Published in final edited form as:

Immunol Allergy Clin North Am. 2023 February ; 43(1): 117–132. doi:10.1016/j.iac.2022.05.012.

Management of Allergic Skin Disorders in Pregnancy

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Keywords

Allergy; pregnancy; lactation; atopic dermatitis; chronic urticaria; contact dermatitis

INTRODUCTION

The safe management of allergic skin disorders during pregnancy is essential to maternal and fetal health. In this review, we address gaps in knowledge on the course and best management of atopic dermatitis (AD), chronic urticaria (CU), and allergic contact dermatitis (ACD) in pregnancy (Figure 1). Each section describes disease activity in pregnancy and disease-specific topical and systemic treatments. Tables 1-3 provide guidance for all relevant topical and systemic therapies during pregnancy, respectively. We briefly address concerns regarding breastfeeding at the end (Table 4). Data is limited on the safety and efficacy of many commonly employed treatments in human pregnancies and therefore, recommendations are largely based on observational studies. We hope publications from FDA-mandated post-marketing pregnancy registries for more recently approved therapies will provide greater clarity on best practices for pregnant patients with moderate to severe allergic skin diseases.

Change to risk classification of drugs in pregnancy

In 2014, the Food and Drug Administration (FDA) published the “Pregnancy and Lactation Labeling Rule” (PLLR) to replace the pregnancy letter categories (i.e., A, B, C, D, and X) previously used to classify drug risk in pregnancy. This new “narrative” system went into effect June 30, 2015, changing the content and format of information presented in prescription drug labeling. The PLLR aims to assist health care providers and pregnant women in assessing risk/benefit and in making informed decisions about taking a medication during pregnancy and lactation[1]. While this amended regulation allows patients more accessible and consistent prescription drug information and thus greater autonomy in their care, this transition may also create a challenge for providers who are more familiar with the old “category” system. To facilitate counseling of relevant medications, we recommend

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Conflicts of Interest or Authors Disclosures: LAB, MD is a consultant for Abbvie, Allakos, Astra-Zeneca, AIBio, Sanofi/Genzyme, DermTech, Sanofi-Aventis, Stealth biotherapeutics and an investigator for Abbvie, Astra-Zeneca, Kiniska, LEO Pharma, Pfizer, Regeneron, and Sanofi. LL is an investigator for Abbvie, AstraZeneca, Kiniska, Sanofi, Pfizer, Regeneron, and DermTech. EP is an investigator for DermTech.

consulting section 8 of the medication's FDA label, found online or in the prescription packaging (e.g., https://www.opzelura.com/prescribing-information.pdf). Section 8 includes risk summaries and animal data for both pregnancy (section 8.1) and lactation (section 8.2) and contact information for pregnancy exposure registries.

FDA approved therapies and general recommendations

For the treatment of AD in pregnancy, recommended therapies include moisturizers, topical steroids, topical tacrolimus, phototherapy, and systemic steroids or cyclosporine as a last resort[2]. Guidelines are similar for the treatment of ACD in pregnancy, with topical steroids being first line and systemic steroids reserved for severe cases[2,3]. For CU in pregnancy, first line treatment is non-sedating second-generation H1 antihistamines; systemic steroids, cyclosporine, and omalizumab may be reserved for recalcitrant cases[4-7].

ATOPIC DERMATITIS

Disease activity in pregnancy

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease, affecting up to 10% of adults in industrialized countries[8] and the most common skin disease in pregnancy[2,9]. AD is characterized by type 2 immune deviation, skin barrier dysfunction, and pruritus[10], as well as bacterial and viral skin infections, allergen sensitization, and collectively, a negative impact on quality of life measures[2]. During pregnancy, the immune system shifts towards a type 2 immune response[2]. The high levels of estrogen and progesterone enhance the activity of Th2 and T regulatory cells, which collectively suppress Th1 and Th17 activity[10]. This shift is thought to reduce the immunologic response against the fetus, creating a favorable environment for acceptance of the allogenic fetus and reducing the risk of miscarriage[2,10]. The type 2 response has a humoral component with the induction of IgE as well as production of the inflammatory cytokines implicated in AD, including IL-4, IL-5, and IL-13. Unfortunately, the immunological state of pregnancy may lead to worsening of AD[2]. Furthermore, the physical and psychological stress of pregnancy may also exacerbate pre-existing AD[2]. Importantly, there is little to no evidence to suggest AD directly affects fertility or rate of miscarriage and does not cause birth defects or preterm birth[11].

The effect of pregnancy on AD disease activity is highly variable with some patients improving, worsening, or staying the same[12]. One report cited 25% of pregnant women see improvements in their AD, 50% deteriorate, and 10% flare in the post-partum period[11]. This is consistent with the estimate that 52-61% of cases worsen during pregnancy, most notably during the second and third trimesters[10,13]. However, a recent cross-sectional study reported only 17.7% of pregnant women experienced worsening of their AD, which led the authors to conclude "most will not experience worsening AD during pregnancy"[14].

A Danish birth registry identified an overrepresentation of premature rupture of membranes and staphylococcal neonatal septicemia in mothers with AD, but no associations with any other significant prenatal, obstetric, or birth outcomes[15]. Rather, it is the potential complications of under-treated, moderate to severe AD (i.e., eczema herpeticum, secondary

staphylococcus infections, neonatal septicemia) that poses maternal and fetal risk[2,8]. Physicians are quite risk-averse and offer very restricted treatment options; consequently, pregnant women with AD are often inadequately managed and so experience recurrent flares and even infections[2].

Disease management and treatment

Adequate management of AD during pregnancy is imperative to reduce maternal and fetal risk. However, treating pregnant or lactating women can be a challenge, as there are no large, well-controlled clinical studies on the effects of AD treatments in this population[8]. Recommendations include advising AD patients prior to conception, with the goal of minimizing baseline disease activity and avoiding irritants and relevant allergens[11]. The European Task Force on Atopic Dermatitis (ETFAD) recommends a safety-first approach for the treatment of future mothers and pregnant or lactating women. In order of preference, safe treatments include moisturizers, topical steroids, and topical tacrolimus; UV therapy or moderate sun exposure; and systemic treatments (i.e., systemic steroids and cyclosporine A) for severe cases[2]. Azathioprine may only be used with strict indications, both methotrexate and mycophenolate mofetil are absolutely contradicted, and there is still not clear data on the risk of dupilumab. The following section provides more detail on the management of AD during pregnancy, including topical, systemic, and emerging therapies. Tables 1-3 provide a quick reference.

Topical treatments—Basic emollients with a high lipid content, tepid baths, and avoidance of basic soaps are key[2]. Topical corticosteroids (TCS) are first line in both pregnant and non-pregnant women due to their minimal systemic side effects, although local side effects may be slightly greater in pregnancy especially when used in areas prone to striae formation. TCS may be used proactively or reactively. They have no association with preterm delivery, birth defects, fetal death, or low Apgar scores, although very potent TCS may be associated with low birthweight[2,16]. Group 6 and 7 TCS are typically not potent enough to be beneficial in AD, groups 3-5 are often suitable, group 2 may be used in the short term, and group 1 should be avoided unless necessary for rescue therapy[2]. Importantly, fluticasone propionate is not metabolized by the placenta and should not be used[2].

To date, there are no studies on the use of topical calcineurin inhibitors (TCI) in pregnancy. Systemic absorption of topical tacrolimus is very low, and available data suggests the risk of congenital defects is not increased[2,17]. Although topical pimecrolimus is absorbed even less[18], its FDA label currently says not to use because of lack of experience. Topical tacrolimus is recommended due to a large amount of existing data and may be preferable to TCS especially for use on the face and areas prone to striae formation[2].

There are no studies on the use of crisaborole in pregnancy. Its FDA label says it is contraindicated, and should not be used preconceptionally, in pregnancy, or during lactation due to lack of experience[2].

Ruxolitinib is a topical potent, selective inhibitor of JAK1 and JAK2, recently FDA approved for short term and non-continuous use in mild to moderate AD in patients 12 years and older. There are no published studies on ruxolitinib in human pregnancies and

observational data is insufficient at this time to make a formal recommendation; it is advised to avoid topical ruxolitinib in the pregnant and breastfeeding population[19].

Topical antibiotics can be used, although it is preferable to escalate the potency of a topical steroid rather than initiate topical antibiotics. Mupirocin is preferred because of its reduce allergenicity as compared to neomycin and bacitracin and its superior efficacy in treating methicillin-sensitive and -resistant *staphylococcus aureus* (MSSA and MRSA) infections[20].

Phototherapy—There are no published studies on the safety and efficacy of phototherapy in pregnancy. Broad-spectrum and narrow-band UVB and UVA1 therapy are not thought to impose a risk to the fetus and can be used liberally if topical therapy fails. UVB therapy does decrease folic acid levels and should be supplemented preconceptionally and in the first trimester[21]. Phototherapy may also exacerbate pregnancy-induced hyperpigmentation (i.e., melasma); facial shielding may be advised depending on patient skin type. Lastly, psoralen plus ultraviolet A (PUVA) therapy is not a safe option because psoralen should not be used three months prior to conception, during pregnancy, or while breastfeeding[2].

Systemic anti-inflammatories—Evidence for treatment of AD in pregnancy with systemic anti-inflammatories is observational and limited. Therapy should be initiated on an individual basis and in close collaboration with an experienced obstetrician. Although systemic corticosteroids (SCS) are used in non-pregnant patients in short courses for acute or severe flares, the risk/benefit ratio for their use is generally considered unfavorable. During pregnancy, SCS increase the risk of gestational diabetes, preeclampsia/eclampsia, premature rupture of membranes, and preterm delivery; repeated treatment courses may lead to decreased birthweight and gastroesophageal reflux disease[2,16]. Therefore, when possible, it is recommended to prioritize other therapies, such as escalating topical steroid therapy[2]. SCS are fortunately rarely needed in pregnant AD patients; however, they are considered reasonably safe to use with proper monitoring of the mother and child. Additionally, in patients with concomitant asthma, the benefits of SCS in controlling asthmatic attacks clearly outweigh the risks during pregnancy[12]. The general recommendation is to limit their use and use only for the patient that has failed adequate administration of topical steroids and UV therapy. Preference is given for prednisolone (and not dexamethasone) at doses only up to 0.5 mg/kg/day for less than two to three weeks[2].

Cyclosporine A (CyA) crosses the placenta but has no increased risk of congenital malformations or fetal death; it may have an increased risk of low birthweight[2]. Most of the data on CyA during pregnancy comes from transplant recipients who generally receive higher doses than dermatologic patients[16]. CyA is considered a safe treatment alternative in cases recalcitrant to other therapies and can be used off-label if there is a clear need for long-term control. CyA is considered the default immunosuppressive treatment for patients that need continuous treatment during pregnancy. Extra attention should be given to the patient’s renal function and blood pressure[2].

Azathioprine (AZA) has been used off-label in cases of severe and uncontrolled AD where phototherapy and other systemic therapies have failed. For example, it has been used in other systemic inflammatory diseases (e.g., bowel disease, rheumatic disease, organ transplants)

during pregnancy without consistent evidence of birth defects[22]. According to its FDA label, AZA is contraindicated during pregnancy. The ETFAD also recommends avoiding AZA during pregnancy but does stipulate that if a woman is already receiving AZA at the time of conception and there are no safer alternatives, treatment can be continued, and the dosage should be reduced by 50%[2].

Methotrexate (MTX) is well known to be associated with severe birth defects even at low doses and is therefore absolutely contraindicated during pregnancy. There is a discrepancy between waiting periods with some sources recommending stopping treatment 6 months before planned pregnancies and others recommending only 1-3 months; the risk/benefit of a shorter waiting period should be discussed on an individual basis[2].

Mycophenolate mofetil (MMF) is considered teratogenic and associated with specific embryonal malformations. MMF is absolutely contraindicated during pregnancy and should never be used in women who are planning pregnancy, pregnant, or breastfeeding. The FDA requires contraceptive counseling and use during and for three months after stopping therapy[2].

Oral antihistamines—Oral antihistamines may be used if clinically indicated. Even in non-pregnant patients, they have limited efficacy in managing AD and have little effect on pruritus[2]. They are sometimes used for their sedative effects, but not considered first choice or an optimal therapy for AD in any patient population. In pregnancy, loratadine, a second generation H1 antihistamine, is preferred based on extensive experience[23]. Cetirizine may also be used and may relieve pregnancy-associated nausea and vomiting[12]. The sedating antihistamines may be used for strict indications with accompanying counseling on the long-term side effects (e.g., motoric and cognitive function) and a risk/benefit discussion[23].

Dupilumab—Dupilumab, a fully human IgG4 monoclonal antibody against the IL-4 receptor alpha that inhibits signaling of both IL-4 and IL-13, is the first biologic treatment FDA approved for the treatment of moderate to severe AD[24] and becoming an increasingly popular option for severe or recalcitrant disease. As an IgG antibody, intrauterine exposure to dupilumab from mid-gestation on is likely to be quite high; it is also excreted in breast milk[24]. Though post-marketing data on dupilumab in pregnancy is limited[9], there are a few case reports of pregnant AD patients treated with dupilumab who achieved dramatic skin improvement and no adverse events for either mother or child[13]. In one report, the patient received a loading dose of 600mg starting at 24 weeks of pregnancy followed by 300mg every other week and had an uncomplicated delivery of a healthy male infant[9]. In another report, the patient was on 300mg every other week at the time of conception and continued dupilumab until almost 25 weeks of gestation and had an uncomplicated delivery of a healthy female infant[24]. Furthermore, animal studies do not indicate direct or indirect harmful effects. The available data has not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes[24]; however, due to lack of experience and limited data, contraception is advised during therapy and dupilumab use during pregnancy is possible only if the potential benefits to the mother are higher than the potential risks to the fetus[8]. It is encouraged to enroll patients in the pregnancy registry

study (https://clinicaltrials.gov/ct2/show/NCT03936335) to monitor outcomes, adverse or otherwise, in women exposed to dupilumab during pregnancy and lactation[24].

JAK inhibitors—The data on the effects of any of the JAK inhibitors on human fertility and pregnancy is scant. Animal models suggest potential effects on fetal development and pregnancy outcomes. Therefore, it is strongly recommended to use effective birth control while taking an oral JAK inhibitor and to avoid becoming pregnant during therapy and for at least four weeks after the last dose[8]. It remains unclear whether these risks are lower with topical JAK inhibitors and moreover, how much the risk relates to the body surface area treated with the topical. Strict avoidance of topical JAK inhibitors in women planning pregnancies is also advisable[19].

Emerging biologics—There are several new monoclonal antibodies that target IL-13, OX40, OX40L, IL-5 receptor alpha, and IL-31 for treatment of AD. In fact, tralokinumab-Idrm, an inhibitor of IL-13, was FDA approved late December 2021 for the treatment of moderate to severe AD in adults 18 years or older[25]. There is no data on the effects of these new biologics on fertility, pregnancy, or breastfeeding and at this point, they should be avoided in pregnancy[8].

In conclusion, there is limited evidence on the use of many AD treatments in human pregnancies and the impact of new medications on fertility is largely unknown. Importantly, the lack of adverse effects on animal fertility does not exclude a potential impact on humans. AD patients should consider planning a pregnancy when their disease is in remission or at least taking the minimum effective dose of medications with the best safety profiles, while ensuring adequate control to prevent secondary complications. Emollients and moisturizers should be used liberally. Low to mid potency TCS are first line therapy[8]. Systemic therapies, including SCS and CyA, may be used on an individual basis with a careful assessment of potential risks and benefits with the patient's dermatologist and obstetrician.

CHRONIC URTICARIA

Disease activity in pregnancy

Chronic urticaria (CU) is characterized by greater than six weeks of recurrent pruritic wheals, angioedema, or both, and has a lifetime prevalence of approximately 20%[26]. It is further divided into chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU), the latter including 9 subtypes[4,5]. Diagnosis is generally clinical and may be difficult as subtypes can co-exist and the differential is broad, including mast cell activation syndrome, polymorphous light eruption, the urticarial form of bullous pemphigoid, drug reactions, cutaneous lupus erythematous, urticarial vasculitis, Schnitzler syndrome, Well's syndrome, and hereditary or acquired angioedema[5,26,27].

Females have a higher prevalence of CU (3:1), greater disease activity, poorer prognosis, and decreased responsiveness to antihistamines or omalizumab[28-34]. The reasons for gender differences and the impact of pregnancy on disease severity remain unclear. Possible explanations include higher rates of autoimmunity in females and influences on sex hormones on menses, pregnancy, menopause, and hormonal therapies[29]. Despite

an undefined pathogenic mechanism for CU, perivascular, Th2 cellular infiltrates are considered its predominant immunologic driver, while elevated plasma Th1/17 cytokines favor a role for type 1 and 3 immunity[35-39]. Central to both CSU and CIndU pathogenesis is mast cell and basophil degranulation with the release of histamine, leukotrienes, prostaglandins, and other proinflammatory mediators[5]. In CSU, triggers of mast cell degranulation include idiopathic and/or circulating autoantibodies: IgE targeting self-antigens (type I autoimmunity) or IgG/IgM activating dermal mast cells and basophils (type IIb autoimmunity) targeting the alpha subunit of the high affinity IgE receptor (FcεR1) or crosslinking IgE present on the high affinity IgE receptor[26,40-42]. Some CU patients experience exacerbations from aspirin, nonsteroidal anti-inflammatory drugs (NSAID)s, food, and/or stress[26,43]. In CIndU, mast cell degranulation stems from an indirect response to physical stimuli, such cold, deep pressure, vibration, and/or sunlight[4]. Provocation tests are commonly employed to diagnose CIndU, whereas CSU remains a clinical diagnosis that occasionally requires a skin biopsy to rule out differential diagnoses[26].

As highlighted in the section on AD disease activity in pregnancy, regulatory T cells play a central role in the immune-tolerant state via a shift towards the Th2 axis, a deviation which may explain gestational exacerbations of Th2-driven diseases (e.g., AD, allergic rhinitis, asthma) or improvement in Th1/Th17 driven-diseases (e.g., psoriasis, rheumatoid arthritis)[44,45]. To date, limited data exists on incidence and disease pattern of urticaria and angioedema in pregnancy; accordingly, CU is not considered a “pregnancy-related dermatosis”[46].

Gestational changes in sex hormones, however, have shown effects on mast cell and basophil activity[28,47,48]. Progesterone inhibits mast cell secretion and basophil activation, while estrogen increases histamine release in rat mast cells and human basophils[49]. These observations may highlight why sex differences in CU prevalence are only observed between puberty and menopause[29]. High levels of synthetic estrogens via consumed substances or pollutants have also demonstrated rapid mast cell and histamine release; in fact, high levels of circulating mast cells have been shown to exacerbate pruritic urticarial papules and plaques of pregnancy (PUPPP)[46,50]. Lastly, a few studies found lower levels of dehydroepiandrosterone (DHEAS), an androgenic immunomodulatory hormone, in CU patients[51,52].

Although the severity of CU may vary in response to hormonal exposures or pregnancy trimesters, no effect on fertility, labor, or delivery has been identified[51,53]. In the first international, multicenter study of CU in pregnancy (PREG-CU UCARE), about half of women (51.1%; n = 148/288) experienced skin improvement and a minority reported new or recurrent angioedema (17.4%, n= 50/288), irrespective of trimester. When stratified by trimester, skin exacerbations were most common in the first and third trimesters[46]. Because CU seems to be more commonly associated with cytokines reflective of type 2 immunity, questions remain regarding the hormonal influences on mast cells and basophils and their releasability[46]. Perhaps elevated levels of progesterone, estrogen, and cortisol are the key contributors to mast cell and basophil degranulation, and therefore CU activity. After birth, 37.4% (n = 265) of woman reported worsening skin symptoms and/or angioedema from their pre-gestational baseline. When stratified by risk factors, exacerbations of CU

during pregnancy were more commonly observed in woman with no previous history of angioedema, or low CU disease activity, untreated disease, or the CIndU subtype before pregnancy[28].

Disease management and treatment

With no cure or ability to predict the timing and likelihood of spontaneous remission, the goal of CU treatment is symptom control[5]. To help guide treatment decisions, validated patient-reported measures, such as urticaria and angioedema activity scores, are becoming customary in clinical practice. Avoidance of eliciting factors and searching for underlying factors is also important. For CIndU tolerance, induction may be a useful option[54]. Pharmacologically, the goal is reducing the downstream features of mast cell and/or basophil mediators (i.e., histamine and leukotrienes) and free total IgE. To control symptoms, treatments should be used daily and not on an as needed basis[26,55].

Systemic treatments—First line treatments are second generation, non-sedating H1 antihistamines with up-titration every 1-4 weeks until fourfold the manufacturer recommended dosage is reached[4,56]. Sedating, first generation antihistamines are generally not recommended, but still employed in particularly refractory cases[57,58]. For patients unresponsive to second generation antihistamines, omalizumab may be added as treatment for either CSU or CIndU[6,59]. Initial dosing is 150 to 300mg every 4 weeks with higher doses (5 mg/kg) or shorter intervals available off-label to patients with insufficient benefit with approved dosing[6,60]. Lastly, cyclosporine A (3.5-5 mg/kg per day) may be added to second generation H1 antihistamines if patients are not sufficiently controlled with these measures[7,61]. In cases of severe exacerbation, short courses of systemic corticosteroids (20 – 50 mg/day prednisone for maximum 10 days) may be added[5,62].

There is a paucity of literature on CU management in pregnant or lactating women. However, treatment algorithms emphasize using the lowest effective medication dose[4]. In the context of the new, 2015 pregnancy and lactation labelling guidelines, the non-sedating, second generation antihistamines remain first-line treatment in Europe and the United States. Utilization is safe during all trimesters, but discontinuation is encouraged 3-7 days prior to delivery to avoid potential side effects in infants from immature metabolism[63,64]. Preferred agents in pregnancy and breastfeeding include low dose loratadine followed by cetirizine, largely due to safety profile and low concentrations in breastmilk[56,65].

Leukotriene antagonists (LTA), including montelukast and zafirlukast (but not Zileuton), may be added with no concern for neonatal structural abnormalities or perinatal problems[12]. More recently, the use of LTA in CU patients with angioedema lesions has been shown to be beneficial[66]. If indicated, cyclosporine may be used but poses a risk for premature labor and gestational toxemia and can achieve high concentrations in breastmilk[67].

Omalizumab—Little is known about the safety and efficacy of omalizumab during pregnancy and breastfeeding. There is reason to suspect that omalizumab may cross the placenta as an anti-IgE/IgE immune complex bound to the neonatal fetal receptor (FcRn), raising concerns that omalizumab could affect fetal immune development[68]. To date, the EXPECT Xolair Pregnancy Registry, the largest prospective observational study on perinatal

and neonatal outcomes in women treated for asthma, has not found an increased risk of congenital abnormalities[69]. Less is known about the safety of omalizumab during pregnancy in CSU patients, with only about 13 cases reported in literature. All cases, however, resulted in normal pregnancies with no gestational or fetal complications[5]. Tables 1-3 provide a quick reference.

ALLERGIC CONTACT DERMATITIS

Disease activity in pregnancy

Allergic contact dermatitis (ACD), a type IV-mediated delayed hypersensitivity reaction, is caused by cutaneous exposure to an exogenous substance that elicits an inflammatory response[70]. It may present as an acute, subacute, or chronic dermatitis, and is characterized by pruritus and typically sharply delineated lesions consisting of erythema, induration, vesicles, and/or desquamation[3]. Although this is a very common inflammatory skin disorder in the general population and more common in females, there is no data on the prevalence of ACD during pregnancy[12]. A history of AD may also be a contributing factor[3].

Disease management and treatment

The mainstay of treatment for ACD is avoidance of the allergen[3]. Thus, identification of the causative allergy is necessary for resolution of ongoing ACD[71] and the gold standard for diagnosis is patch testing. It is advised patch testing should be deferred until after pregnancy[71] and women who are breastfeeding should also not be patch tested[12]. However, there is no clear evidence of adverse effects on pregnancy outcomes or evidence to suggest the immunologic changes of pregnancy would alter the accuracy of patch testing[71]. Tables 1-3 provide a quick reference.

Topical and systemic treatments—The same treatment guidelines for AD in pregnancy apply to ACD in pregnancy as the recommended therapies overlap. Mid potency TCS are recommended as first line treatment for exacerbations in non-pregnant patients[3] and are also safe to use in pregnant patients for severe ACD. In the pregnant population it is recommended to use only up to 0.5 mg/kg/day for 2-3 weeks and to avoid >20 mg/day if possible[2]. Antihistamines have generally not been shown to be helpful in treating the pruritus associated with ACD and are therefore not recommended in pregnant ACD patients[12].

CONCERNS REGARDING BREASTFEEDING

In general, few to no studies have examined the safety of various dermatologic treatments on breastfeeding and recommendations are based on observational studies. TCS and TCI are safe to use, with the caveat they should ideally be applied immediately after breastfeeding and the nipple should be cleaned before the next feeding[2]. SCS are safe to use as rescue therapy, but breastfeeding should be delayed four hours after ingestion[2]. For CyA and AZA, their use is highly debated and may only be used under extreme circumstances[2]. Both MTX and MMF are contraindicated during breastfeeding[2]. Finally, biologics including dupilumab

and omalizumab are not recommended at this time due to a lack of safety data, although case reports have shown no adverse effects[24,69]. Table 4 provides a quick reference.

SUMMARY

This review has covered the management of atopic dermatitis, chronic urticaria, and allergic contact dermatitis during pregnancy and while breastfeeding. We demonstrated the complex interplay of the hormonal and immunologic effects of pregnancy on allergic skin disorders. We focused on disease course, safety and efficacy of topical and systemic treatments, and postpartum considerations to best advise patients with gestational planning. The Hippocratic oath to “do no harm” must be balanced with the need to achieve adequate management of these disorders, as poorly controlled allergic skin disease also affects the health of mother and child.

Financial Disclosure:

Atopic Dermatitis Research Network (ADRN) 3 grant U01AI152011

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Key Points:

- The most prevalent allergic skin disorders in pregnancy include atopic dermatitis, chronic urticaria, and allergic contact dermatitis
- Disease activity of these skin disorders may vary in pregnancy
- Treatments may include topical and systemic medications
- To ensure maternal and infant health and to prevent secondary complications, it is vital to balance prescribing effective yet safe medication dosages and maintaining adequate disease control

Synopsis:

This article reviews the disease course and treatment of atopic dermatitis, chronic urticaria, and allergic contact dermatitis in pregnancy. It focuses on topical and systemic therapies in the context of pregnancy and breastfeeding. Because disease activity may vary in pregnancy, prescription stewardship is imperative; a balance between disease control, minimum effective dosing, and medication safety profiles should be maintained. Secondary complications and risks to maternal or infant health should also be avoided.

CLINICAL CARE POINTS

- Consider planning a pregnancy when the allergic skin disorder is under good control or during remission
- Prescribe the minimum effective dose of medications with the best safety profiles
- Ensure adequate control to prevent secondary complications
- Dermatologists and allergists need to work closely with obstetricians when more aggressive systemic treatments are necessary

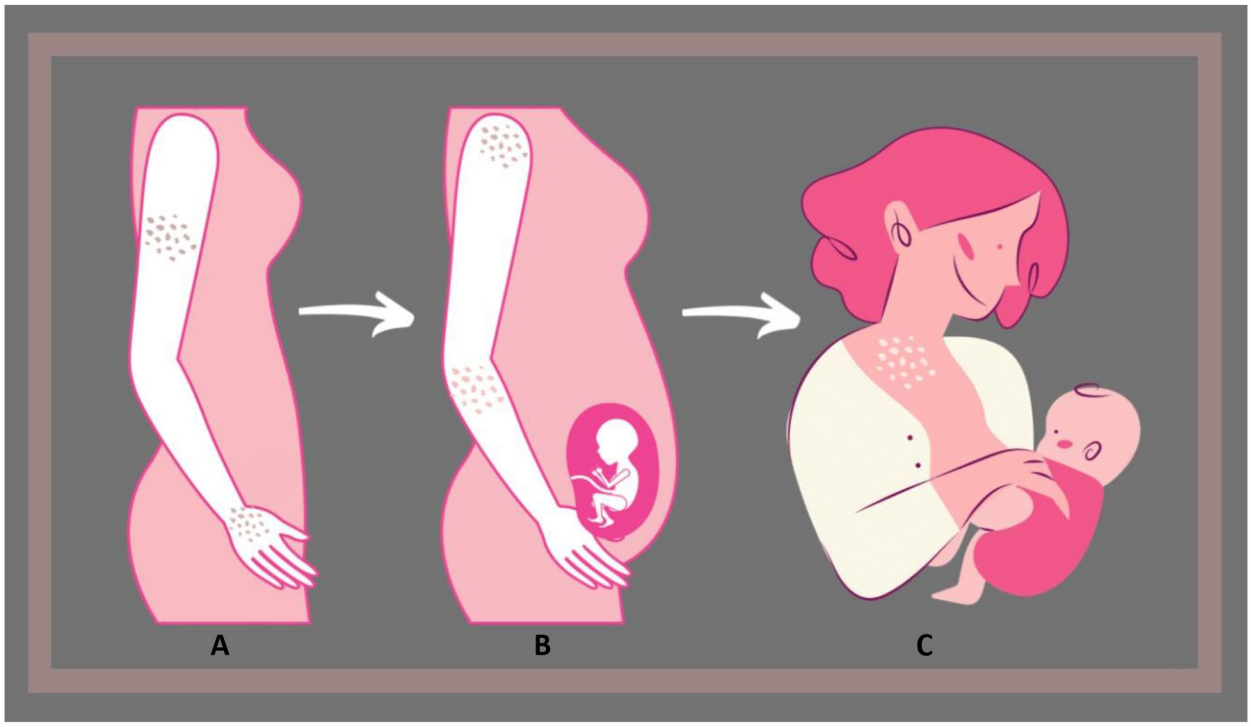

Figure 1.

It is important to understand how the common allergic skin diseases (i.e., atopic dermatitis, chronic urticaria, and allergic contact dermatitis) and their treatments impact the health of A) women of childbearing potential, B) women and fetuses during the gestational period, and C) women and infants while breastfeeding. *Images were obtained on Canva.com and modified via color and object overlays.*

Table 1.

Guidance for Topical Therapy During Pregnancy

Therapy	Recommendations
Moisturizers	• First line • Patient's choice
Topical corticosteroids (TCS)	• First line • Low-mid potency recommended • High potency as rescue therapy or on limited skin areas • Fourth generation preferred • Avoid fluticasone propionate • Consider UV therapy if use exceeds 200 g/month
Topical calcineurin inhibitors (TCI)	• Use on limited skin areas is permissible • Preferred use on face and areas prone to striae formation • Tacrolimus recommended (not much data on safety or efficacy of pimecrolimus)
Topical phosphodiesterase-4 inhibitors (PDE-4i; Crisaborole)	• Not recommended due to lack of experience/data
Topical antibiotics	• Escalate TCS first
Topical JAK inhibitors (JAKi; Ruxolitinib)	• Not recommended due to lack of experience/data

Table 2.

Topical Steroid Potencies

Potency	Examples
Least potent (Group 7)	• Hydrocortisone 1%, 2.5% cream, ointment, lotion
Low (Group 6)	• Desonide 0.05% cream, lotion • Fluocinolone acetonide 0.01% cream • Triamcinolone 0.025% cream, lotion
Lower-mid (Group 5)	• Fluocinolone acetonide 0.025% cream • Triamcinolone 0.1% lotion, 0.025% ointment
Medium (Groups 4)	• Fluocinolone acetonide 0.025% ointment • Mometasone furoate 0.1% cream, lotion • Triamcinolone acetonide 0.1% cream, ointment
High (Group 3)	• Betamethasone dipropionate 0.05% cream • Mometasone furoate 0.1% ointment
High (Group 2)	• Betamethasone dipropionate 0.05% cream, ointment • Desoximetasone 0.25% cream, ointment • Fluocinonide 0.05% cream, ointment
Super-high (Group 1)	• Betamethasone dipropionate, augmented 0.05% ointment • Clobetasol propionate 0.05% cream, lotion, ointment • Fluocinonide 0.1% cream • Halobetasol propionate 0.05% cream, lotion, ointment

Table 3.

Guidance for Systemic Therapy During Pregnancy

Therapy	Recommendations
Systemic corticosteroids	• May be used as rescue therapy • Prioritize other therapies first (i.e., escalate TCS) • Prednisolone preferred • Recommend use only up to 0.5 mg/kg/day and avoid >20 mg/day • Use no more than 2-3 weeks
Cyclosporine	• Reserve as rescue therapy for severe disease • Default first line immunosuppressive for continuous treatment/long-term control • Can cause maternal hypertension and renal dysfunction
Azathioprine	• May be used under strict indications if no other therapy is possible • Avoid initiating after conception • Halve dose if already taking at time of conception
Methotrexate	• Absolutely contraindicated • Wait 1-6 months after stopping treatment to conceive
Mycophenolate mofetil	• Absolutely contraindicated • Women should use non-hormonal contraception until 2-3 months after stopping therapy
Oral antihistamines	• Not considered first choice or optimal therapy for AD in any patient population • Loratadine first choice • Cetirizine second choice (may also relieve pregnancy-associated nausea)
Dupilumab	• Not advised at this time due to lack of experience/data • Case reports show no adverse effects • Limited data have not identified a drug-associated risk
Systemic JAK inhibitors	• Avoid becoming pregnant during treatment and for at least 4 weeks after last dose
Phototherapy	• UVB (broadband or narrow) or UVA1 recommended • PUVA not advised
Omalizumab	• May be used as rescue therapy • Registries show no increase in rate of birth defects or miscarriage

Table 4.

Guidance for Therapies During Breastfeeding

Therapy	Recommendations
Topical corticosteroids	• Safe to use • Apply immediately after feeding • Clean nipple before next feeding
Topical calcineurin inhibitors	• Safe to use • Apply immediately after feeding • Clean nipple before next feeding
Topical PDE-4 inhibitors (PDE-4i; Crisaborole)	• Not recommended
Topical JAK inhibitors (JAKi; Ruxolitinib)	• Not recommended
Phototherapy	• Safe to use
Systemic corticosteroids	• Safe to use as rescue therapy • Wait to breastfeed 4 hours after ingestion
Oral antihistamines	• Safe to use • Nonsedating, second generation preferred • Use caution with first generation and monitor child for irritability/drowsiness
Cyclosporine	• May be used off-label under strict indications
Azathioprine	• Use debated • Wait to breastfeed for 4 hours after ingesting or discard milk produced within 4 hours after dose • Monitor child for signs of immunosuppression/periodically check child blood counts
Methotrexate	• Contraindicated
Mycophenolate mofetil	• Contraindicated
Dupilumab	• Not recommended for time being due to lack of experience/data • Case reports show no adverse effects
Omalizumab	• Safe to use