefts was observed for any other route of corticosteroid administration (oral, nasal, inhalant) [21•]. A clear dose-response or potency-response relationship for the use of topical corticosteroids was not shown.

Another recent study analyzing data from the U.K. General Practice Research Database specifically looked at the safety of topical corticosteroids in pregnancy [6•]. They identified 35,503 women prescribed topical corticosteroids during pregnancy. Compared with 48,630 unexposed women, there was no difference in orofacial clefts, preterm delivery, and fetal deaths, but use of potent and very potent topical corticosteroids was associated with fetal growth restriction.

A total of 53 orofacial clefts (1.6/1,000 live births) were identified in the whole group with no difference between exposed and unexposed women, stratification according to first trimester exposure, potency of steroids and type of orofacial clefts (lip/palate/combined) neither showed a relationship to corticosteroid use.

Looking at fetal growth restriction (234 babies in total) in a global analysis, an association with topical glucocorticoid use was not detected (adjusted relative risk [RR] 1.1; 95 % CI 0.8–1.5). In contrast, a stratified analysis showed a significant risk for fetal growth retardation with maternal exposure to potent and very potent topical corticosteroids (adjusted RR 2.08; 95 % CI 1.4–3.1), whereas no effect was shown for mild to moderate topical corticosteroids (adjusted RR 0.85; 95 % CI 0.59–1.21). A small increase of RR was seen according to dosage of potent/very potent topical corticosteroids. Because fetal growth restriction is associated with increased periparturient mortality and the risk of metabolic disease in adulthood, this potential side-effect has to be taken seriously. On the other hand, Chi and coworkers calculated a number needed to harm of 168 on the basis of their data, which means that treatment of 168 women with potent to very potent topical steroids results in one more case of fetal growth restriction.

There are no clinical trials concerning which topical steroid should be preferred if treatment is indicated. Theoretically, substances with high inactivation rates in the placenta (e.g., prednisolone, hydrocortisone) are preferable to substances with low or no metabolism by 11 β -hydroxysteroid dehydrogenase, such as budesonide or fluticasone, but systemic absorption and other mechanisms of inactivation as well as biologic activity also have to be considered. A new evidence-based guideline (S3) on topical steroids in pregnancy was published in 2011 [22•]. The authors recommend mild- to moderate-potency topical corticosteroids as first-line therapy and suggest that use of potent/very potent topical steroids should be limited to short periods of time, if possible. If not, close obstetrical monitoring of fetal growth should be

performed. However, the risks of systemic corticosteroid treatment (small-for-date babies and preterm delivery) are considered to be greater. On theoretical grounds, treatment with topical corticosteroids in areas with high systemic absorption (intertriginous areas, flexures, eyelids) should be limited to a minimum.

Systemic Corticosteroids

If systemic corticosteroid treatment is indicated in pregnancy, prednisolone is the corticosteroid of choice, because it is inactivated up to 90 % by 11 β -hydroxysteroid dehydrogenase in the placenta [23]. Halogenated corticosteroids, such as dexamethasone and betamethasone as well as methylprednisolone, pass the placental barrier to a greater extent and are used to enhance lung maturation or to treat the fetus if appropriate. Depending on nature and severity of disease, 0.5–2 mg/kg body weight are used as initial dose. Maintenance dose should be below 10–15 mg/day, especially during the first trimester. Main concerns with systemic corticosteroid use in pregnancy are orofacial clefts (especially first trimester use), fetal growth retardation (prolonged use), and impaired adrenal function in the newborn (prolonged peripartur use).

Increased rates of oral clefts have been observed in experimental models with rodents after systemic corticosteroids administration. In contrast, in a nationwide Danish study on 832,636 live births with 1,232 isolated orofacial clefts, among those 84 after exposure to corticosteroids in pregnancy, general use of corticosteroids (any route of administration) was not associated with orofacial clefts [21••]. When analyzing different routes of administration surprisingly use of dermatological corticosteroids was associated with an increased risk of cleft lip or a combination of cleft lip and cleft palate (OR 1.45; 95 % CI 1.03–2.05), whereas inhaled, nasal, or oral corticosteroid use in the first trimester of pregnancy was not associated with any increased risk. The overall prevalence of orofacial clefts in the Danish study population was between 0.9 and 1.17 in 1,000 live births. Of note, in 2,195 women with oral intake of corticosteroid use, no orofacial cleft was observed.

If duration of systemic corticosteroid therapy is less than 4 weeks, effects on fetal growth are unlikely, but long-term therapy is associated with fetal growth restriction and preterm delivery (Park-Wyllie, Mazzotta 2000, Gur, Diav-Citrin 2004).

Antihistamines

Older, sedating antihistamines are in worldwide use against nausea in pregnancy, therefore, they are preferably used to treat itch in pregnancy especially during the first trimester, although there is substantial data from accidental use in

early pregnancy that modern nonsedating antihistamines, such as cetirizine and loratadine, are safe to use as well. Guidelines recommend use of older sedating antihistamines as well as commonly used nonsedating ones, such as cetirizine and loratadine in pregnancy [24, 25]. During late stages of pregnancy, sedating antihistamines should be avoided because of the risk of fetal depression after delivery.

Conclusions

Any women presenting with an itchy skin condition in pregnancy should be investigated thoroughly to get an accurate diagnosis. In disorders with potential adverse effects on the fetus (esp. pemphigoid gestationis, intrahepatic cholestasis of pregnancy), an interdisciplinary approach is mandatory.

Close follow-up may be helpful to ensure adequate treatment while minimizing the risks of side-effects. It is important to discuss potential risks of treatment as well as the risks of undertreatment to come to a rationale decision with the patient and to avoid additional anxiety and stress.

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