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Atopic Dermatitis in Pregnancy: Current Status and Challenges

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Atopic dermatitis (AD) is the most common pregnancy dermatosis. This evidence-based review article provides an evaluation of AD in gestation. Our literature search revealed 4 epidemiologic studies on AD in pregnancy, and a total of 55 articles that provide the basis for this review. The limitations of epidemiologic studies included herein are critically reviewed. The management of AD in gestation is reviewed with an emphasis on drug safety. Further studies are required to determine whether it is the intrinsic ("nonallergic" or "atopiform dermatitis") and/or extrinsic (IgE-associated) AD that is affected by pregnancy, and to establish the postpartum prognosis of "new atopic dermatitis" (AD presenting for the first time in pregnancy). A revision of the diagnostic criteria will allow a more accurate confirmation of the prevalence of AD, and especially "new atopic dermatitis," in pregnancy as well as differentiation of AD from specific dermatoses of pregnancy, such as prurigo and pruritic folliculitis. Addressing the above issues and unraveling the etiopathogenesis of AD in pregnancy will help clarify a suggested overlap with the above specific dermatoses.

Target Audience: Obstetricians & Gynecologists and Family Physicians

Learning Objectives: After the completing the CME activity, physicians should be better able to correctly diagnose and safely treat atopic dermatitis in pregnancy; differentiate atopic dermatitis from other pregnancy dermatoses; and appraise the controversies and challenges in the field.

Atopic dermatitis (AD) is a common gestational dermatosis and needs to be differentiated from other dermatoses, including the specific dermatoses of pregnancy.^{1,2} Specific dermatoses of pregnancy include herpes (pemphigoid) gestationis, polymorphic eruption of pregnancy (PEP) (also known as pruritic urticarial papules and plaques of pregnancy), prurigo of pregnancy (PP), and pruritic folliculitis of pregnancy

(PFP).³ The above historic classification of specific dermatoses was challenged by Shornick who suggested classifying intrahepatic (obstetric) cholestasis of pregnancy (ICP) in specific dermatoses and PFP under PP.⁴ A recent reclassification⁵ that included ICP in the specific dermatoses of pregnancy and grouped AD, PP, and PFP under "atopic eruption of pregnancy" (AEP) has been debated,⁶ and the concept of AEP challenged.⁷ Still, little is known about the etiopathogenesis of AD in gestation, PP, and PFP.

METHODS

Extensive searches were undertaken to identify all articles, abstracts, and communications relevant to AD in pregnancy in all languages over the past 35 years,

The authors, faculty and staff in a position to control the content of this CME activity and their spouses/life partners (if any) have disclosed that they have no financial relationships with, or financial interest in, any commercial organizations pertaining to this educational activity.

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using the following search engines: MEDLINE/Pubmed, Ovid, Cochrane, and Embase. We also hand-searched the bibliographies of each included article. Other sources included proceedings and abstracts of symposia, theses, textbooks, and monographs. We also searched databases and sources relevant to drug safety in pregnancy, such as the United States Pharmacopeia Dispensing Information, Teratogen Information Service, Reproductive Toxicology Service, The American Academy of Pediatrics reviews, and Briggs' textbook. All articles selected for inclusion in this review were evaluated by all authors independently with regard to their evidence-based contribution to this field. Key search words included "atopic dermatitis," "atopiform dermatitis" (AFD), "eczema," "pregnancy," "gestation," "maternal," "risk factors," "diagnostic criteria," and "IgE" (immunoglobulin E). The search revealed 4 important epidemiologic studies^{5,8-10} that will be discussed herein and are summarized in Table 1. Two of these studies used Hanifin and Rajka's diagnostic criteria for AD,¹¹ whereas the other 2 used the UK Working Party's criteria.¹²

CLINICAL FEATURES

Most pregnant patients with AD present with lesions on the flexural aspects of the extremities,⁶ although truncal involvement is not uncommon.⁵ Less common presentations are follicular, facial, hand/foot eczema, and eczema of the nipple and/or areola.⁹ Up to 2% of breast-feeding mothers develop eczema of the areola and/or nipple, and approximately half of these have AD.¹³ The prevalence of several important (xerosis) or associated features (keratosis pilaris, atypical vascular responses, ocular/periorbital changes, hyperlinear palms, ichthyosis, perifollicular accentuation, lichenification/prurigo lesions) of AD¹⁴ has not been reported in recent studies on AD in gestation.^{5,9,10} AD can develop bacterial (typically from *Staphylococcus aureus*) or herpetic superinfection (eczema herpeticum) in pregnancy,^{13,15} although there is no epidemiologic data on this. Cases of recurring AD in pregnancy due to sensitization caused by contact allergens, such as ultrasound gel, have been reported,¹⁶ but the role of allergens in the pathogenesis of AD in pregnancy has not been systematically investigated. Worsening of hand eczema in the postpartum period is often secondary to use of diapers and other irritants during direct infant care.¹ The differential diagnosis of gestational AD is shown in Table 2. The differentiation of AD from PP, PEP, PFP, and ICP can be challenging, especially when

the latter entities present with eczematous clinical features in early gestation.

As shown in Table 2, a clinical overlap was suggested among gestational AD, PP, and PFP, indicating a close relationship among these entities. These diseases were grouped together under a new disease complex (AEP) in a recent study.⁵ The study indicated that AEP starts earlier in gestation (onset before the third trimester in 75% of patients) than other specific dermatoses of pregnancy and comprises both patients with widespread eczematous features and papules (E-type AEP; 47% of AEP) and typical prurigo lesions (P-type AEP; 33% of AEP). As per study, 80% of AEP patients never had AD, but were viewed as atopic based on personal and/or family history of atopy and/or elevated serum IgE levels. However, as noted by Cohen and Kroumpouzou,⁶ the clinical overlap in the study is based mainly on historic data (personal or family history of atopy and/or dry skin) from medical records, which can be hard to verify in a retrospective study, as well as serum total IgE elevations, which should not have been used as a diagnostic criterion without IgE measurements in a control group of pregnant patients (mentioned in the section "diagnostic criteria"). Furthermore, a significant number of PP patients satisfied only minor criteria of atopy^{5,9} or never had AD.¹⁸ The association between PP and atopy was not confirmed in a large prospective study on 3192 pregnant women who were followed up for pruritic skin disease.¹⁸ Ingber indicated that the clinical presentation of pruritic papules on the extensor aspects of the extremities in PP is not the distribution of widespread and papular types of AD and suggested that AEP should be restricted to the widespread and papular types of AD in pregnancy.⁷

EPIDEMIOLOGIC EVIDENCE

As shown in Table 1, the methodology used in the studies (retrospective vs. prospective, hospital- vs. population-based, questionnaire vs. doctor inspection, U.K. Working Party's vs. Hanifin and Rajka's diagnostic criteria) was inconsistent, which makes comparisons among these studies challenging. Although an older prospective study had not showed an increased incidence of AD in gestation,¹⁸ 2 recent studies indicated an unexpectedly high incidence of AD, including "new AD" (up to 79% of AD cases), in pregnancy (Table 1).^{5,9} These studies showed that AD is the most common pregnancy dermatosis, accounting for 36% to 49.7% of all pregnancy dermatoses. A recent study indicated that 46% of females

TABLE 1
Characteristics of epidemiologic studies on ad in gestation and their outcomes

First Author (Ref)	Study Characteristics	No. Patients	Diagnostic Criteria (Ref)	Results	Limitations	Study Conclusions
Ambros-Rudolph et al ⁵	Retrospective survey; 2-center study; medical record review	251	UK WP ¹²	44% primigravidae, 34% h/o AD in previous pregnancies; 79% of pts with "new AD" (all with "atopic background"); ↑ serum IgE 71%; onset in trimesters (%): 36/40/24	"Atopic background" in pts with "new AD" not specified; total serum IgE used as diagnostic criterion (uncontrolled); postpartum course and prevalence of EAD vs. EAD not studied	AD is the most common gestational dermatosis; "new AD" more common than deterioration of pre-existing AD; PP and PFP can be classified under AEP
Kemmet and Tidman ⁸	Retrospective; cross-sectional; medical record review	50	H&R ¹¹	52% deterioration vs. 24% improvement; onset before the 20 th week (80.7%)	No data on PHx and FHx; postpartum course and prevalence of EAD vs. EAD not studied	AD more likely to worsen than improve in pregnancy; mechanisms of deterioration may be similar to those involved in premenstrual flares of AD
Vaughan Jones et al ⁹	Prospective (cohort); specialist clinic	72	UK WP	PHx of AD 27.7% and FHx 50%; onset in trimesters (%): 24/44/32; ↑ serum IgE 18%	Total serum IgE used as diagnostic criterion (uncontrolled); postpartum course and prevalence of EAD vs. EAD not studied	AD is the most common gestational dermatosis; "new AD" more common than deterioration of pre-existing AD; PP may be closely related to AD (↑ serum IgE levels in 4/12 PP pts)
Cho et al ¹⁰	Retrospective; cross-sectional; questionnaire design	23	H&R	61% deterioration vs. 4% improvement; symptom aggravation higher in IAD (100%) compared to EAD (47.1%) group; onset in trimesters (%): 36/40/24	Small sample size in subgroups (IAD, EAD); no data on PHx and FHx; postpartum course not studied; total serum IgE used as diagnostic criterion (uncontrolled)	AD more likely to worsen than improve in pregnancy; IAD more affected than EAD; total serum IgE levels show no correlation with deterioration of AD during pregnancy

AD indicates atopic dermatitis; EAD, extrinsic atopic dermatitis; h/o, history of; FHx, family history; H&R, Hanifin and Rajka's criteria; IAD, intrinsic atopic dermatitis; PFP, pruritic folliculitis of pregnancy; PHx, personal history; PP, prurigo of pregnancy; pts, patients; UK WP, U.K. Working Party's criteria; ↑, increased

TABLE 2
Key clinical features that help differentiate skin diseases in pregnancy from AD

Differential Diagnosis of AD in Pregnancy	
ICP ¹⁷	Pruritus with no primary skin lesions 80% of ICP cases after 30 weeks' gestation Liver function abnormalities common, bile acid level elevation is diagnostic
PP ^{2,5}	Intensely pruritic lesions on the extensor extremities Onset at 25–30 wks' gestation No consistent PHx/FHx atopy Suggested clinical overlap with gestational AD/AEP
PEP ²	Primigravidae, mean onset at 35 weeks Various morphologies, including urticarial, eczematous, and/or polymorphic Involves abdominal striae, spares periumbilical areas
PFP ^{2,5}	Papular and/or acneform, primarily follicular truncal eruption Reported in any trimester No consistent PHx/FHx atopy Suggested clinical overlap with gestational AD
Contact dermatitis	Distribution and Hx helpful Often no Hx of atopy; contact dermatitis may be superimposed to AD
Drug reaction	Response to removal of offending allergen Most often morbilliform or urticarial Hx of exposure to drug
Infestations	Response to removal of suspected drug Intense pruritus Hx and distribution suggestive May see specific clinical signs, i.e., burrows (scabies) No response to steroids

AD indicates atopic dermatitis; FHx, family history of; Hx, history; ICP, intrahepatic cholestasis of pregnancy; PEP, polymorphic eruption of pregnancy; PFP, pruritic folliculitis of pregnancy; PHx, personal history of; PP, prurigo of pregnancy; wks, weeks.

with AD experience deterioration of the disease in pregnancy or in relation to their menstrual cycle.¹⁰ Of the patients who experienced deterioration during pregnancy, 14% experienced mild, 57% moderate, and 29% severe deterioration. According to another study, 24% of female patients with AD experience improvement and 52% experience deterioration of the disease in pregnancy.⁸ Only 20% to 40% of patients are estimated to have a preexisting history of eczema; the rest developed eczematous lesions for the first time during pregnancy.^{5,9} Three-quarters of these patients developed symptoms within the first 2 trimesters (Table 1), and it has been suggested that the earlier onset of AD in pregnancy can help differentiate it from specific dermatoses of pregnancy.⁵ Approximately 34% of women reported a history of similar skin changes in previous pregnancies.⁵ There

is a personal history of atopy (asthma, eczema or hay fever) and/or infantile AD in 27% of pregnant females with AD, and there is a family history of atopy in 50% of cases and infantile AD in 19% of the offsprings.⁹

IS “NEW AD” IN PREGNANCY INTRINSIC AD (AFD)?

The unexpectedly high prevalence of “new AD” in pregnancy (80% of all AEP cases) in the largest study, to date,⁵ raises the question whether pregnant patients with “new AD” have “pure atopy” or, instead, a transient eczematiform eruption that may not recur postpartum or may recur only in pregnancy. It is important to clarify whether AEP is a homogeneous picture. Along the same lines, it needs to be determined whether patients with “new AD” in pregnancy have extrinsic (IgE-associated) (EAD) or intrinsic (“nonallergic”/constitutional) AD (IAD). The former was defined by the Nomenclature Review Committee of the World Allergy Organization¹⁹ as the phenotype of an IgE-antibody high responder, whereas the latter indicates the phenotype of AD in the absence of detectable allergen-specific IgE.¹⁸ Patients with IAD (term synonymous to AFD), as opposed to those with EAD, have no associated respiratory disease (bronchial asthma, allergic rhinitis), show normal total serum IgE levels, no specific IgE, and negative skin prick tests to aeroallergens or foods.^{20,21} Furthermore, the inflammatory microenvironment in IAD is different from classical EAD and can be distinguished by phenotyping of epidermal dendritic cells.²² IAD is considered as a subgroup of AD with a different genotype.²³ The prevalence of AFD in the AD population varies from 10% to 45%. Features of AFD include a female predominance, a later age at onset, absence of history of respiratory diseases, and milder disease activity.²¹

The results of a recent small study, which showed that there is more the IAD than the EAD that is affected by pregnancy, indicate that “new AD” in pregnancy may be predominantly IAD.¹⁰ Along the same lines, the study showed no correlation between IgE levels and deterioration of AD during gestation. The median IgE in the study that showed a high prevalence of “new AD” in pregnancy was 156 kU/L (normal <100 kU/L).⁵ This mild IgE elevation is consistent with the IAD than EAD. Nevertheless, the reliability of Cho et al's study¹⁰ may be limited by the small sample size in the subgroups. However, the prevalence of personal and/or family history of atopic diseases in patients with AD in gestation in the

only prospective study to date⁹ (Table 1) was lower than that reported in classic EAD (virtually all EAD patients have personal and/or family history of atopy).²¹ The later patient age at onset of AD in the “new AD” group is also suggestive of IAD. These observations along with the results of study by Cho et al support the diagnosis of IAD in a significant percentage of patients with “new AD” in gestation.

WHICH ARE THE LIMITATIONS OF THE DIAGNOSTIC CRITERIA?

The diagnostic criteria used in epidemiologic studies^{5,8-10} (Table 1) were those established in pediatric populations (proposed originally by Hanifin and Rajka and modified by the UK Working Party)^{11,12} (Table 3), with any limitations that this can portend (different age populations, variability among ethnic, socioeconomic groups and settings, population- vs. hospital-based validation, etc). It is recommended that the UK criteria be used as a 12-month period prevalence measure, which makes their application to a pregnant population challenging.²⁴ Table 3 shows criteria (“chronic/relapsing course” and “rash

under age 2 years”) that cannot be easily applied to “new AD” in pregnancy. As shown in Table 3, both sets of criteria are insufficient when it comes to atypical (nonflexural) presentations of AD, as the diagnosis in these cases relies solely on historic information (personal and/or family history of atopy, history of dry skin, history of flexural involvement). Patients with specific dermatoses of pregnancy (PEP, PP, and PFP), however, often present with similar historic background, which makes the differentiation of these entities from AD very difficult. One may not group all these entities together based on historic data without clarification of their etiopathogenesis. Lumping AD, PP, and PFP together, under the new appellation “AEP,”²⁵ may have biased the prevalence of AD in gestation.⁶ Furthermore, any flexural skin eruption (such as “eczematiform” lesions of PEP and acral, secondary lesions in ICP) can be mistakenly labeled as “AD” if there is personal and/or family history of atopy.

The studies that used the UK criteria^{5,9} also used total serum IgE levels (uncontrolled) as an additional diagnostic criterion, which, however, is not included in the UK criteria. Including, however, mild serum IgE elevations in the criteria in these studies^{5,9} may have contributed to an overestimate of the prevalence of AD in gestation, and especially that of “new AD.”²⁵ It is important to note that only high IgE levels, e.g., >2000 U/mL, were included in the “minor criteria” of Hanifin and Rajka,¹¹ and the American Academy of Dermatology included a high concentration of total and allergen-specific IgE in the “important” features of pediatric AD.¹⁴ Furthermore, PEP also showed IgE elevations (uncontrolled) in these studies, and the high prevalence of AEP may have been biased also by the inclusion of PEP patients with “eczematiform” features in the AEP group. Finally, serum total IgE levels should not be used as a diagnostic criterion for AD in pregnancy because the regulation of IgE in pregnancy is complex and has been poorly clarified.^{6,25,26} Among others, maternal serum IgE during pregnancy can be affected by offspring sex, ethnic and genetic factors, lifestyle, and psychosocial stress.^{27,28}

From the above, it can be concluded that the currently used sets of criteria cannot reliably differentiate between AD and specific dermatoses of pregnancy, and the ideal set of diagnostic criteria for AD in pregnancy still has to be established. To achieve this, a consensus on the nomenclature and subgroups of AD in pregnancy first needs to be reached.

TABLE 3
Sets of diagnostic criteria that have been used in studies on AD in pregnancy^{5,8-10}

AD Diagnostic Criteria	H&R ¹¹	UK WP ¹²
Mandatory+++		1+++
Major++	3/4++	
Minor+	3/23+	3/5+
Itchy skin condition >12 mo		+++
Pruritus	++	
Typical morphology and distribution of skin lesions	++	+
Chronic/relapsing course*	++	
Personal or family h/o atopy	++	+
H/o dry skin	+	+
H/o flexural involvement		+
Rash under age 2 y*		+
22 other minor criteria (include ↑ serum IgE)	+	
Validation of criteria ²⁴	Twice (hospital setting)	Extensive (hospital and population settings)

*Criteria that cannot be easily applied in gestation to “new AD.”
H&R indicates Hanifin and Rajka’s criteria; H/o, history of; UK WP, U.K. Working Party’s criteria; ↑, elevated.

ETIOPATHOGENESIS

Pregnancy is characterized by decreased maternal cell-mediated immunity (Th1 response) but intact humoral immune (Th2) response, which helps prevent fetal rejection.²⁹ A predominant Th2-biased immunity seems to be associated with the improvement of predominantly Th1-driven diseases such as psoriasis and deterioration of mainly Th2-driven diseases such as systemic lupus and AD. The placental Th2 drive, that is associated with an increase in interleukin-4 during gestation, may be critical to the induction of IgE that could be relevant to the exacerbation of AD in pregnancy.³⁰ Nevertheless, the study by Cho et al¹⁰ showed no correlation between IgE levels and deterioration of AD during pregnancy, which indicates that the etiopathogenesis of AD in pregnancy may not be primarily related to the induction of IgE and/or it is the IAD (non-IgE-associated subtype of AD) that is mostly affected by pregnancy. The authors suggested that although IAD patients do not show aggravation by specific allergens, other factors such as hormones or stress may have some impact on the clinical manifestations of IAD in pregnancy. Studies with larger sample size that will examine allergen-specific IgE levels may clarify whether there is a role for allergen exposure and environmental factors in gestational AD.²⁵

Stress is a major trigger factor in nongestational and pediatric AD,¹⁴ and pregnancy is a major stress to the patient.³¹ Nevertheless, the role of stress and other emotional factors in the pathogenesis of AD in gestation has not been studied. Most pregnant women are unwilling to use topical or systemic treatments, but a recent study showed that the cessation of medications itself independent to pregnancy was not a substantial cause of AD aggravation.¹⁰ Experimental studies indicate that estrogens may affect mast cell activation, whereas progesterone suppressed histamine release and potentiated IgE induction in animal studies³²; however, early studies in humans showed that sex hormones have little or no effect on humoral IgE levels during pregnancy.³³

The role of epidermal barrier disruption in the pathogenesis of AD has been emphasized recently³⁴ but never studied in gestation. The conceptual focus in AD has shifted from immunological mechanisms, i.e., IgE and Th2 primacy (immunocentric view), to epidermal barrier disruption (corneocentric view).^{23,34} Barrier disruption allows greater exposure to environmental toxins, microbes, and other allergens, which may stimulate immune responses in AD. Furthermore, barrier disruption may lead to greater transepidermal water

loss, which can exacerbate AD. The importance of barrier disruption is indicated by the demonstration of protease and lipid defects in AD as well as the association between filaggrin null mutations of ichthyosis vulgaris and AD.³⁴ The impact of change in hormone and immune status during gestation on the skin barrier function needs to be clarified. Epidermal barrier function, transepidermal water loss, and filaggrin expression need to be investigated in pregnancy, and they may provide clues to the etiopathogenesis of AD in gestation.

MANAGEMENT AND DRUG SAFETY

Management options for AD in pregnancy and maternal/fetal risks are outlined in Table 4. Dry skin care and avoidance of irritants and allergens remain an integral part of AD management. Gestational AD is typically treated with emollients, low- to mid-potency topical steroids and oral antihistamines.^{25,35} If a patient is already receiving systemic treatment for eczema, it is recommended that there should be a drug-free interval before conception, the duration of which depends on the medication. Methotrexate should be discontinued for at least 3 months before conception, whereas there is no minimum withdrawal interval for PUVA (psoralen with ultraviolet light A).

Mid- or high-potency nonhalogenated topical steroids can be used relatively safely throughout pregnancy for severe symptomatic AD in small surface areas³⁶; their use, however, on large body surface areas is associated with systemic absorption and risks similar to those observed with systemic steroids such as intrauterine growth retardation.³⁷ An association with small babies, especially with potent topical steroid use, resulted from a small cohort study.³⁸ Two case-control studies^{36,39} showed an increased odds ratio for cleft lip and/or palate with maternal use of topical corticosteroids in the first trimester of pregnancy, but the reliability of the finding is limited by the small sample size.⁵¹ Cohort studies with larger sample size, considering corticosteroid potency, dosage, and indications, are needed to confirm risks from topical steroids in pregnancy.⁵²

Systemic first-generation antihistamines, such as diphenhydramine and chlorpheniramine, are safe during gestation (category B) and often required for pruritus control.²⁵ They have not been associated with congenital malformations,⁵³ and an association between antihistamine use during the last 2 weeks of pregnancy and retrolental fibroplasia in premature infants⁴⁰ has not been confirmed by other studies. Second generation antihistamines, such as loratadine

TABLE 4
Management options for AD in pregnancy and their safety profile

Management Options	Indications	Pregnancy Category	Maternal and Fetal Risks
Emollients	Indicated in all cases	N/A	None
Topical corticosteroids	First-line Rx; use judiciously, minimize use in first trimester	C	IUGR with use over large areas ³⁷ ; small babies with potent topical steroids ³⁸ ; oral cleft with first trimester use ^{36,39}
Oral antihistamines First generation (diphenhydramine, chlorpheniramine) Second generation (cetirizine, loratadine)	First-line Rx	B	An association between antihistamine use during the last 2 weeks of pregnancy and retrolental fibroplasia in premature infants ⁴⁰ not confirmed
UVB	Second-line Rx	N/A	None
Oral corticosteroids (prednisone, prednisolone)	Second-line Rx; avoid use in first trimester	B	Fetal growth retardation ⁴¹ ; miscarriage, prematurity, lower median birth weight, and ↑ rate of major anomalies with first trimester use ⁴² ; oral cleft with first trimester use ⁴³⁻⁴⁶
Topical immunomodulators (pimecrolimus, tacrolimus)	Third-line Rx; may be used only on small areas	C	Not teratogenic but safety not entirely established
Cyclosporin	Third-line Rx; may be used for severe or refractory AD	C	Maternal risks include renal impairment, hematologic, and liver toxicities ⁴⁷ ; fetal growth restriction ⁴⁸
Azathioprine	Third-line Rx; use in severe or refractory AD controversial	D	Maternal and neonatal hematologic toxicities ^{49,50} ; fetal risks include sporadic malformations, abortion, prematurity, IUGR, and low birth weight ⁴⁹
Oral antibiotics (penicillins, cephalosporins, erythromycin base and ethylsuccinate)	Bacterial superinfection	B	None
Intravenous acyclovir	HSV superinfection	B	No teratogenicity or IUGR; although safety not entirely established, benefits from Rx outweigh the risks

AD indicates atopic dermatitis; HSV, herpes simplex virus; IUGR, intrauterine growth retardation; N/A, nonapplicable; Rx, treatment; UVB, ultraviolet light B.

and cetirizine (category B), are considered safe in gestation and can be used for symptomatic relief. AD that has not responded satisfactorily to topical steroids can be managed with the addition of ultraviolet light B treatment that is considered the safest second-line adjunctive treatment of AD in gestation.¹³

A short course of oral steroid, such as prednisolone, may be used in the third trimester for severe symptomatic or recalcitrant AD. The risk of fetal adrenal suppression secondary to a short course of oral steroid is low, as shown by the fact that the maternal-fetal gradient of prednisolone is 10:1.⁵⁴ Oral steroids have been originally associated with fetal growth retardation in pregnant patients who used them for asthma.⁴¹ A prospective controlled study showed higher rate of miscarriage and preterm births, a lower median birth weight, and a 2.5-fold increase in the overall rate of major anomalies in pregnant women who used systemic corticosteroids

in the first trimester.⁴² An association between systemic steroid use in the first trimester and oral cleft has been shown in a handful of studies.⁴³⁻⁴⁶

Topical calcineurin inhibitors (pimecrolimus, tacrolimus) are pregnancy category C and should be used with caution during pregnancy, although their bioavailability is limited (<5%) and their use has not been associated with fetal anomalies.³⁵ Because of the lack of epidemiological studies on topical calcineurin inhibitors in pregnancy and the fact that systemic tacrolimus is teratogenic, accepted practice remains to restrict their use to localized areas only in poorly controlled eczema that has not responded to ultraviolet light B.¹³

If systemic agents other than oral steroids are needed for severe or recalcitrant AD, cyclosporine is the safest option. Cyclosporine is not a teratogen but is nephrotoxic, and its administration in pregnant rabbits caused a permanent nephron deficit in living

newborns.⁵⁵ Since the medication readily cross the placenta and can be associated with maternal risks (i.e., renal impairment, hematologic and liver toxicities),⁴⁷ it should be used for the shortest duration possible (typically <3 months). The fetal growth restriction (8%–45%) that was reported in renal transplant recipients⁴⁸ was probably related to the underlying maternal disease (hypertension, renal function),^{13,47} although a contribution from cyclosporine and other immunosuppressive drugs cannot be excluded. Patients taking cyclosporine during pregnancy need regular monitoring of blood cell count, renal and liver function, and blood pressure.

The use of azathioprine as a third-line treatment for recalcitrant AD in gestation remains controversial. Although azathioprine is not teratogenic, it has been associated with sporadic congenital malformations, increased rates of abortion, prematurity, intrauterine growth retardation, low birth weight, and neonatal leukopenia or pancytopenia.^{13,49} A significant correlation has been found between maternal leukocyte counts at 32 weeks' gestation and at delivery and cord blood leukocyte count.⁵⁰ In the same study, neonatal leukopenia and thrombocytopenia were prevented with reduction of azathioprine dose in the third trimester. Pregnant transplant recipients are typically advised to continue the medication in pregnancy. Since there are no studies of patients taking azathioprine for eczema who become pregnant, continuation of treatment must be decided on a case-by-case basis.¹³ Other eczema treatments, such as methotrexate, mycophenolate mofetil, intravenous immunoglobulins, interferon- γ , and psoralen with ultraviolet light A, are contraindicated in pregnancy.

Bacterial infections (typically caused by *Staphylococcus aureus* that colonizes >90% of eczema lesions) are an important cause of exacerbations and should be treated promptly.^{13,25} Systemic antibiotics, such as penicillins, cephalosporins, and erythromycin base or ethylsuccinate, are safe during gestation and can be administered in superinfected AD. Prompt intravenous acyclovir treatment is warranted if there is strong clinical suspicion of herpetic superinfection.¹⁵

MATERNAL AND FETAL RISKS

There is no evidence that eczema in pregnancy affects fetal outcome.⁹ Pregnant women who use large amounts or potent topical corticosteroids over large body surface areas should be warned of the possibility of low birth weight babies.^{37,38} The risks from systemic steroids (see previous section) need to be discussed with the pregnant patient. Fetal risks,

such as premature delivery, intrauterine growth retardation, and miscarriage that are associated with fetal herpes simplex infection, are minimized when eczema herpeticum is treated promptly with acyclovir.^{13,15} Maternal risks are related to eczema superinfection and adverse effects from systemic drug use.³⁵

CONCLUSIONS

After completing this CME activity, physicians should be able to correctly diagnose AD in pregnancy as well as differentiate it from other pregnancy dermatoses. Furthermore, physicians should be able to use judiciously the existing management options, thus minimizing maternal and fetal risks. Moreover, participants to this CME activity will become familiar with challenges and controversies in the field, especially those regarding the prevalence, diagnostic criteria, postpartum prognosis, and subtypes of AD in pregnancy.

As shown in this article, more studies are needed to elucidate the mechanisms that lead to development or deterioration of AD in pregnancy. Studies into allergen-specific IgE need to be performed to investigate whether allergen exposure may play a role in AD in gestation. The function of epidermal barrier in pregnancy and the role of stress and emotional factors in the etiopathogenesis of AD during gestation warrant investigation. The unexpected high prevalence of "new AD" that was reported in 2 studies^{5,9} was then debated⁶ as, among others, may have been biased by the inclusion of serum total IgE elevations in the diagnostic criteria. Serum total IgE elevations should not be used in the diagnosis of AD in pregnancy because the regulation of IgE in normal pregnancy has not been clarified.^{6,26–28} To provide more conclusive data about the role of IgE, it is necessary first to measure serum total IgE levels in a control group of pregnant women without any skin disease and, furthermore, measure allergen-specific IgE levels in both AD and control groups.

This article indicates also that the diagnostic criteria for AD in gestation need to be revised, which will allow an accurate confirmation of the prevalence of "new AD" in pregnancy. Along these lines, it is important to clarify whether patients with "new AD" in pregnancy represent cases of EAD versus IAD (AFD). Pregnancy-associated AFD may not recur postpartum, and patient counseling about "allergen cleansing" would be unnecessary in this subgroup of patients. In the future, dermatologists should be able to counsel the pregnant patient with AD about the postpartum prognosis of their condition, including

how often pregnancy-associated AFD can recur and/or convert to a “pure,” allergen-induced (IgE-mediated) AD. Prospective, large-scale, epidemiologic studies are needed to address these issues.

Another important issue is whether specific dermatoses of pregnancy, such as PP and PFP, which often present with nonspecific histopathology and pruritus, should be grouped together with AD. A study⁵ that suggested classifying these specific dermatoses under AEP did not provide new etiopathogenetic data to justify this reclassification.^{6,25} The proposed reclassification was based primarily on the clinical history of these patients,⁵ although some PP patients satisfied only minor criteria of atopy^{5,9} or never had AD,¹⁸ and the majority of PFP patients did not have an atopic background. Furthermore, the clinical features of PFP are not eczematous. The notion of AEP encompassing AD, PP, and PFP remains controversial, and these entities may not be grouped together before their pathophysiology and diagnostic criteria are further clarified.

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