

INVITED ARTICLE

Treatment of atopic dermatitis in pregnancy

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ABSTRACT: Atopic dermatitis (AD), also referred to as eczema, is one of the most frequently observed skin diseases in pregnant patients. The presentation and histopathology of this condition during pregnancy is identical to that of the non-pregnant individual. AD is a T-helper 2 dominant disease and may worsen during pregnancy, which favors this population of T-lymphocytes. AD management during pregnancy requires special precautions to avoid harming the fetus. Herein is an exploration of the different options available for the treatment of the pregnant patient with AD. The management of concomitant bacterial and viral infections is also discussed.

KEYWORDS: atopic dermatitis, eczema, lactation, medication safety, pregnancy

Introduction

Atopic dermatitis (AD) is the most common gestational dermatosis (1–3). In several studies, AD accounted for 36–49% of all pregnancy dermatoses (2,4). Most pregnant patients with AD present with lesions on the flexural aspects of the extremities, although truncal involvement is not uncommon. Less common presentations are follicular, facial, hand/foot eczema, and eczema of the nipple and/or areola (2,4,5). The histopathology of AD during pregnancy is identical to that of non-pregnant patients (4).

Pregnancy may alter the severity of patients with preexisting AD. In a small study of 23 patients (6), 61% experienced deterioration and 4% noted

improvement of AD during pregnancy; the remaining 35% of patients observed no change in their symptoms. This is in accordance with previous studies showing that more than half of patients report worsening of AD symptoms during pregnancy (7,8). Of those patients experiencing symptom aggravation, most experienced deterioration during the second or third trimesters of pregnancy. In another study (2), there was no specific correlation of pregnancy-associated AD severity with either parity or gestation.

Pregnancy creates an immunologic state where homeostasis exists between the mother and the fetus, two antigenically different tissues. To prevent fetal rejection, normal pregnancy demonstrates a lack of strong maternal cell-mediated immune function and T-helper 1 (Th1) cytokine production (e.g., interleukin (IL)-12 and interferon γ) and a strong humoral immune response with T-helper 2 (Th2) cytokine production (e.g., IL-4, IL-10). AD is widely accepted as a Th2-dominant disease, and the alteration in the Th1/Th2 cytokine balance is believed to be responsible for the frequently increased severity of AD during pregnancy (9–11). Further, stress is a major trigger factor in

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nongestational and pediatric AD (12), and, often, pregnancy can be stressful to the patient (13). Nevertheless, the role of stress and other emotional factors in the pathogenesis of gestational AD has not been rigorously evaluated.

There are also some experimental data suggesting sex hormones have an influence on the symptoms of AD, as estrogen affects mast cell activation, while progesterone suppresses histamine release, but increases immunoglobulin (Ig)E induction in rodent animals (14). Nonetheless, there is no correlation between IgE levels and the exacerbation of AD during gestation; therefore, the etiology of AD in pregnancy may be independent of the induction of IgE, or, alternatively, the non-IgE-associated subtype of AD is most active in pregnancy (1,6).

There is no evidence to suggest that AD directly causes infertility or increased rates of miscarriage, birth defects or prematurity (8). However, AD may be complicated by bacterial infection (typically from *Staphylococcus aureus*) or herpetic superinfection (eczema herpeticum (EH)) during pregnancy (1). Although EH has not been reported to lead to intrauterine infection, herpes simplex virus may be associated with premature delivery, intrauterine growth restriction, and miscarriage. This article discusses the current knowledge of the relative safety of the therapeutic options available in the treatment of the pregnant patient with AD. First discussed are the safest therapies, followed by a description of therapies thought to be less safe or unsafe. Also reviewed is the use of these therapies in the lactating patient.

Management of AD

Successful treatment of AD during pregnancy requires a multifaceted approach that incorporates skin hydration, pharmacologic therapy, and the identification and elimination of flare factors such as irritants, allergens, infectious agents, and emotional stressors. Treatment plans should be tailored to each patient, including the severity and chronology of the dermatitis, and the trigger factors that are unique to the patient (15). For women of child-bearing age, patients should be counseled pre-conception about the possible exacerbation of AD in pregnancy, treatment options during pregnancy, and the need to discontinue certain medications prior to conception. Presented in Table 1 is a broad categorization of the available therapies and their safety measures.

Table 1. Treatment options for atopic dermatitis in pregnancy and their safety measures (8)

Safe	Emollients, topical corticosteroids, oral antihistamines, ultraviolet B light
Relatively safe (caution)	Oral corticosteroids, cyclosporine, azathioprine, topical calcineurin inhibitors
Avoid	Methotrexate, mycophenolate mofetil, psoralens plus ultraviolet A light (PUVA)

Safe

Cutaneous hydration

Cutaneous hydration remains an integral part in the treatment of all patients with AD. Patients with AD have reduced skin barrier function and dry skin. These features contribute to increased disease severity by allowing the development of skin fissuring. These areas of compromised skin serve as portals of entry for skin pathogens, irritants and allergens. Lukewarm soaking baths for at least 20 minutes followed by the application of an occlusive emollient to retain moisture can provide symptomatic relief (15). Hydration coupled with emollient use serve to restore and preserve the stratum corneum barrier, and may decrease the need for topical calcineurin inhibitors and corticosteroids (15,16).

Hydration also promotes transepidermal penetration of topical glucocorticoids, if needed. Furthermore, dressings may serve as an effective barrier against persistent scratching, allowing more rapid healing of excoriated lesions. Wet dressings are recommended for use on areas of dermatitis refractory to therapy. Baths and wet dressings should be followed by topical emollient use to prevent drying and fissuring (15,16).

Pregnant patients should bathe only once daily and should use warm or cool water (15,16). Soap should be confined to the armpits, groin, scalp, and feet (16). Washcloths and brushes should be avoided. After rinsing, the skin should be patted dry and then immediately covered with a thin film of an over-the-counter emollient, or a topical corticosteroid, as needed (15,16).

Topical corticosteroids

Topical corticosteroids are first-line prescription-only therapies in the management of pregnant patients with AD (17). Topical corticosteroids are categorized as class C drugs by the Food and Drug

Administration (FDA). Theoretically, topical corticosteroids pose a significantly decreased risk because of the small amount of systemic absorption relative to systemic corticosteroids. Although animal studies have revealed a partially dose-dependent teratogenic effect, there is increasing evidence affirming the safety of topical corticosteroids. Alarming, an earlier study showed a significant association of topical corticosteroid use with orofacial clefting (18). However, more recent investigations have not identified a similar relationship. Specifically, a large Hungarian population-based case-control study did not detect an increased risk in congenital malformations in infants with in utero exposure to topical corticosteroids (19). Additionally, a large retrospective case-control study identified no association of topical corticosteroids with orofacial cleft formation (20). Further, two Danish population-based studies revealed no increased risk of preterm delivery or malformations in infants delivered to mothers who used topical corticosteroids during pregnancy, although there was a dose-dependent relationship with low birth weight (21,22).

Chi et al. have made some evidence-based recommendations for the use of topical steroids in pregnancy (23). If effective, low- to mid-potency topical corticosteroids are preferable. High-potency topical corticosteroids should be used as second-line therapy and for a brief period. Consider more fastidious obstetrical care given the possibility of an increased risk of fetal growth restriction. The genitals, eyelids, and flexures are characterized by thinner skin and consequently higher rates of cutaneous absorption, and therefore use of topical corticosteroids to these areas should be either more limited or completely avoided. Subsequent to the brief and effective use of high-potency topical corticosteroids patients should employ emollients and low- to mid-potency glucocorticoids for maintenance therapy. There are no studies delineating the effect on infants of topical corticosteroids when used on nursing mothers with AD, but it is generally safe to use up to a Class 2 topical corticosteroid on the nipple in a breast-feeding mother.

Oral antihistamines

The treatment of pruritus in AD may require systemic therapy. A large number of pregnancies exposed to first-generation antihistamines have been studied, and there is no definitive increased teratogenic risk. The data on the second-generation antihistamines are more limited, but

also show no increased teratogenic risk to-date. However, having a longer history of use, first-generation antihistamines are favored (24). Diphenhydramine has been associated with increased risk of cleft palate when used in the first trimester (25), but other studies have not supported this finding. Both chlorpheniramine and diphenhydramine are considered to be safe in the first trimester and are acceptable in gestation. Exposure to hydroxyzine during the first trimester has been linked with a slightly increased risk (5.8%) of congenital anomalies than that of the general population (26), but neither hydroxyzine nor brompheniramine have been definitively shown to have an increased risk. Therefore, both of these antihistamines are less preferred, but may be used, as needed.

Second-generation antihistamines are less sedating, but are less preferred for treating pruritus in AD given more limited data (27). Second-generation antihistamines may be considered when first-generation drugs are too sedating or ineffective (24). These second-generation drugs are generally safe (28,29). Animal studies investigating loratidine and cetirizine (the active metabolite of hydroxyzine) found no increased risk of teratogenicity, whereas fexofenadine was associated with adverse fetal effects (24). Loratidine is the preferred second-generation antihistamine in pregnancy (30–34).

Antihistamines should be used cautiously in the last month of pregnancy, possibly causing infant withdrawal symptoms (i.e., tremulousness, irritability, poor feeding, diarrhea, and tonic-clonic seizures) lasting up to 4 weeks after birth (35,36). The associations are strongest when high doses of the medications are used. Diphenhydramine has also been found to have oxytocin-like effect peripartum, particularly when it is administered intravenously or in overdose, and may result in uterine hyperstimulation and fetal distress (37,38). Antihistamines are also associated with retrolental fibroplasia (or, retinopathy of prematurity), especially within the last 2 weeks prior to premature delivery (39). With judicious and careful use, these antihistamines can be safely administered peripartum to pregnant patients with AD.

There is minimal secretion of first-generation antihistamines in breast milk (40). In a telephone follow-up study of breast-feeding mothers taking first-generation antihistamines, 10% of mothers noted irritability and colicky symptoms in their infants, and another 1.6% reported drowsiness. None of these reactions warranted medical attention (40). However,

second-generation antihistamines are preferred in lactation as these drugs are less sedating and thought to have less of an effect on milk production, although the possibility that antihistamines decrease milk production has not been substantiated by clinical investigations. Loratidine and fexofenadine are found in low levels in breast milk and are both acceptable in nursing mothers. Loratidine is the preferred choice of all antihistamines during breast-feeding (41).

Doxepin is contraindicated during lactation as it is sedating with reports of adverse effects in nursing infants (41). An 8-week-old breast-fed infant was found limp, pale, and almost not breathing after the maternal dosage was increased from 10 mg daily to 25 mg three times daily (42). Another 9-day-old nursing infant experienced poor suck and swallowing, vomiting, weight loss, and hypotonia attributed to the mother taking 35 mg of doxepin daily (43).

Phototherapy

Natural sunlight usually provides some degree of relief to patients with AD. However, if the sunlight occurs concomitantly with high heat or humidity, thereby triggering sweating and possibly pruritus, it may exacerbate the disease (15). AD that has not responded satisfactorily to topical steroids can be managed with the addition of ultraviolet (UV) phototherapy (8). The best results have been achieved with UV light A (UVA)1 (340–400 nm), broadband UV (UVA + UVB 290–400 nm) and narrow band UVB (311 nm) (44,45). UVA phototherapy appears to target epidermal Langerhans cells and eosinophils, whereas UVB is effective at blocking the function of antigen-presenting cells and altering keratinocyte cytokine production (15). Narrow-band UVB has also been shown to reduce microbial colonization (44,46). Given the lack of penetration beyond the superficial layers of the skin, UV phototherapy leaves the fetus unharmed and is likely safe in pregnancy (47,48), although high cumulative doses of both narrowband and broadband UVB have been linked to a decline in serum folic acid levels, which could potentially increase the risk of neural tube defects in the fetus (49).

Relatively safe

Systemic corticosteroids

Systemic corticosteroids are classified as pregnancy category C, and may induce dramatic

clinical improvement, but there is a risk of severe rebound flare that may occur once the corticosteroid is discontinued. A short course of an oral corticosteroid, such as prednisone, 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 corticosteroid is low, as the maternal–fetal gradient of the drug is 10:1 (1,50).

A large retrospective study (51) examining the repetitive administration of antenatal corticosteroids revealed no difference in birth weight, but infants exposed to corticosteroids were of lesser gestational age and had a higher clinical incidence of gastroesophageal reflux. Other investigations suggest that repeat courses of corticosteroids may reduce birth weight and increase the risk of intrauterine growth restriction (52,53). One study showed an increased risk of cerebral palsy with repeated corticosteroid administration compared with a single dose antenatally (52).

A 2-year follow-up study of infants exposed to repeated corticosteroid exposure in utero showed that the rate of survival devoid of major disability was similar to a matched group not having been exposed to corticosteroids. There were no significant differences between the groups in body size, blood pressure, use of health services, respiratory morbidity, or child behavior scores, although children exposed to repeated doses of corticosteroids were more likely than those exposed to placebo to warrant assessment for attention problems (54). Another study evaluating intellectual and motor development, school achievement, and social-emotional functioning in children exposed to systemic corticosteroids showed no increased risk (55).

A prospective study and meta-analysis of all epidemiologic studies on antenatal corticosteroid use showed no statistical difference in the rate of major anomalies between the corticosteroid-exposed and control groups, but there was a noted 3.4-fold increased risk of oral cleft, specifically when exposure to corticosteroids occurred during the first trimester (56). Therefore, systemic steroids should be used cautiously and briefly during pregnancy and only with patients refractory to multiple other practical therapies.

Systemic corticosteroids may be used during lactation as minimal drug levels are achieved in breast milk and therefore do not appear to be a significant risk to the nursing infant (57,58). Breast milk levels are usually less than 0.1% of the mother's ingested corticosteroid dose, which is less than 10% of the infant's endogenous cortisol production

(59). Regardless, some recommend that the nursing mother waits 4 hours after ingesting a dose of a systemic corticosteroid before breast-feeding as peak levels of steroids in breast milk occur 2 hours after a dose and subsequently decline rapidly (60,61).

Topical tacrolimus

Tacrolimus is classified as pregnancy category C. Most investigations of tacrolimus in pregnancy have been conducted on transplant recipients taking systemic tacrolimus. In a large retrospective study of patients treated with systemic tacrolimus for organ transplantation, there was increased risk of prematurity (62). Overall, these pregnancies resulted in favorable outcomes. In another fairly large clinical trial conducted on liver transplant recipients receiving systemic tacrolimus, there was also increased risk of preterm birth and low birth weight, although weight was appropriate for gestational age (63). Preterm delivery is a feature that has been consistently observed in solid-organ transplant patients receiving any form of systemic immunosuppression. Topical tacrolimus, resulting in very low systemic levels, is presumed to have less of an association with prematurity although rigorous investigations are lacking (61).

While there have been reports of fetal anomalies associated with intrapartum tacrolimus use, it is not fully elucidated if the anomalies are a result of tacrolimus or due to the setting of transplantation, where women often have significant medical problems and receive a number of other medications that could pose risk to the fetus. Topical tacrolimus should be used cautiously intrapartum and it is advisable to restrict its use to localized areas only in poorly controlled AD that has not responded to other modalities, such as emollients, topical corticosteroids or, if practical, UV phototherapy (8,47).

The concentration of systemic tacrolimus in breast milk is substantial when compared with maternal serum levels; the tacrolimus concentration of breast milk is approximately 23–50% of that found in the maternal serum (64,65). However, it is estimated that the baby ingests less than 1% of maternal dose (64). This low exposure suggests that maternal treatment with tacrolimus may be compatible with breast-feeding (64). If topical tacrolimus is utilized in the nursing mother, the nipple should be spared as oral absorption by the feeding infant can be significant.

Cyclosporine

If systemic agents other than oral corticosteroids are needed for severe or recalcitrant AD, cyclosporine is the safest option. Cyclosporine is a potent immunosuppressive drug that acts primarily on T cells by suppressing cytokine transcription. Treatment with cyclosporine has been found to reduce the severity of AD and improve quality of life. Discontinuation of treatment may result in rapid relapse of skin disease, although some patients may have sustained remission (15).

Cyclosporine has been labeled category C by the FDA, and crosses the placental blood barrier (66,67). Investigations on transplant recipients using cyclosporine during pregnancy suggest there may be an increased risk of prematurity and low birth weight in infants, although there was no increased risk of congenital malformations (68–70). Therefore, cyclosporine may be considered after a trial of the more established therapies. Patients taking cyclosporine during pregnancy need regular monitoring of the blood cell count, renal and liver function, and blood pressure (1). Pregnant patients exhibiting renal insufficiency or drug-induced hypertension should discontinue cyclosporine (48). Cyclosporine is secreted into breast milk, with a broad range in the milk-to-maternal serum concentration ratio. There is limited data to elucidate the dangers of breast-feeding in mothers taking cyclosporine. Breast-feeding is typically discouraged, but may be considered if no other option is either effective or practical. In this instance, the infant levels of cyclosporine should be monitored (16,71).

Azathioprine

Azathioprine is pregnancy category D. A randomized controlled trial in non-pregnant patients showed that azathioprine reduced disease severity by approximately 37% (8,72). The use of azathioprine as a treatment for recalcitrant AD during pregnancy remains controversial. Azathioprine readily crosses the placenta, and its use during pregnancy has been associated with miscarriage, preterm delivery, fetal growth restriction, and low birth weight (1,8,73). However, the fetus seems to be protected from teratogenic effects, as its liver lacks the enzyme needed to convert azathioprine into active metabolites (8,74), and no compelling data of an association with congenital malformations in humans exist. The case reports of azathioprine in pregnancy come from its use in pregnant transplant recipients, and current advice to these patients is to continue its use. There are no

existing reports of pregnant patients taking azathioprine for the treatment of AD.

Rarely, azathioprine used during pregnancy has been associated with neonatal leukopenia, pancytopenia, or the inhibition of neonatal hematopoiesis, although this should be predictable by maternal leukopenia in the third trimester (8,75). A significant correlation has been found between maternal leukocyte counts at 32 weeks' gestation and at delivery and cord blood leukocyte count (76). In the same study, neonatal leukopenia and thrombocytopenia were prevented with reduction of azathioprine dose in the third trimester.

Women taking azathioprine are usually discouraged from breast-feeding their infants because this drug is secreted into breast milk (77). Further, the manufacturer's data sheet states that breast-feeding is contraindicated (78). There are concerns of pancreatitis, bone marrow suppression, and increased susceptibility to infections in nursing infants with azathioprine exposure (77). However, in a study of 11 mothers taking azathioprine during lactation, there was no increased risk of infections in the infants when compared with controls (77).

Avoid

Methotrexate (MTX)

MTX has been used for AD patients with recalcitrant disease, although controlled trials are lacking. MTX is category X and should be avoided in pregnancy, as the drug is teratogenic and has been associated with limb, growth, central nervous system, and craniofacial anomalies (79). Patients contemplating pregnancy should not receive MTX for a minimum of 3 months prior to conception (discussed further in the psoriasis article on dermatoses of pregnancy).

Mycophenolate mofetil (MMF)

MMF is frequently used for the treatment of AD, but there is increasing evidence supporting the possible teratogenicity of MMF. This risk is fully elaborated in the article on treating pregnant patients with psoriasis.

Psoralen and UVA light (PUVA)

PUVA may be considered for non-pregnant patients with severe, widespread AD although studies comparing it with other modes of UV phototherapy and systemic medications are

limited (15). PUVA is classified as pregnancy category C. Given the theoretical risk of mutagenesis and teratogenesis, PUVA should be avoided in pregnancy despite investigations showing a lack of association with congenital malformations or infant mortality (48,80,81).

Controlling concomitant infection

Bacterial and viral infections are an important cause of AD exacerbation and should be treated promptly in pregnant patients. Eczematous lesions should be cultured if there is a suspicion of secondary infection, and the patient should be treated with antibiotics active against *S. aureus*. Penicillins and cephalosporins may be used in patients not colonized with resistant *S. aureus* strains as these antibiotics are safe during both pregnancy and lactation (41,82). Dicloxacillin is a pregnancy category B drug and shows incomplete placental transfer (83). Oxacillin and mupirocin are other pregnancy category B drugs with anti-staphylococcal activity. Methicillin-resistant staphylococci may require culture and sensitivity testing to assist in appropriate antibiotic selection (15). Erythromycin base or ethylsuccinate may also be employed (1).

Monitoring for EH, a generalized herpes simplex infection manifested by monomorphic vesicles, crusts, or scalloped erosions, is important (84). EH is treated in pregnant patients with oral acyclovir, a pregnancy category B drug (84). Acyclovir is not likely harmful to the nursing infant as the level in breast milk is approximately 1% of a typical infant dosage (41). Exposure to acyclovir during pregnancy and lactation is not associated with an increased risk of adverse effects in infants and mothers (85).

Conclusion

AD is relatively common in pregnant women. Where possible, preparation for conception should include strategies to minimize disease activity at baseline, as AD may deteriorate during pregnancy. This should include advice about avoiding irritants and allergens, the use of emollients, and how to apply topical treatments. Emollients are indicated in all cases of AD. Topical corticosteroids are a first-line treatment and should be used judiciously; use should be minimized in the first trimester. Oral antihistamines are also generally safe intrapartum. UV phototherapy is a second-line modality that may be used in conjunction with emollient and

topical corticosteroid use. Furthermore, short courses of oral corticosteroids may be used as a second-line treatment. Topical tacrolimus is a third-line treatment and should be confined to limited areas. Cyclosporine is another third-line treatment that may be used in severe or refractory AD. PUVA and MTT should be avoided in pregnancy. Safe oral antibiotics should be used to treat bacterial superinfection and oral acyclovir for HSV superinfection.

References

- Koutroulis I, Papoutsis J, Kroumpouzou G. Atopic dermatitis in pregnancy: current status and challenges. *Obstet Gynecol Surv* 2011; **66** (10): 654–663.
- Ambros-Rudolph CM, Müllegger RR, Vaughan-Jones SA, Kerl H, Black MM. The specific dermatoses of pregnancy revisited and reclassified: results of a retrospective two-center study on 505 pregnant patients. *J Am Acad Dermatol* 2006; **54** (3): 395–404.
- Ingber A. Atopic eruption of pregnancy. *J Eur Acad Dermatol Venereol* 2010; **24** (8): 984.
- Vaughan Jones SA, Hern S, Nelson-Piercy C, et al. A prospective study of 200 women with dermatoses of pregnancy correlating the clinical findings with hormonal and immunopathological profiles. *Br J Dermatol* 1999; **141**: 71–81.
- Cohen LM, Kroumpouzou G. Pruritic dermatoses of pregnancy: to lump or to split? *J Am Acad Dermatol* 2007; **56**: 708–709.
- Cho S, Kim HJ, Oh SH, Park CO, Jung JY, Lee KH. The influence of pregnancy and menstruation on the deterioration of atopic dermatitis symptoms. *Ann Dermatol* 2010; **22** (2): 180–185.
- Kemmett D, Tidman MJ. The influence of the menstrual cycle and pregnancy on atopic dermatitis. *Br J Dermatol* 1991; **125**: 59–61.
- Weatherhead S, Robson SC, Reynolds NJ. Eczema in pregnancy. *BMJ* 2007; **335**: 152–154.
- Kang K, Poster AM, Nedorost ST, Steven SR, Cooper KD. Atopic dermatitis. In: Bologna JL, Jorizzo JL, Rapini RP, et al, eds. *Dermatology*. New York: Mosby, 2003: 199–214.
- Wilder RL. Hormones, pregnancy, and autoimmune disease. *Ann NY Acad Sci* 1998; **840**: 45–50.
- Akdis M, Trautmann A, Klunker S, Blaser K, Akdis CA. T cells and effector functions in atopic dermatitis. *Curr Allergy Asthma Rep* 2002; **2**: 1–3.
- Eichenfield LF, Hanifin JM, Luger TA, et al. Consensus conference on pediatric atopic dermatitis. *J Am Acad Dermatol* 2003; **49**: 1088–1095.
- Parcels DA. Women's mental health nursing: depression, anxiety and stress during pregnancy. *J Psychiatr Ment Health Nurs* 2010; **17**: 813–820.
- Chen W, Mempel M, Schober W, Behrendt H, Ring J. Gender difference, sex hormones, and immediate type hypersensitivity reactions. *Allergy* 2008; **63**: 1418–1427.
- Leung DY, Eichenfield LF, Boguniewicz M. Chapter 14. Atopic dermatitis (atopic eczema). In: Goldsmith LA, Katz SI, Gilchrist BA, Paller AS, Leffell DJ, Dallas NA, eds. *Fitzpatrick's dermatology in general medicine*, 8th ed. New York: McGraw-Hill, 2012.
- Papadakis MA, McPhee SJ, Rabow MW. Chapter 6. Dermatologic disorders. In: Papadakis MA, McPhee SJ, Rabow MW, eds. *Current medical diagnosis & treatment*. New York: McGraw-Hill Professional Publishing, 2013.
- Brown KD, Banuchi V, Selesnick SH. Chapter 47. Diseases of the external ear. In: Lalwani AK, ed. *Current diagnosis & treatment in otolaryngology – head & neck surgery*, 3rd ed. New York: McGraw-Hill, 2012.
- Edwards MJ, Agho K, Attia J, et al. Case-control study of cleft lip or palate after maternal use of topical corticosteroids. *Am J Med Genet* 2003; **120A**: 459–463.
- Czeizel AE, Rockenbauer M. Population-based case-control study of teratogenic potential of corticosteroids. *Teratology* 1997; **56** (5): 335–340.
- Carmichael SL, Shaw GM, Ma C, et al. Maternal corticosteroid use and orofacial clefts. *Am J Obstet Gynecol* 2007; **197** (6): 585.e1–585.e7.
- Mygind H, Thulstrup AM, Pedersen L, Larsen H. Risk of intrauterine growth retardation, malformations and other birth outcomes in children after topical use of corticosteroid in pregnancy. *Acta Obstet Gynecol Scand* 2002; **81** (3): 234–239.
- Hviid A, Mølgaard-Nielsen D. Corticosteroid use during pregnancy and risk of orofacial clefts. *CMAJ* 2011; **183** (7): 796–804.
- Chi C-C, Kirtschig G, Aberer W, et al. Evidence-based (S3) guideline on topical corticosteroids in pregnancy. *Br J Dermatol* 2011; **165** (5): 943–952.
- Kar S, Krishnan A, Preetha K, Mohankar A. A review of antihistamines used during pregnancy. *J Pharmacol Pharmacother* 2012; **3** (2): 105–108.
- Saxén I. Letter: cleft palate and maternal diphenhydramine intake. *Lancet* 1974; **1** (7854): 407–408.
- Briggs GG, Freeman RK, Yaffe SJ, eds. *Drugs in pregnancy and lactation*, 5th ed. Baltimore: Williams & Wilkins, 1998.
- Schatz M, Petitti D. Antihistamines and pregnancy. *Ann Allergy Asthma Immunol* 1997; **78** (2): 157–159.
- Weber-Schoendorfer C, Schaefer C. The safety of cetirizine during pregnancy. A prospective observational cohort study. *Reprod Toxicol* 2008; **26**: 19–23.
- Kallen B. Use of antihistamine drugs in early pregnancy and delivery outcome. *J Matern Fetal Neonatal Med* 2002; **11**: 146–152.
- Gilbert C, Mazzotta P, Loebstein R, Koren G. Fetal safety of drugs used in the treatment of allergic rhinitis: a critical review. *Drug Saf* 2005; **28**: 707–719.
- Diav-Citrin O, Shechtman S, Aharonovich A, et al. Pregnancy outcome after gestational exposure to loratadine or antihistamines: a prospective controlled cohort study. *J Allergy Clin Immunol* 2003; **111**: 1239–1243.
- Moretti ME, Caprara D, Coutinho CJ, et al. Fetal safety of loratadine use in the first trimester of pregnancy: a multicenter study. *J Allergy Clin Immunol* 2003; **111**: 479–483.
- Kallen B, Olausson PO. No increased risk of infant hypospadias after maternal use of loratadine in early pregnancy. *Int J Med Sci* 2006; **3**: 106–107.
- Schwarz EB, Moretti ME, Nayak S, Koren G. Risk of hypospadias in offspring of women using loratadine during pregnancy: a systematic review and meta-analysis. *Drug Saf* 2008; **31**: 775–788.
- Lione A, Scialli AR. The developmental toxicity of the H1 histamine antagonists. *Reprod Toxicol* 1996; **10**: 247–255.
- Serreau R, Komiha M, Blanc F, Guillot F, Jacqz-Aigrain E. Neonatal seizures associated with maternal hydroxyzine

- hydrochloride in late pregnancy. *Reprod Toxicol* 2005; **20**: 573–574.
37. Brost BC, Scardo JA, Newman RB. Diphenhydramine overdose during pregnancy: lessons from the past. *Am J Obstet Gynecol* 1996; **175**: 1376–1377.
38. Hara GS, Carter RP, Krantz KE. Dramamine in labor: potential boon or a possible bomb? *J Kans Med Soc* 1980; **81**: 134–136, 55.
39. Zierler S, Purohit D. Prenatal antihistamine exposure and retrolental fibroplasia. *Am J Epidemiol* 1986; **123**: 192–196.
40. So M, Bozzo P, Inoue M, Einarson A. Safety of antihistamines during pregnancy and lactation. *Can Fam Physician* 2010; **56** (5): 427–429.
41. LactMed: Drugs and Lactation Database. A peer-reviewed and fully referenced database of drugs to which breastfeeding. 2012.
42. Matheson I, Pande H, Alertsen AR. Respiratory depression caused by N-desmethyldoxepin in breast milk. *Lancet* 1985; **2** (8464): 1124.
43. Frey OR, Scheidt P, von Brenndorff AI. Adverse effects in a newborn infant breast-fed by a mother treated with doxepin. *Ann Pharmacother* 1999; **33** (6): 690–693.
44. Wollenberg A, Ehmann LM. Long term treatment concepts and proactive therapy for atopic eczema. *Ann Dermatol* 2012; **24** (3): 253–260.
45. Darsow U, Wollenberg A, Simon D, et al. European Task Force on Atopic Dermatitis/EADV Eczema Task Force. ETFAD/EADV eczema task force 2009 position paper on diagnosis and treatment of atopic dermatitis. *J Eur Acad Dermatol Venereol* 2010; **24**: 317–328.
46. Dotterud LK, Wilsaard T, Vorland LH, Falk ES. The effect of UVB radiation on skin microbiota in patients with atopic dermatitis and healthy controls. *Int J Circumpolar Health* 2008; **67**: 254–260.
47. Lam J, Polifka JE, Dohil MA. Safety of dermatologic drugs used in pregnant patients with psoriasis and other inflammatory skin diseases. *J Am Acad Dermatol* 2008; **59** (2): 295–315.
48. Gudjonsson JE, Elder JT. Chapter 18. Psoriasis. In: Goldsmith LA, Katz SI, Gilchrist BA, Paller AS, Leffell DJ, Dallas NA, eds. *Fitzpatrick's dermatology in general medicine*, 8th ed. New York: McGraw-Hill, 2012.
49. Park KK, Murase JE. Narrowband UV-B phototherapy during pregnancy and folic acid depletion. *Arch Dermatol* 2012; **148** (1): 132–133.
50. Gabbe SG. Drug therapy in autoimmune disease. *Clin Obstet Gynecol* 1987; **26**: 635–641.
51. Chin SO, Brodsky NL, Bhandari V. Antenatal steroid use is associated with increased gastroesophageal reflux in neonates. *Am J Perinatol* 2003; **20** (4): 205–213.
52. Wapner RJ, Sorokin Y, Mele L, et al. Long-term outcomes after repeat doses of antenatal corticosteroids. *N Engl J Med* 2007; **357** (12): 1190–1198.
53. Gur C, Diav-Citrin O, Shechtman S, Arnon J, Ornoy A. Pregnancy outcome after first trimester exposure to corticosteroids: a prospective controlled study. *Reprod Toxicol* 2004; **18** (1): 93–101.
54. Crowther CA, Doyle LW, Haslam RR, et al. Outcomes at 2 years of age after repeat doses of antenatal corticosteroids. *N Engl J Med* 2007; **357**: 1179–1189.
55. Schmand B, Neuvel J, Smolders-de Haas H, Hoeks J, Treffers PE, Koppe JG. Psychological development of children who were treated antenatally with corticosteroids to prevent respiratory distress syndrome. *Pediatrics* 1990; **86** (1): 58–64.
56. Park-Wyllie L, Mazzotta P, Pastuszak A, et al. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. *Teratology* 2000; **62** (6): 385–392.
57. Greenberger PA, Odeh YK, Frederiksen MC, Atkinson AJ Jr. Pharmacokinetics of prednisolone transfer to breast milk. *Clin Pharmacol Ther* 1993; **53**: 324–328.
58. McKenzie SA, Selley JA, Agnew JE. Secretion of prednisolone into breast milk. *Arch Dis Child* 1975; **50**: 894–896.
59. Elliott AB, Chakravarty EF. Immunosuppressive medications during pregnancy and lactation in women with autoimmune diseases. *Womens Health (Lond Engl)* 2010; **6** (3): 431–440.
60. Temprano KK, Bandlamudi R, Moore TL. Antirheumatic drugs in pregnancy and lactation. *Semin Arthritis Rheum* 2005; **35** (2): 112–121.
61. Bae YS, Van Voorhees AS, Hsu S, et al. National Psoriasis Foundation. Review of treatment options for psoriasis in pregnant or lactating women: from the Medical Board of the National Psoriasis Foundation. *J Am Acad Dermatol* 2012; **67** (3): 459–477.
62. Kainz A, Harabacz I, Cowlrick IS, Gadgil SD, Hagiwara D. Review of the course and outcome of 100 pregnancies in 84 women treated with tacrolimus. *Transplantation* 2000; **70** (12): 1718–1721.
63. Jain AB, Reyes J, Marcos A, et al. Pregnancy after liver transplantation with tacrolimus immunosuppression: a single center's experience update at 13 years. *Transplantation* 2003; **76** (5): 827–832.
64. Gardiner SJ, Begg EJ. Breastfeeding during tacrolimus therapy. *Obstet Gynecol* 2006; **107** (2 Pt 2): 453–455.
65. Nyberg G, Haljamae U, Frisette-Fich C, Wennergren M, Kjellmer I. Breast-feeding during treatment with cyclosporine. *Transplantation* 1998; **65**: 253–255.
66. Ryan C, Amor KT, Menter A. The use of cyclosporine in dermatology: part II. *J Am Acad Dermatol* 2010; **63** (6): 949–972.
67. Armenti VT, Ahlswede KM, Ahlswede BA, et al. Variables affecting birthweight and graft survival in 197 pregnancies in cyclosporine-treated female kidney transplant recipients. *Transplantation* 1995; **59**: 476–479.
68. Bar Oz B, Hackman R, Einarson T, Koren G. Pregnancy outcome after cyclosporine therapy during pregnancy: a meta-analysis. *Transplantation* 2001; **71**: 1051–1055.
69. Armenti VT, McGrory CH, Cater JR, Radomski JS, Moritz MJ. Pregnancy outcomes in female renal transplant recipients. *Transplant Proc* 1998; **30** (5): 1732–1734.
70. Lamarque V, Leleu MF, Monka C, Krupp P. Analysis of 629 pregnancy outcomes in renal transplant recipients with Sandimmune. *Transplant Proc* 1997; **29**: 2480.
71. Stanley CW, Gottlieb R, Zager R, et al. Developmental well-being in offspring of women receiving cyclosporine post-renal transplant. *Transplant Proc* 1999; **31**: 241–242.
72. Montnemery P, Nihlen U, Goran Lofdahl C, Nyberg P, Svensson A. Prevalence of self-reported eczema in relation to living environment, socio-economic status and respiratory symptoms assessed in a questionnaire study. *BMC Dermatol* 2003; **3**: 4.
73. Tendron A, Gouyon JB, Decramer S. In utero exposure to immunosuppressive drugs: experimental and clinical studies. *Pediatr Nephrol* 2002; **17**: 121–130.
74. Janssen NM, Genta MS. The effects of immunosuppressive and anti-inflammatory medications on fertility, pregnancy, and lactation. *Arch Intern Med* 2000; **160**: 610–619.

75. Armenti VT, Radoski JS, Moritz MJ, et al. Report from the national transplantation pregnancy registry (NTPR): outcomes of pregnancy after transplantation. *Clin Transpl* 2004: 103–114.
76. Davison JM, Dellagrammatikas H, Parkin JM. Maternal azathioprine therapy and depressed haemopoiesis in the babies of renal allograft patients. *Br J Obstet Gynaecol* 1985; **92**: 233–239.
77. Habal FM, Huang VW. Review article: a decision-making algorithm for the management of pregnancy in the inflammatory bowel disease patient. *Aliment Pharmacol Ther* 2012; **35** (5): 501–515.
78. Meggitt SJ, Anstey AV, Mohd Mustapa MF, Reynolds NJ, Wakelin S. British Association of Dermatologists' guidelines for the safe and effective prescribing of azathioprine 2011. *Br J Dermatol* 2011; **165** (4): 711–734.
79. Hyoun SC, Običan SG, Scialli AR. Teratogen update: methotrexate. *Birth Defects Res A Clin Mol Teratol* 2012; **94** (4): 187–207.
80. Stern RS, Lange R. Outcomes of pregnancies among women and partners of men with a history of exposure to methoxsalen photochemotherapy (PUVA) for the treatment of psoriasis. *Arch Dermatol* 1997; **127**: 347–350.
81. Gunnarskog JG, Kallen AJ, Lindelof BG, Sigurgeirsson B. Psoralen photochemotherapy (PUVA) and pregnancy. *Arch Dermatol* 1993; **129**: 320–323.
82. McCall CO. Chapter 52. Eczema, psoriasis, cutaneous infections, acne, and other common skin disorders. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds. *Harrison's principles of internal medicine*, 18th ed. New York: McGraw-Hill, 2012.
83. Pacifici GM. Placental transfer of antibiotics administered to the mother: a review. *Int J Clin Pharmacol Ther* 2006; **44** (2): 57–63.
84. Papadakis MA, McPhee SJ, Rabow MW. Chapter 6. dermatologic disorders. In: Papadakis MA, McPhee SJ, Rabow MW, eds. *Current medical diagnosis & treatment* 2013. New York: McGraw-Hill, 2013.
85. Drake AL, Roxby AC, Kiarie J, et al. Infant safety during and after maternal valacyclovir therapy in conjunction with antiretroviral HIV-1 prophylaxis in a randomized clinical trial. *PLoS One* 2012; **7** (4): e34635.