

# THE DIAGNOSIS AND MANAGEMENT OF ECZEMA IN PREGNANCY

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## SUMMARY

Only four specific dermatoses of pregnancy are currently recognised, namely pemphigoid gestationis, polymorphic eruption of pregnancy, atopic eruption of pregnancy, and intrahepatic cholestasis of pregnancy. Atopic eruption of pregnancy is a somewhat confusing term and seems to be synonymous with atopic eczema. Three forms of atopic eczema in pregnancy are recognised: exacerbated atopic dermatitis, E-type atopic eruption of pregnancy, and P-type atopic eruption of pregnancy. The E- and P-types present during pregnancy. The mainstay of treatment is liberal use of emollients and topical corticosteroids. For widespread, incapacitating eczema not responding to optimised topical therapy, ultraviolet light, prednisone, cyclosporine or azathioprine should be considered.

## INTRODUCTION

The term 'eczema' is derived from the Greek word *ekzein* which literally means 'to boil out'. In patients with eczema the condition flares up ('boils out') periodically. Flares may be precipitated by irritation of the skin, infection, stress and other factors. The term 'dermatitis' refers to inflammation of the skin analogous to 'appendicitis', inflammation of the appendix, 'hepatitis', inflammation of the liver, etc. The terms 'dermatitis' and 'eczema' are nowadays generally regarded as synonymous. Some authors still use the term 'dermatitis' to include all types of cutaneous inflammation, so that all eczema is dermatitis, but not all dermatitis is eczema. The term 'dermatitis', however, should be used with care, as some patients regard it as implying an occupational cause. Unfortunately, there is still no international agreement on the use of these terms.

The commonest forms of eczema are atopic, seborrhoeic, allergic contact, primary irritant, photoallergic, phototoxic, nummular, asteatotic, stasis, dyshidrotic, and drug-induced eczema. Eczema associated with infection (e.g. dermatophyte, molluscum contagiosum), or infestation (e.g. scabies, pediculosis), so-called 'ide' reactions, are additional variants. In approximately 30% of cases eczema cannot be placed in one of these categories (unclassified eczema).

The term 'atopy' was first coined in medicine in 1923 by two allergists, Coca and Cook. They defined atopy clinically as a proclivity to develop allergic rhinitis, allergic asthma, and allergic urticaria. These patients possessed a distinctive antibody, named by them 'reagin' or 'skin-sensitising antibody' because intradermal skin

tests to a variety of inhalant allergens, e.g. trees, weeds, grasses, dust, moulds, and danders, elicited wheals at sites of some injections. When Sulzberger, in the early 1930s, encountered atopic patients with skin lesions that favoured antecubital and popliteal fossae, he initially called the disorder 'neurodermatitis of atopic type', then 'atopic eczema' and, finally, 'atopic dermatitis'. Atopic eczema, allergic rhinitis, conjunctivitis and asthma are atopic diseases that develop against a complex genetic background, the so-called atopic diathesis. The word atopic in the term atopic eczema is simply an indicator of the frequent association with atopy and the need to separate this clinical phenotype from the other forms of eczema which have other causes and distinct patterns.<sup>1-3</sup>

The specific dermatoses of pregnancy represent a heterogeneous group of ill-defined pruritic skin diseases unique to pregnancy. With the exception of pemphigoid gestationis (PG), the pathogenesis of these diseases is as yet unrevealed, and there is limited literature on their clinical characteristics. This lack of data is a result in part of the infrequency with which these dermatoses are seen at any one institution. As a consequence, their terminology has been confusing and misleading, and their classification is still the subject of ongoing controversy. Over the past 25 years a number of classifications have been proposed. In 2006, Ambros-Rudolph and co-workers<sup>4</sup> proposed a streamlined classification based on the results of a comprehensive retrospective two-centre study on 505 pregnant patients (Table I). Atopic eruption of pregnancy (AEP) was diagnosed in 256 cases, PG in 21, polymorphic eruption of pregnancy (PEP) in 109, and intrahepatic cholestasis of pregnancy (ICP) in 15. AEP is also known as eczema of pregnancy, atopic eczema of pregnancy and atopic dermatitis of pregnancy. Atopic eczema is the only form of eczema that is more common in pregnancy. Other forms of eczema may be present coincidentally.

## TYPES OF ATOPIC ERUPTION OF PREGNANCY

Three forms of AEP are recognised. For clarity the nomenclature suggested by the authors<sup>4</sup> will be adhered to.

**Exacerbated atopic dermatitis** [20% (52/256) in Ambros-Rudolph study<sup>4</sup>]

These patients have a history of atopic eczema before pregnancy, with an exacerbation during pregnancy. The morphology, distribution and evolution of skin lesions in atopic eczema are highly characteristic. During the infant phase (birth to 2 years) red, scaly lesions develop typically on the cheeks usually sparing the perioral, perinasal and diaper areas. The chin is typically involved and cheilitis is common. A small but significant number of infants develop a generalised eruption. Involvement of the scalp is not uncommon. Sometimes the cubital/popliteal fossae or other parts of the limbs are involved. During the childhood phase (2-12 years) eczema involves the flexural areas (i.e. the antecubital fossae and popliteal fossae) but also the neck, wrist and ankles. The extensor surfaces of the limbs are involved less frequently. During the adult phase (12 years and older) lesions involve areas similar to those

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**Table 1. Proposed rationalised classification of the specific dermatoses of pregnancy**

Proposed classification	Synonym(s)
Pemphigoid gestationis	Herpes gestationis
Polymorphic eruption of pregnancy	Pruritic urticarial papules and plaques of pregnancy Toxic erythema of pregnancy Toxic rash of pregnancy Late-onset prurigo of pregnancy
Atopic eruption of pregnancy	Prurigo of pregnancy Prurigo gestationis Early-onset prurigo of pregnancy Papular dermatitis of pregnancy Pruritic folliculitis of pregnancy Eczema in pregnancy
Intrahepatic cholestasis of pregnancy	Cholestasis of pregnancy Pruritus/prurigo gravidarum Obstetric cholestasis Jaundice of pregnancy

Adapted from: Ambros-Rudolph *et al.*<sup>4</sup>

**P-type atopic eruption of pregnancy** [33% (84/256) in Ambros-Rudolph study<sup>4</sup>]

These patients have a clear atopic background (i.e. family history of atopic eczema, allergic asthma, allergic conjunctivitis and allergic rhinitis), but their skin lesions first develop during pregnancy. These patients present with pruritic papules which may be localised or more widespread. Pruritus elicits scratching of lesions with excoriation and ulceration and, quite commonly, secondary infection.

Skin lesions of AEP commonly start during early pregnancy with first trimester onset in 36% of cases and second trimester onset in 40% of cases. In approximately one-third of cases in multiparous women a history of similar skin changes in previous pregnancies is reported. When a patient with atopic eczema becomes pregnant, the course of eczema cannot be predicted with certainty. Approximately 30% improve, 30% worsen and 40% remain the same.

involved during the childhood phase. Additionally hand eczema, periocular eczema and anogenital eczema are common. Morphologically, lesions may be acute, subacute or chronic. Acute eczema is characterised by oedema, erythema, vesiculation, exudation and, crusting. Chronic eczema is characterised by lichenification (Fig. 1). Lichenification refers to thickening of the skin with exaggeration of the normal markings. Enclosed are flat-topped, shiny, quadrilateral coalescing papules. Subacute eczema shows features overlapping with acute and chronic eczema. Lesions are commonly slightly elevated, red, brownish or purplish in colour with variable scaling.

In most cases pregnancy biases T-cell immunity towards a type 2 helper response. This is thought to be important for the continuation of normal pregnancy. However, a type 2 response is associated with atopy and this may explain why eczema deteriorates during pregnancy. Whether skin barrier function or expression of filaggrin changes during pregnancy is not known. Filaggrin is a protein needed for terminal differentiation in the epidermis. The gene coding for filaggrin is commonly mutated in eczema.



Fig. 1. Chronic (lichenified) eczema of the elbow region. Note excoriated, scabbed lesions.

**E-type atopic eruption of pregnancy** [47% (120/256) in Ambros-Rudolph study<sup>4</sup>]

These patients have a clear atopic background (i.e. family history of atopic eczema, allergic asthma, allergic conjunctivitis and allergic rhinitis), but their skin lesions first develop during pregnancy. These patients present similarly to those with exacerbated atopic dermatitis.

**DIAGNOSIS**

The diagnosis of eczema in pregnancy is based on the history and clinical findings. The patient may have a history of previously diagnosed eczema prior to pregnancy. A history of other atopic conditions such as hay fever, asthma and conjunctivitis is important in those patients where eczema presents for the first time during pregnancy. The morphology and distribution of lesions are of paramount importance. There is no laboratory test which indicates that the patient is suffering from atopic eczema. The serum IgE value has no diagnostic value. Skin biopsy in acute eczema shows a normal stratum corneum, marked spongiosis (intracellular oedema), and an infiltrate of lymphocytes, with or without eosinophils. Chronic eczema displays compact orthokeratosis, acanthosis of the epidermis (thickening), vertical streaking of collagen bundles in the papillary dermis, and lymphocytes in the superficial dermis. Subacute eczema reveals features of both the above. Skin biopsy is seldom indicated as a diagnostic procedure.

**COMPLICATIONS**

Little or no evidence exists to suggest that eczema directly affects fertility, rates of miscarriage, birth defects or premature birth.<sup>5</sup>

Eczema during pregnancy may be complicated by herpes simplex virus (HSV) infection. This condition is known as eczema herpeticum and is one form of Kaposi's varicelliform eruption. Intrauterine infection by HSV has not been reported. However, HSV infection may be associated with premature delivery, intrauterine growth retardation and miscarriage. HSV infection is diagnosed by Tzanck smear, biopsy of a vesicle and culture. Acyclovir is safe in pregnancy and prompt treatment is indicated.

*Staphylococcus aureus* colonises more than 90% of eczema lesions. Staphylococcal superinfection may exacerbate eczema and should be treated promptly. Active infection is characterised by pain, fever, erythema, oedema, red papules, pustules and crusting. Amoxycillin/clavulanic acid (Augmentin) or flucloxacillin (Floxapen) are the drugs of choice.

The risk of an atopic diathesis is increased in the offspring. The percentage of affected babies is not

known. Whether probiotics during pregnancy and/or lactation modify the risk of atopy in the newborn is controversial. Maternal smoking during pregnancy and lactation may increase the risk of atopic eczema.

## MANAGEMENT

Liberal application of emollients (moisturisers) remains an integral part of eczema management in all patients. Examples of 'creamy' emollients include Epizone A, Neutraderm and Neutraplus (also contains the humectant, 10% urea). More 'fatty' emollients are Epizone E and Oilatum gel. Taking tepid baths, avoiding soap, avoiding bubble baths and avoiding shampooing in the bath are all important additional management strategies. Moderate to potent topical steroids (e.g. betamethasone valerate (Betnovate), betamethasone dipropionate (Diprosone)) remain the mainstay of treatment for mild to moderate eczema.<sup>6</sup> Very potent topical steroids should preferably not be used. An antihistamine such as hydroxyzine hydrochloride (Aterax), 25 mg 1-3/day, may be indicated to control pruritus. Systemic steroids (0.5-1 mg/kg/day) are seldom indicated. Nevertheless, these drugs control eczema rapidly. A major risk is flare of the eczema when the drug is stopped. There is little evidence to support the association of cleft lip and palate in humans. Oral steroids may be linked to fetal growth restriction. Much of the evidence for this comes from their use in patients with asthma.<sup>7</sup> If optimisation of topical steroids fails to control disease, treatment with narrowband ultraviolet light (UVL) (311 nm) is a safe second-line treatment in pregnancy.

Topical calcineurin inhibitors (CNIs), such as tacrolimus and pimecrolimus, are increasingly used as second-line agents for eczema. Pimecrolimus (Elidel) is available in South Africa. The manufacturers advise avoidance of these drugs during pregnancy. The bioavailability of the topical CNIs is limited and its use has not been associated with fetal anomalies. Systemic tacrolimus is not teratogenic and congenital malformations are not reported. Intrauterine growth restriction may occur. If eczema remains poorly controlled in spite of optimal first-line treatment, including UVL, topical CNIs may be considered. Use should be restricted to localised areas.

If systemic treatment is indicated cyclosporine (2.5-3 mg/kg/day) is another option. These patients need close monitoring in a hospital setting by dermatologists and obstetricians – full blood count, renal function and blood pressure. The drug should be used for the shortest duration possible – preferably less than 6 months. This is to avoid the risk of renal impairment in the mother. There are no specific data on cyclosporine for atopic eczema in pregnancy. Cyclosporine does cross the placenta, but information from organ transplantation suggests that it is relatively safe.

Another important second-line treatment is azathioprine (50-150 mg/day). In non-pregnant patients disease severity is reduced by approximately 37%. This drug crosses the placenta. Use of azathioprine during pregnancy has been associated with miscarriage, preterm delivery and fetal growth restriction. The fetus is protected from the teratogenic effects of the drug. The fetal liver lacks the enzyme that converts azathioprine into active metabolites. Azathioprine may rarely be associated with neonatal leucopenia, pancytopenia or inhibition of neonatal haematopoiesis. This may be predicted by maternal leucopenia in the third trimester. All patients receiving this drug need a regular haematogram and liver function tests. In patients whose eczema is controlled with azathioprine or cyclosporine before pregnancy, careful counselling and liaison with obstetricians is mandatory.

Methotrexate is an effective drug in moderate to severe eczema. This drug is contraindicated in pregnancy and breastfeeding mothers.

It must be emphasised that liberal use of emollients, correct use of topical corticosteroids and sometimes UVL, form the basis of the treatment of choice in most patients with eczema in pregnancy.

A useful website for information about the teratogenicity of systemic medication in pregnancy is [www.otispregnancy.org/](http://www.otispregnancy.org/)

## DIFFERENTIAL DIAGNOSIS

In the differential diagnosis of AEP, PEP, ICP and other forms of eczema should be considered.

**Polymorphic eruption of pregnancy** commonly appears during the third trimester of pregnancy.<sup>8</sup> PEP occurs in 0.4-0.8% of pregnant women. The eruption is most frequently seen in primigravidas. Lesions may be localised or more widespread. The eruption commences characteristically on the lower abdomen and/or proximal thighs, particularly within or adjacent to the striae distensae, with periumbilical sparing. With disease progression, the eruption may involve all parts of the body including the palms and/or soles, and the face. Morphologically, lesions are mainly urticarial (red, oedematous patches), but vesicular lesions and target lesions may also be seen. A target lesion shows two components, namely an outer reddish plaque with central dusky discoloration. Urticarial, vesicular or targetoid lesions are extremely uncommon in AEP. Hyperacute eczema may occasionally appear urticarial and/or vesicular.

PEP is associated with a higher prevalence of male babies, and a greater incidence of caesarean section. The significance of such male preponderance remains unexplained.

Histology shows epidermal changes, such as focal spongiosis and parakeratosis, in one-third of cases. There is variable oedema of the superficial dermis. A superficial infiltrate of lymphocytes is noted and lymphocytic vasculitis is occasionally encountered. Direct and indirect immunofluorescence are negative. The latter feature distinguishes PEP from PG (Fig. 2).



Fig. 2. A patient with pemphigoid gestationis. Reddish plaques, some of which are crusted, are present on the abdomen. Note involvement of the umbilicus.

**Intrahepatic cholestasis of pregnancy** was evident in 15 patients in the Ambros-Rudolph study.<sup>4</sup> These patients present with pruritus. Eczema is not a primary feature. Secondary changes related to scratching are evident. These include excoriations, excoriated papules

(prurigo papules) and eczematization. The histology and indirect immunofluorescence findings are nonspecific. Serum bile acids are elevated. The incidence of prematurity and stillbirths is increased. Liberal application of emollients and an antihistamine (e.g. Aterax) usually alleviate symptoms.

**Allergic contact dermatitis** was diagnosed in 11 patients (10.5%) in the Ambros-Rudolph study.<sup>4</sup> The incidence of allergic contact dermatitis is not increased in pregnancy. Nickel, a component of costume jewellery, is the commonest cause of allergic contact dermatitis (Fig. 3). Widespread involvement related to autosensitization may sometimes be confused with AE. Treatment of allergic contact dermatitis is along the same lines as AD, namely emollients, topical steroids, and sometimes UVL. Systemic steroids are seldom indicated.



Fig. 3. Chronic (lichenified) eczema on the abdomen. Note the prominent papular element. Patch testing with nickel was positive.

**Autoimmune progesterone dermatitis (AIPD)** is an uncommon form of eczema that occurs cyclically related to the luteal phase of the menstrual cycle.<sup>9</sup> Lesions are usually eczematous, but may also be urticarial, bullous or erythema multiforme-like. The eruption is induced by hypersensitivity to endogenous progesterone. Lesions may be localised or generalised. Pregnancy may worsen or improve the condition. Topical steroids are the treatment of choice.

Miscellaneous skin diseases coinciding with pregnancy in the Ambros-Rudolph study are listed in Table II. An extensive electronic literature search revealed no data on eczema in HIV-positive pregnant patients.

## DISCUSSION

AEP is the only form of eczema that occurs more commonly in pregnancy. Pregnancy, together with infection, stress and trauma are all factors that may exacerbate eczema. Other forms of eczema are not more common in pregnancy. Hyperacute eczema, which is uncommon in atopic eczema, may sometimes be confused with PEP and even PG. Intrahepatic cholestasis of pregnancy with a considerable component of prurigo papules may be confused with P-type AEP.

The mainstay of treatment is emollients and topical steroids. Systemic treatment is indicated in severe cases. Prednisone is then the drug of choice, especially if control is possible with relatively low dosage. When unacceptably high levels of corticosteroids are required to achieve disease control, the use of steroid-sparing immunosuppressive medications may become necessary. Cyclosporine or azathioprine are the drugs of choice. The regimen of systemic treatment requires

**Table II. Miscellaneous skin diseases coinciding with pregnancy observed in the Ambros-Rudolph study (N = 104)**

Inflammatory disease	54 (52%)
Pityriasis rosea	14
Acne (involving face and trunk)	13
Urticaria (other than drug induced)	8
Psoriasis	6
Lichen planus	5
Lupus erythematosus	3
Haemorrhagic pigmented dermatosis	2
Leukocytoclastic vasculitis	1
Linear IgA dermatosis	1
Pemphigus vulgaris	1
Cutaneous infections/infestations	27 (26%)
Viral	8
Mycotic	7
Scabies	6
Multiple arthropod bites	4
Bacterial	2
Drug reactions	12 (11.5%)
Morphology: exanthema/urticaria	6/6
Caused by antibiotics/NSAIDs/other drugs	4/3/5
Contact dermatitis (with secondary spreading)	11 (10.5%)

Adapted from: Ambros-Rudolph *et al.*<sup>4</sup>

close collaboration between the obstetrician and the dermatologist.

For the foreseeable future the proposed classification and algorithmic approach (Fig. 4 – see next page) will assist physicians to diagnose and treat the pruritic dermatoses of pregnancy. It is not a question of academic lumping and splitting, but of best serving the pregnant patient with pruritus who requires urgent clinicopathological correlation of her condition and possibly associated fetal risks.

## Declaration of conflict of interest

The author declares no conflict of interest.

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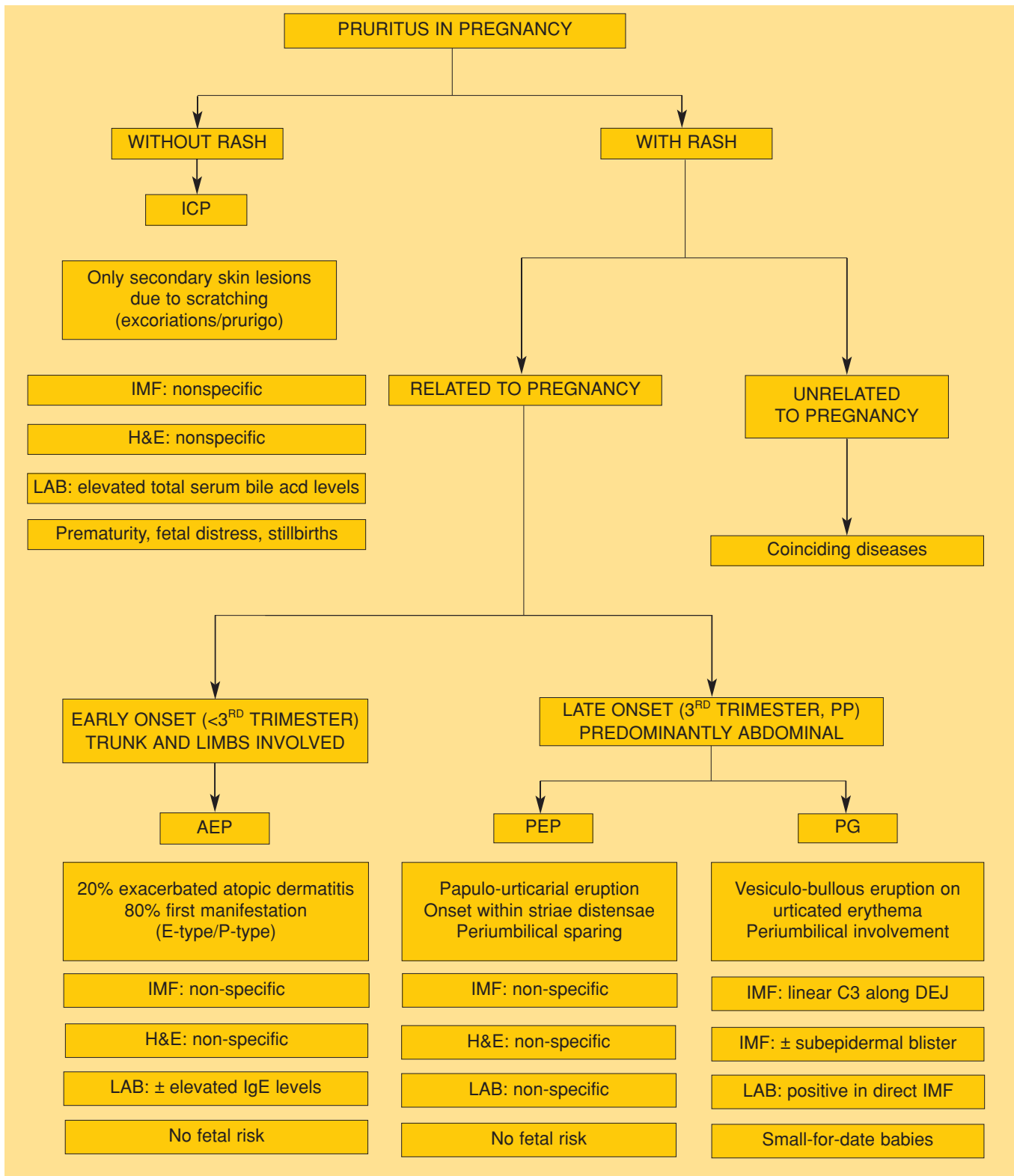


Fig. 4. Algorithm for differential diagnosis of pruritic skin diseases in pregnancy. ICP – intrahepatic cholestasis of pregnancy; IMF – immunofluorescence microscopy; H&E – hematoxylin-eosin; LAB – laboratory investigations; PP – post partum; AEP – atopic eruption of pregnancy; PEP – polymorphic eruption of pregnancy; PG – pemphigoid gestationis; DEJ – dermoepidermal junction.

Adapted from: Ambros-Rudolph *et al.*<sup>4</sup>