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Review Article

Atopic Eruption of Pregnancy: A Recent, but Controversial Classification

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Abstract

Introduction: Atopic Eruption of Pregnancy (AEP) has recently been introduced as a new disease complex in a recent reclassification and it is the most common dermatosis of pregnancy. It encompasses Atopic Eczema (AE), Prurigo of Pregnancy (PP) and Pruritic Folliculitis in Pregnancy (PFP).

Material and methods: The authors carried out a literature search in Medline using Pub med, investigating what is presently known about the classification, etiopathogenesis, diagnosis, management and prognosis of AEP.

Results: AE during pregnancy includes women who already have eczema, but experience an exacerbation of the disease during pregnancy and women with their first manifestation of AE during pregnancy. The biases T cell immunity towards a type 2 T helper response is important for continuation of a normal pregnancy, but worsens the imbalance already present in most atopic patients. About 25% of patients improve and more than 50% experience deterioration during pregnancy. PP has been reported in all trimesters of pregnancy and has been associated with obstetric cholestasis in women with an atopic background. PFP is a rare specific dermatosis of pregnancy that develops usually during the second or third trimesters.

Conclusion: Although the concept of AEP is developing rapidly, the notion of AEP enclosing other specific dermatoses of pregnancy remains controversial. It is necessary to clarify through prospective large-scale studies the relationship between PP, PFP and AE.

Keywords: Atopic dermatitis; Atopic eruption of pregnancy; Dermatoses of pregnancy; Pruritus; Narrow band Ultraviolet B (UVB); Psoralen Plus Ultraviolet a (PUVA)

Introduction

Pregnancy has many complex endocrinological, immunological, metabolic and vascular changes, which may influence the skin in various ways [1-3]. Skin findings in pregnancy can be classified as physiologic skin changes, alterations in pre-existing skin diseases and the specific dermatoses of pregnancy [4].

Atopic Eruption of Pregnancy (AEP) has recently been introduced as a new disease complex in a recent reclassification of dermatoses of pregnancy [4-7] and it is the most common pregnancy dermatosis. [7,8]. This condition can be defined as skin changes associated with positive personal and/or family history of atopy (eczema, hay fever or allergic asthma) and/or elevated serum IgE levels using Hanafin and Rajika's criteria [6]. It encompasses Atopic Eczema (AE) during pregnancy, Prurigo of Pregnancy (PP) and Pruritic Folliculitis in Pregnancy (PFP). Significant overlap, both clinically and histopathologically was demonstrated among patients with AE, PP, and PFP [4,7]. It comprises both patients with patchy eczematous features [1] (E-type AEP; 47% of AEP), whereas one-third of patients present with papular lesions (P-type AEP). The latter occur as a small disseminated erythematous papules or prurigo-type nodules [4,7,9], mostly located on the shins and arms [1] (P—type AEP; 33% of AEP) [4].

Material and Methods

The authors carried out a literature search in Medline using Pub med, for all epidemiological studies published as original articles up to April 2014, investigating what is presently known about the classification, etiopathogenesis, diagnosis, management and prognosis of AEP.

Results

Etiopathogenesis

During pregnancy there is an immunologic state, whereas natural homeostasis exists between antigenically different tissues [1,10,11]. To prevent fetal rejection, normal pregnancy is characterized by a lack of strong maternal cell-mediated immune function and Th1 cytokine production interleukin (IL) (IL-2, IL-12, inter feron-gamma) [1,2,11] is reduced. There is a dominant humoral immune response and Th2 cytokine production (IL-4, IL-10) [1,7,11]. This biases T cell immunity towards a Th2 cytokine response is important for continuation of a normal pregnancy [8,11]. Although, the etiology of AEP is not yet fully elucidated, a Th2 response during pregnancy worsens the imbalance already present in most atopic patients [8,10,12]. It is unknown if the skin barrier function or expression of fillagrin changes during pregnancy [8,12]. It was postulated that the persistence of the placental Th2 drive may be a major factor for

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the increasing prevalence of allergic diseases over the past 30–40 years [7]. A recent study indicated that it is more the intrinsic ('non allergic') than the extrinsic (IgE-associated) eczema that is affected by pregnancy [2]. Patients with intrinsic AE, as opposed to those with the extrinsic type, have no associated respiratory disease, showing normal total serum IgE levels, no specific IgE and negative skin prick tests to aeroallergens or foods [13]. The regulation of IgE in normal pregnancy has not been adequately clarified and the significance of mild IgE elevations must be clarified in the future [13].

Diagnosis

AE is the only form of eczema that is more common in pregnancy and includes women who already have eczema, but experience an exacerbation of the disease during pregnancy. This accounts for approximately 20% of AE, sometimes leading to erytrodermia and women with their first manifestation of eczema during pregnancy, accounts for the remaining 80% of cases [5,7,14,15]. This high prevalence of AE probably is caused by the use of minor criteria of atopy in the diagnosis of the eczema and the accuracy of which is difficult to confirm retrospectively and consequently needs to be confirmed in the future [15]. These patients present with atopic skin changes for the first time during pregnancy, but they often have a history of atopic diathesis and often have first degrees with eczema, asthma, and/or hay fever [14]. Although AE manifests throughout pregnancy, affecting all three trimesters, it usually occurs much earlier than the other specific dermatoses of pregnancy. Skin lesions of AE commonly start during early pregnancy with first trimester onset in 36% of cases and second trimester onset in 40% of cases [5,7,8,14]. A recent study indicated that 46% of females with AE experience deterioration of the disease in pregnancy or in relation to their menstrual cycle [16,17].

One third of women have history of similar eruption in previous pregnancies [14,18]. There is a personal history of atopy in 27% of pregnant females with AE, a family history of atopy in 50% of cases and an infantile eczema in 19% of the offspring [17,18].

The diagnosis of eczema in pregnancy is based on the history and clinical findings [5]. The patients may have a history of previously diagnosed eczema prior to pregnancy [5]. A history of other atopic conditions, such as hay fever, eczema, or allergic asthma is important in patients where eczema presents for the first time during pregnancy [5,12,16,19,20]. Acute lesions, such as pruritic, erythematous papules and vesicles, or extensive weeping areas covered with serous exudates may be present, as well as subacute and chronic lesions, including excoriated papules, plaques, scaling, and lichenification [7,21,22]. Typical atopic sites, which are usually involved, are face, neck, anterior chest, and flexural surfaces of extremities [7]. If AE is presenting for the first time during pregnancy the rash is usually much milder [14]. There are no laboratory tests which indicate that the patient is suffering from AE [8]. The serum IgE value has no diagnostic value [5,21]. Skin biopsy is seldom necessary [5].

Differential diagnosis includes in particular the other specific dermatoses of pregnancy [18]. The sparing of striae distensae and the significantly earlier presentation help to differentiate AEP from polymorphic eruption of pregnancy, whereas normal total serum bile acid levels help to differentiate AEP from intrahepatic cholestasis of pregnancy [7,19]. Moreover, dermatoses coinciding with pregnancy, like scabies, pityriasis rosea, allergic rashes, drug eruptions, and rashes secondary to as viral or bacterial infection must be excluded [7].

PP affects approximately 1 in 300 to 1 in 450 pregnant females [18]. Although PP has been reported in all trimesters of pregnancy, it usually starts at approximately 25–30 weeks of gestation and it persists until delivery [18]. It manifests with grouped, intensely pruritic papules over the extensor surfaces of the extremities, and occasionally on the abdomen [4]; with disease progression, the trunk and extremities are equally involved. Excoriations and crusting secondary to scratching are always seen and nodular lesions, similar to those of prurigo nodularis are often present. The disease usually resolves in the immediate postpartum period, although lesions may occasionally persist for up to 3 months. Recurrence with subsequent pregnancies is variable. The pathogenesis of PP has not been elucidated [3,10]. PP has been associated with obstetric cholestasis in women with an atopic background, based on the report of an association between personal and family history of AE and serum IgE elevations in PP [3,10]. However, some patients with PP only have minor criteria of atopy [15,18] and the association between PP and atopy was not confirmed in a prospective study on more than 3000 pregnant women with pruritic diseases of pregnancy [4]. PFP is a rare specific dermatosis of pregnancy (> 30 cases reported) that develops usually during second or third trimester [18]. This disease is usually misdiagnosis as infectious folliculitis [10,12]. PFP resolves spontaneously by delivery or one month postpartum, but may recur in subsequent pregnancies [16]. The lesions are pruritic follicular erythematous papules and/or acneiform pustules, which predominate on the trunk and less often on the extremities [4,10]. The exact etiology of PFP is unclear, but it has been hypothesized that PFP could be a form of hormonally induced acne, although the comedonal component that is typically seen in steroid acne is missing in PFP [4,10]. A recent reclassification of PFP under AEP was based on only one case [12,18]. The association of PFP and atopy has not been confirmed yet and this classification is much controversial [4].

Management and treatment

When possible, women should be advised before conception about avoiding irritants and allergens, the use of emollients and how to apply treatments [8,23]. Emollients remain an integral part of eczema management in all patients and should be applied several times a day to prevent skin dryness [8,17]. It is important to find an emollient that suits the individual patient. Urea (3–10 %) and anti pruritic additives (menthol, polidocanol) can be safely employed during pregnancy [7].

Taking tepid baths, using mild, non alkaline synthetic detergents capable of replacing cutaneous lipids and avoiding bubble baths are all important additional strategies [5,17,23]. Emollient cream should be applied to the skin while still damp from the bath [7,24].

When it is necessary to treat eczema it is better to apply low potency corticosteroids, for short periods [17,23,25]. The hazards of adverse events with corticosteroids are increased in areas with high absorption, such as genitals, eyelids and flexures [25]. Topical corticosteroids are usually applied once daily and they should always be used in combination with moisturizers [17]. Emollients, together with topical corticosteroids for several days will usually lead to quick improvement of skin lesions [1]. There aren´t studies available

to establish if newer lipophilic topical corticosteroids, such as mometasone furoate, fluticasone propionate and methylprednisolone aceponate are associated with less risk of fetal growth restriction [25]. However, a better side effect profile for use in pregnancy is suggested. If the rash cannot be suppressed sufficiently, stronger topical steroids may be used in low doses and for short periods by dermatologists [9,17], but they may be associated with a rebound flare when stopped [8]. Systemic corticosteroids have a greater bio disponibility than topical corticosteroids, but they also have more potential for fetal toxicity than topical corticosteroids, namely reduction in fetal birth weight and an increase in preterm delivery [25]. Prednisolone 30 mg daily may be required initially, with the dose tapered over 1 week [7,25]. If needed for longer, the maintenance dose should not exceed 10 mg/day in the first trimester. Side-effects, such as maternal hypertension and gestational diabetes mellitus are rare, because corticosteroids in AEP are usually used as short-time therapy (less than 4 weeks) [7,25]. In rare cases when a high-dose therapy over many weeks is necessary, fetal growth should be monitored by ultrasound [9,19].

Oral steroids have been associated with cleft lip and palate defects in mice and fetal growth retardation in patients who used oral steroids for chronic autoimmune diseases [9]. Nevertheless, it remains unknown whether the effects of maternal disease contributed more to fetal retardation than those of oral steroids [9,19]. The current evidence suggests a lack of association between their use by the mother and the development of cleft lip or palate defects, preterm delivery and fetal death [9,18].

When eczema remains uncontrolled despite optimization of topical steroids some patients may also benefit from narrow band Ultraviolet B (UVB), which is considered the safest second-line treatment for gestational AE [10]. This has been shown to reduce disease severity by more than 30% in a randomized control trial [8]. Although UVB is safe in pregnancy, psoralen plus ultraviolet A (PUVA) should not be used as a first-line treatment because of its potential adverse effects on the fetus [5,10].

The main symptom of AE is itch, which can be bad enough to interfering with sleep [5,17,26]. The oral antihistamines may help to improve the itch [17,25,27]. The antihistamines considered safe for use in pregnancy are the non-sedating antihistamines loratadine and cetirizine [14,25,27]. The old sedating antihistamines, such as, clemastine, Dimethindene, (dex) chlorpheniramine are usually considered safe and are recommended for use in pregnant women; hydroxyzine should be avoided [14,25,27].

The new topical imunomodulators such as tacrolimus and pimecrolimus are not approved for use in pregnancy [7,8]. If systemic agents other than oral steroids are needed for several/ recalcitrant AD, cyclosporine is the safest option [11] and this should be used for the shortest duration possible, usually inferior to 6 months, in order to avoid the increasing risk of renal impairment in the mother [8]. Cyclosporine crosses the placenta, but information for organ transplantation suggests that it is relatively safe in pregnant women [8].

Another second line drug is azathioprine, which readily crosses the placenta and its uses during pregnancy has been associated with miscarriage, preterm delivery and fetal growth restriction [8]. However, the fetus seems to be protected from teratogenic effects, because the fetus's liver lacks the enzyme that convert azathioprine into active metabolites and no association with congenital malformations in humans exists [8,18].

Methotrexate, another alternative therapeutic in severe cases is contraindicated in pregnancy and breastfeeding mothers [8,18].

Complications

Little or no evidence exists to suggest that eczema affects fertility, rates of miscarriage, birth defects or premature birth [5]. Eczema during pregnancy may be complicated by Herpes Simplex Virus (HSV), a condition known as eczema herpeticum [5,28,29] and HSV infection may be associated with premature delivery, intrauterine growth retardation and miscarriage [5]. Consequently, prompt acyclovir treatment and obstetric evaluation is warranted. Aciclovir is secure and should be used if there is strong clinical suspicion of eczema herpeticum to minimize fetal risks [5,28]. Bacterial infections are an important cause of exacerbation of atopic dermatitis and should be treated promptly to avoid further deterioration [8], mainly caused by Staphylococcus aureus [5]. Super infected AE may require systemic antibiotics; penicillin, cephalosporins and macrolides are safe in pregnancy [18,29,30]. Topical antibiotics, such as bacitracin or neomycin, are sometimes used, but may cause skin sensitization. Mupirocin and fusidic acid seem to be less sensitizing, but are more expensive [14,23].

Prognosis

Pregnancy seems to have an effect on the prognosis of eczema in most women with this disease. About 25% improve and more than 50% experience deterioration at any stage of pregnancy and a slightly higher rate is seen in the second trimester [8]. There are approximately 10% of flares in the postpartum period [8].

Conclusion

The specific dermatoses of pregnancy represent a heterogeneous group of ill-defined pruritic skin diseases unique to pregnancy [3,5,15]. Their terminology has been confusing and there are many controversial issues [5,15,18]. Although, the concept of AEP is developing rapidly, the notion of AEP enclosing other specific dermatoses of pregnancy remains controversial, especially because some PP patients and the vast majority of PFP patients' don´t have an atopic background [18]. In the future it is also important to study if AE developing for the first time in pregnancy represents "intrinsic" and/or "extrinsic" (IgE-mediated) dermatoses and establish its postpartum prognosis [18,20]. The diagnostic criteria for AE in pregnancy need to be reviewed, in order to allow a more precise confirmation of the prevalence of AE. It is also necessary in the future years to elucidate the position for environmental and/or food allergens in the etiopathogenesis of AEP, and to clarify through prospective large-scale studies, the etiology and the relationship between PP, PFP and AE [18,20].

Dermatologists, obstetricians and primary care practitioners should be aware of the clinical characteristics of these disorders and the potential maternal/fetal risks and with treatment.

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