# Asthma, Allergic and Immunologic Diseases During Pregnancy

## A Guide to Management

Jennifer A. Namazy
Michael Schatz
*Editors*

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# Preface

> The management of the pregnant allergic patient presents a challenge to the attending physician. It is a barbed challenge replete with therapeutic pitfalls and dangers strewn all along the way from early pregnancy through childbirth…
>
> – Angelo Maietta, MD, FACA, *Annals of Allergy* 1955

More than 60 years later, this statement is still relevant. The "therapeutic pitfalls" exist because many of the commonly used medications have very little human safety data. The "dangers strewn along the way" today consist of fear of possible adverse outcomes to mother and baby from medications or the disease themselves. This "phobia" of medication use during pregnancy has led many women and clinicians to discontinue much needed medications during pregnancy. And, despite this, over the last three decades, first-trimester use of medications by pregnant patients has increased more than 60% [1].

We hope this book will provide primary care providers and specialists with a common understanding of asthma, allergic, and immunologic diseases during pregnancy. With a general understanding of allergic disease, providers may perform adequate preconception planning, manage patients effectively, and consult with specialists when needed.

This book brings together world-renowned experts with a broad spectrum of clinical experience and research interests to provide the reader with a comprehensive review of asthma, allergic, and immunologic diseases during pregnancy. Drs. Woessner and Brauer begin the book with an overview of nonpharmacologic management of allergic diseases during pregnancy, particularly of respiratory conditions. Next is Dr. Chambers' review of the safety of asthma and allergy medications during pregnancy. Dr. Murphy then provides an overview of the interrelationships between asthma and pregnancy followed by a summary of the management of asthma during pregnancy by Dr. Namazy. This is followed by a series of chapters devoted to the management of other specific conditions during pregnancy: rhinitis and sinusitis by Drs. Carroll, Bulkhi, and Lockey; anaphylaxis by Dr. Calabria; atopic and contact dermatitis by Drs. Fonacier and Mawhirt; urticaria and angioedema by Drs. Joshi and Khan; hereditary angioedema by Drs. Zuraw and Christiansen; drug allergy by Dr. Macy; and primary immunodeficiency by

Drs. Kakkar and Hajjar. These chapters are followed by a discussion of the obstetric management of high-risk allergic patients by Dr. Dombrowski. Finally, Dr. Leonard provides a chapter on the prevention of asthma and allergic diseases during childhood.

And let us remember the additional wise words of Dr. Maietta, "The allergic expectant mother may be fearful lest her allergic symptoms disrupt pregnancy or the pregnancy aggravate her allergy. These emotional reactions should be understood and treated continuously with cheerful reassurance…." We hope that this book will give readers confidence in their gestational management such that they can provide optimal care as well as this needed "reassurance."

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# Chapter 1
# Non-pharmacologic Aspects of Management: "Asthma and Allergic and Immunologic Diseases During Pregnancy – A Guide to Management"

**David Lawrence Brauer and Katharine Margaret Woessner**

## Introduction

Pregnancy represents a unique physiologic state that makes management of chronic disease more challenging, particularly when considering use of pharmacologic therapies in the context of risk for possible teratogenicity and poor maternal-fetal outcomes [1]. Allergic diseases are among the most commonly encountered disorders affecting 18–30% of women in the United States during their childbearing years, with asthma and allergic rhinitis being the most common [2]. Allergic rhinitis, asthma, and atopic dermatitis represent the three main allergic disease states that can be expected to be encountered during pregnancy. Non-pharmacologic approaches to the management of atopic disorders in pregnancy need to be a key part of any disease state management plan. This need is the greatest during the first trimester. This chapter focuses on effective avoidance strategies and other non-pharmacologic approaches to the management of common allergic disease in the pregnant patient, allowing for better outcomes while at the same time limiting exposure to unnecessary medical therapy.

## Allergic Rhinitis

Nasal symptoms are common in the pregnant population, occurring in about 30% of pregnant women. Apart from pre-existing conditions, hormones associated with pregnancy can affect nasal blood flow and local mucus glands leading to either the

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appearance of previously nonexistent symptoms or worsening of pre-existing nasal disease. Among the etiologies responsible for nasal symptoms during pregnancy, allergic rhinitis, vasomotor (non-allergic) rhinitis, sinusitis, and rhinitis medicamentosa are the most common that require treatment. The course of pre-existing allergic rhinitis during pregnancy is somewhat unpredictable and unique to each individual patient. Allergic rhinitis that has existed prior to pregnancy is known to improve, worsen, or remain stable during pregnancy [2]. Allergic rhinitis typically presents in patients with prominent nasal and ocular symptoms, such as rhinorrhea, nasal pruritus, sneezing, ocular pruritus, and ocular irritation. Allergic rhinitis can be commonly triggered by environmental factors such as pollens, dust mites, molds, and animal dander. As such, avoidance of allergens is a key modality of treatment in patients with allergic rhinitis. Although allergy skin testing can be beneficial for identifying causative allergens, due to the very small risk of systemic reaction, skin prick testing should be avoided during pregnancy. Serum IgE testing for environmental allergens is now widely available and represents a safer alternative for evaluation of causative allergens in pregnant women [3].

## Asthma

Asthma typically can present with symptoms such as shortness of breath, wheezing, cough, and chest tightness. Confirmation of the diagnosis is ideally made through demonstrating evidence of reversible airway obstruction, which can be quantified by spirometry or pulmonary function testing that shows a forced expiratory volume in 1 s (FEV1) increase of greater than or equal to 12% after inhalation of a short-acting bronchodilator such as albuterol. An elevated fraction of exhaled nitric oxide (FeNO) can also be suggestive of the diagnosis in the right clinical context. Although in nonpregnant patients, a methacholine challenge test can be used to establish the diagnosis of asthma, this is not recommended in pregnant women [3]. Similarly, patients with asthma have improvement, worsening, or unchanged severity of disease during pregnancy, with each possibility occurring in approximately one third of patients. In regard to asthma, it is vitally important to maintain optimal management during pregnancy, as poor asthma control can be associated with premature birth, preeclampsia, low birth weight, and neonatal and maternal hypoxia [2, 4].

## Atopic Dermatitis

Atopic dermatitis is a multifaceted disease involving a spectrum of skin barrier dysfunction, skin dryness, inflammation, and pruritus. The onset is typically early in life and is thought to often represent the first step in the “atopic march” followed in many cases by food allergy, asthma, and allergic rhinitis. Although there is an allergic and

inflammatory component to atopic dermatitis, epidermal skin barrier dysfunction is thought to represent the primary pathologic mechanism [5]. The treatment of atopic dermatitis in both pregnant patients and the general population is cutaneous hydration and use of emollients. Adequate cutaneous hydration and use of emollients can help protect and restore the barrier of the stratum corneum and thus decrease the need for additional therapy. It is recommended for patients to take soaking baths that are lukewarm for a minimum of 20 min, to be immediately followed by application of occlusive emollient, which can both help retain moisture and decrease symptoms. Effective emollients such as petrolatum can be found in a variety of moisturizing agents, with thicker ointments and higher concentrations of petrolatum likely to provide more significant improvement. For atopic dermatitis lesions that are not improving with therapy, the use of wet dressings can also be employed. For patients who are pregnant, bathing should be restricted to only once per day, consisting of warm or cool water, and when possible, it is recommended that soap be restricted to the scalp, feet, armpits, and groin and that brushes or washcloths not be used. The use of a non-soap cleanser may prove less damaging to the skin barrier. After the patient has rinsed, skin should be dried by patting, and then immediately an emollient should be applied. All of these interventions are safe to perform during normal pregnancy. Due to the skin barrier dysfunction and skin fissuring that results in atopic dermatitis, the skin can develop small passages via which allergens may enter and thus worsen inflammation [6]. As such, the avoidance of plant- or biologic-based products to the skin is advised. Allergen avoidance as discussed below can play an important role in the management of atopic dermatitis as well.

## Allergen Avoidance Measures (Table 1.1)

In general, the initial non-pharmacologic treatment approach for allergic rhinitis, asthma, and atopic dermatitis in pregnancy does not differ from that in nonpregnant patients. The avoidance of known irritants and allergens is a cornerstone of allergic rhinitis and allergic asthma therapeutic strategy and should be recommended to all patients first [2]. In the following sections, many of the major allergens and appropriate avoidance measures will be described.

**Table 1.1** Allergen avoidance measures summary

| Allergen | Avoidance measures |
|---|---|
| Pet dander | Pet removal, limited avoidance, frequent pet washing, HEPA filters |
| Mouse/ cockroach | Integrated pest management |
| Mold | Mold removal, water leak repair, improved ventilation |
| House dust mites | Dust mite pillow/mattress covers, frequent vacuuming, minimize carpet in home, HEPA filters |

## *Pet Dander Allergens*

Pregnant patients with known pet dander sensitivity should be advised that removal of the pet from the environment is the most effective environment control measure. In particular, dogs and cats are significant indoor allergen sources common to many allergic patients. *Fel d1* (*Felis domesticus* allergen 1) is an important cat allergen and is carried through the air in particles greater than 2.5 μ in size. *Fel d1* is known to stay airborne for significantly extended periods of time. The major allergenic dog proteins, *Can f1* and *Can f2* (Canis familiaris allergens 1 and 2), are similar although not as persistent in the air as those from cats. Both cat and dog allergens are found in their excretions and secretions and on their dander [7]. In a study looking at 20 patients with allergic asthma and pet sensitivity, of the patients who removed their pet and then were followed up at 1 year, none of these patients required inhaled corticosteroids, as opposed to 9/10 of the patients who retained their pets in the control group [8]. In many cases, complete removal of the pet is either impractical or undesired. Clinicians often recommend frequent washing of cats and dogs in an effort to reduce pet dander allergen levels in the home and thus also decrease allergic rhinitis symptoms. It has been demonstrated that the level of *Can f1* in the home as well as on the dog themselves and their dander can be decreased significantly with at least twice per week shampooing and blow drying of the dog. It has been shown that *Can f1* levels return to prewashed levels within a 3–4-day period [9]. In regard to cats, it has been demonstrated that washing cats weekly results in a limited decrease of *Fel d1* both in the patient's home and on the cat, in particular after 1 week [10]. Considering the difficult nature of frequently washing animals, this strategy has not found widespread acceptance [11]. More likely to be successful in some instances would be a strategy of limited avoidance, such as ensuring the patient's pet be limited to the outdoor area of the home or at least restricted from entering the patient's bedroom. The use of air purifiers with high-efficiency particulate air filters (HEPA filters) in the management of animal dander allergy is discussed below.

## *Mouse and Cockroach Allergens*

In regard to pest allergens, such as mouse and cockroach which are especially problematic in low-income and urban environments, environmental non-pharmacologic control measures are also of significant importance [11]. For mouse allergen exposure, studies have typically employed the use of integrated pest management to reduce the concentration of mouse allergen. Integrated pest management (IPM) involves an approach consisting of a multifaceted intervention, which includes the sealing up of cracks and holes in the home, the setting of mouse traps, the meticulous disposal of food, intensive cleaning procedures, and, when required, the use of rodenticide. The studies that have looked at IPM had

used a variety of approaches ranging from providing education regarding IPM strategy to the actual professional implementation of these interventions [12]. It has been shown that a reduction in mouse allergen of at least 50–75% in the home is directly linked to significant improvements in clinical asthma outcomes [13–15]. Some of these studies have also shown that professionally performed IPM has led to a reduction in home mice allergen concentrations of 70–75%, while one study showed that a comparable reduction was achieved with the provision of IPM education to patients alone. However, it should be noted that a second study only showed minimal change in mouse allergen concentration when looking at IPM education-only interventions compared to controls [13–16]. As such, it appears that professionally delivered IPM interventions are effective at achieving clinically relevant reductions in mouse allergen concentration levels in the home; however the efficacy of IPM education-only interventions for patients has yet to be definitively proven as reliable [11]. For pregnant patients with known mouse sensitivity and concurrent allergic rhinitis and/or asthma, IPM education or the recommendation to obtain professionally delivered IPM interventions, when necessary, is highly advisable.

Similar to mouse allergen environmental control measures, for patients sensitized and exposed in the home to cockroach allergen, integrated pest management (IPM) strategies are often employed as well. Although there are over 4500 cockroach species, only four are indoor pests, Periplaneta americana, Blatta orientalis, Blattella germanica, and Supella longipalpa, with the major allergens being *Bla g1*, *Bla g2*, and *Per a1* [7]. As with mouse allergen strategies, cockroach IPM consists of a multifaceted interventional approach that can include the sealing of holes and cracks in the home, the use of pesticide, intensive cleaning targeted at reducing the reservoir of cockroach allergen, and disposal of food in a meticulous manner. These interventions have been demonstrated to provide a significant decrease in home cockroach allergen level compared to controls in the homes of children with asthma in urban, low-income areas. In fact, it has been shown that the levels of cockroach allergen can be decreased significantly by 80–90% using IPM strategies [17–21]. Furthermore, there has been demonstrated clinical benefit correlated to reduced cockroach allergen exposure in the home, with data showing a clinical benefit when a reduction of at least 50–90% in either allergen concentration of cockroach or mean number of trapped cockroaches was achieved [19, 22]. There is also a suggested clinical benefit observed in children with asthma but without cockroach sensitivity, who are exposed to cockroach allergen in their home environment. However, the benefit is not as pronounced as shown in children who are cockroach allergen sensitive [22]. Thus, as with mouse allergen exposure, it can be extrapolated that IPM should be part of the comprehensive management strategy advised to cockroach-sensitive pregnant patients affected by allergic rhinitis and/or asthma. Insecticide sprays should not be used, either by the patient themselves or by professional IPM services, in an effort to avoid the irritant effects of these chemical aerosolized compounds which can exacerbate airway disease [11].

### *Other Animal Allergens*

Other animals, such as horses, birds, and rabbits, are also common allergens that can exacerbate patient symptoms. The major allergen from horses, *Equ c1*, has been found in horse salivary glands, urine, and dander [23]. Although there is very little research performed looking at bird sensitization, a recent study showed bird sensitization to be lower than that found to a dog or cat, possibly due to the smaller number of pet birds [24]. Other smaller pets that are furry, such as hamsters, rabbits, and guinea pigs, have become more commonplace in recent decades, with upwards of 5% of households in the United States and Europe having a small furry pet. However, quantitative measurements of these allergens in house dust are suboptimal [23]. As with other animal allergens, avoidance measures are advised for sensitized and symptomatic patients.

## *Mold*

Asthma morbidity has been linked with mold and/or damp home environments in multiple studies [25–27]. Mold is known to become problematic in home environments affected by an excess of moisture. Moisture excess can be secondary to a number of factors, including ventilation problems, intrusion of water, plumbing problems, and other structural issues. It has been demonstrated that levels of carbon dioxide correlate with fungal allergen concentration, supporting the concept that ventilation deficiencies promote mold growth. Mold allergen concentrations are most elevated in ambient temperatures ranging from 20 to 22.5 °C [28]. The allergenic fungi that are most studied are *Aspergillus*, *Alternaria*, *Penicillium*, *Fusarium*, *Cladosporium*, *and Epicoccum* [7]. It has been shown that asthma outcomes improve following mold and dampness remediation interventions. These interventions include a variety of approaches: stopping intrusion of rainwater, removing mold from surfaces, repairing leaks in plumbing, and installing proper ventilation. These interventions have been demonstrated in studies to improve asthma outcomes, including decreased medication use, less symptom days, and decreased utilization of health-care resources [29–31]. Respiratory symptom risk and exposure to mold are associated, whether the patient has mold allergen sensitization or not. Fungal allergen sensitization is thought to increase the morbidity risk [32, 33]. It is recommended that patients with mold sensitization and allergic asthma use a central heating, ventilation, and air conditioner (HVAC) system with appropriately changed filters in an effort to reduce the movement of fungal spores from the outdoors to inside the home. When employing mold remediation, it is recommended by the National Institute of Occupational Safety and Health to use at least an N-95 mask during removal of visible mold due to the risk of aerosolized particulates [11]. Thus, for patients with allergic rhinitis and known mold sensitization, or for patients with allergic asthma regardless of mold sensitization, it is advisable to enact mold

remediation measures for a home environment known to be susceptible to significant mold colonization.

### *House Dust Mites*

House dust mites are ubiquitous in many environments around the world. The principal allergen is derived from the mite feces, which are typically 20–30 μ in diameter, with the major mite species being *Euroglyphus* and *Dermatophagoides*. Dust mites are especially prevalent in warm (greater than 20 °C), humid, and dark environments, such as pillows, mattresses, stuffed animals, and carpets [7, 34]. In patients with known house dust mite sensitivity and related symptoms, environmental control measures are both commonplace and highly recommended. Interventions focused on the bedroom, due to the large percentage of time spent there, are typically emphasized [34]. The encasement of the mattress and pillows in a finely woven fabric capable of preventing dust mite feces passage is the primary intervention. It is also recommended that bedding be washed in warm or hot water on a regular basis, and it is known that if a clothing dryer is used, virtually all dust mites are killed [35–37]. Dust mite growth is well known to be facilitated by humid environments. Although it is understood that relative humidity level thresholds of 45–50% are usually needed to achieve control, trials investigating dehumidification have shown mixed results, possibly due to the fact that even a short period of higher humidity can be enough to allow reproduction and survival of house dust mites [38–40]. In regard to carpets and upholstery, it is recommended that for dust mite-allergic patients, the amount of carpet in the home be minimized and that carpet be regularly vacuumed, cleaned, and sun dried if possible. Furthermore, if high humidity is difficult to control, it is suggested to avoid upholstered material as much as possible [34]. Activities such as vacuuming and manipulating bedding, furniture, or other materials known to harbor dust mites can disturb the allergen and cause it to become airborne [41]. It is advisable that vacuuming be performed by a person other than the dust mite-allergic patient if possible.

## High-Efficiency Particulate Air Filters

Another strategy considered by many patients is the use of air filters. Many different types of air filters exist, with the most highly recommended being the high-efficiency particulate air filters (HEPA filters). Other types of air filters, such as electrostatic precipitators and ionizers, function by electrically charging air particles in order to remove them. However, it is known that these devices emit ozone and as such should be avoided [42]. When considered for cases of known pet-allergic patients, it has been shown that HEPA filters have led to about a 30–40% decrease in cat allergen that is airborne when compared to placebo filters. However, it does not appear that

HEPA filters seem to significantly affect settled pet allergen dust levels, and most importantly, the use of these filters does not seem to significantly improve either allergic rhinitis or asthma symptoms [43, 44]. In fact, it is known that cat allergen in particular can be found in homes long after the cat has been removed, due to the allergen's inherent adherent nature. Despite these findings, a single study did show that the combined practice of frequent vacuuming in conjunction with the use of HEPA filters that were free-standing and placed in multiple rooms in the home did have an association with asthma outcome improvement, even though there was only minimal change in the actual levels of settled dust allergen [45]. As such, it is possible that the combination of high-efficiency particulate air filters in conjunction with other environmental controls such as vacuuming to reduce settled dust allergen may have a clinical benefit in both allergic rhinitis and asthmatic pregnant patients with known pet dander-allergic sensitivity; however to date there does not seem to exist overwhelming evidence to support this supposition.

In regard to the use of HEPA filters to decrease house dust mite allergens, a previous 8-week randomized double-blinded study examined the potential of these filters to reduce bedroom particulates, symptoms, and medication use in patients who had known sensitivity to house dust mites. The study did demonstrate that HEPA filters did in fact reduce bedroom particulates; unfortunately the improvement in the patient's symptoms was minimal [46]. These findings in part could be due to the fact that dust mite allergen is typically not airborne unless disturbed. However, another study that was also randomized, double-blinded, and placebo-controlled looked at patients with a history of allergic rhinoconjunctivitis and a known allergic sensitivity to dog, cat, or house dust mite. In the study, the combined uses of HEPA filter in the patient's bedroom along with dust mite bed pillow barrier encasings demonstrated a significantly decreased level of bedroom dust particles compared to placebo. In addition, there was a significant improvement in ocular and nasal symptoms at nighttime in the patient group receiving the combined environmental interventions; however it should be noted that daytime symptoms did not improve in this patient group [47]. Altogether this suggests that the benefit of high-efficiency particulate air filters in allergic rhinitis and/or asthmatic patients is best realized in combination with other environmental control measures.

## Allergen Immunotherapy

Apart from other non-pharmacologic interventions, desensitization of allergic disease utilizing allergen immunotherapy also has a proper role in the treatment of allergic rhinitis and allergic asthma during pregnancy. Subcutaneous immunotherapy (also known as "allergy shots") has been used for treatment of allergic disease for approximately 100 years and has been shown to be highly effective for allergic rhinitis, allergic asthma, and insect venom allergies. Subcutaneous immunotherapy consists of a series of subcutaneous injections with known environmental or venom allergens, initially starting with increasing dosages until a maintenance dose is

achieved. The maintenance dose can be continued for several years or indefinitely, depending on the patient and the particular allergens. Previous studies have demonstrated the safety of continuing subcutaneous immunotherapy during pregnancy. The first study published by Metzger et al. in 1978 demonstrated that out of a total of 121 pregnancies, no significant change in prematurity, hypertension, congenital malformations, or proteinuria was demonstrated. Also, no abnormal births were found to result from the seven generalized reactions that occurred [48]. The safety of continuing immunotherapy was further verified by a retrospective study published in 1993. With this study, the incidence of proteinuria, HTN, and prematurity was actually lower for the group of women continuing subcutaneous immunotherapy, and no birth complications were observed with the three patients who experienced systemic reactions [49, 50]. In many patients, subcutaneous immunotherapy results in sustained desensitization to the allergens, even after discontinuation of immunotherapy. More recently, the use of sublingual immunotherapy (grass, ragweed, or dust mite tablets dissolved daily under the tongue) has entered mainstream practice as an alternative in some instances as well. The safety of sublingual immunotherapy has been previously investigated, with a study of 155 patients during 185 pregnancies receiving sublingual immunotherapy with dust mite or a five allergen mixture, with 6-year follow-up demonstrating no systemic reactions in the sublingual immunotherapy patients, with only local reactions observed versus the control arms. Twenty-four of these patients were started on sublingual immunotherapy during pregnancy for the first time. Thus, the safety of sublingual immunotherapy has been suggested both for patients previously on sublingual immunotherapy before pregnancy and for those initiating sublingual immunotherapy during pregnancy [51].

Thus, pregnant patients who were previously on stable subcutaneous immunotherapy without significant complications can safely continue on immunotherapy maintenance dosing throughout their pregnancy. For women of childbearing age, the consideration for starting subcutaneous immunotherapy prior to pregnancy may be a wise proactive choice in some instances to avoid the need for medication during pregnancy, especially in allergic asthmatics. However, subcutaneous immunotherapy should not be initiated during pregnancy, and dosages should not increase during pregnancy due to the possibility of systemic reactions. In the event a patient becomes pregnant during the low-dose buildup phase of subcutaneous immunotherapy, injections should be discontinued. An unusual exception may be for the patient with a history of anaphylaxis secondary to venom hypersensitivity and an ongoing risk of exposure [2].

## Irritant Exposures

Tobacco smoking is a well-established risk factor for a multitude of diseases in the worldwide general population. In pregnancy, smoking also has a wide variety of negative impacts on both maternal and fetal health, including in asthmatic pregnant

patients. Smoking has been associated with worsened asthma medication requirements and also decreased asthma pharmacologic therapy response. A recent study demonstrated that the relative risk of an asthma exacerbation during pregnancy was significantly higher in current and former smokers when compared to never-smokers, and it also showed that even never-smokers who had only passive exposure to tobacco had a significantly increased risk of asthma exacerbation during pregnancy [47]. The study reported that never-smokers who had passive exposure to tobacco had a significantly lower FEV1% predicted, when compared to patients who were never-smokers and did not have passive exposure to tobacco. Since it is known that asthma exacerbations are linked to an increased risk of poor pregnancy outcomes, it is absolutely critical that pregnant women be advised to stop smoking immediately and avoid exposure to secondhand smoke [52]. Furthermore, a correlation between smoke exposure in utero or in infancy and the childhood development of rhinitis and asthma has been established [53]. Beyond tobacco smoke, mothers with asthmatic disease should also avoid other potential irritants, such as pollutants and other noxious chemicals, as much as possible due to their potential to lead to exacerbations of disease [2].

## Other Non-pharmacologic Approaches in Asthma and Allergic Rhinitis

A recent review of other non-pharmacologic approaches to asthma treatment in pregnancy evaluated the efficacy of certain approaches, such as education, a fraction of exhaled nitric oxide (FeNO)-based treatment algorithm, and progressive muscle relaxation (the deliberate application of tension to particular muscle groups followed by release of that tension), which did demonstrate some beneficial effects for management of asthma in pregnancy. However, the review in the end emphasized that no firm conclusions were able to be established regarding the true benefit of these approaches due to various limitations in prior studies [54]. Other non-pharmacologic approaches for improving asthma symptoms may also include stress reduction management and breathing exercises, as asthma symptoms can be worsened by psychological stress factors. Breathing exercises that have been previously suggested involve the use of breathing patterns that reduce hyperventilation as well as hyperinflation, thus leading to a normalization of carbon dioxide levels and theoretically then reducing the sensation of breathlessness and bronchospasm. However, when examined previously in children with asthma, clear evidence for its effectiveness has not been demonstrated [55]. In regard to psychological stress factors and asthma, appropriate psychiatric evaluation should be obtained for pregnant patients with asthma presenting with concurrent psychiatric illness, and for patients with stress-related symptoms, appropriate stress reduction measures should be considered.

For allergic rhinitis, the use of saline rinses can facilitate mucous passage and reduce nasal congestion in some patients. Also, the use of external nasal strips may

help relieve nasal passage obstruction in some cases. For the treatment of allergic disease and asthma, although some patients may consider the use of probiotics as a supplement to standard medical care, there are no studies in pregnant women that show a therapeutic benefit for probiotics in regard to allergic sensitization, asthma, or atopic dermatitis. Furthermore, at this time there are no society recommendations supporting the use of probiotics to treat allergic manifestations or asthma [56, 57]. In regard to other nontraditional interventions such as acupuncture, no studies to date have been performed to evaluate the effects of acupuncture on allergic disease or asthma in the pregnant patient.

## Conclusion

The approach to the non-pharmacologic treatment of allergic diseases in pregnancy closely reflects the non-pharmacologic approach to management of these conditions in the general population. In the pregnant patient, the importance of avoiding unnecessary medical therapy is of the upmost importance due to concerns of the effects of pharmacologic therapy on fetal health. It is strongly recommended to maximize non-pharmacologic approaches as appropriate in an effort to minimize pharmacologic interventions. In some instances, adequate relief may be achieved solely with non-pharmacologic interventions, and in many cases, the need for pharmacologic therapy can be reduced by concurrent use of non-pharmacologic approaches. At all times, it is critically important to appropriately ensure the well-being of both mother and baby. Due to the strong influence of the environment on allergic disease, environmental control measures and non-pharmacologic therapies can have a large impact on disease severity and patient symptoms in both a safe and effective manner.

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# Chapter 2
# Safety of Asthma and Allergy Medications During Pregnancy


**Christina Chambers**

## Introduction

Asthma and allergy are among the most common conditions in women of reproductive age. Allergic diseases are thought to be present in approximately 20% of women who are in their childbearing years. Data also suggest that at least 8% of pregnant women have a current diagnosis of asthma and that the prevalence of asthma in pregnant women and women of reproductive age appears to be increasing [1, 2].

Maternal asthma itself, and in particular poorly controlled asthma, has been associated in some studies with increased risks of adverse pregnancy outcomes including spontaneous abortion, stillbirth, major birth defects, preeclampsia, preterm delivery, and infants who are small for gestational age [3, 4]. While approximately one-third of asthmatic women will experience remission or reduction in asthma symptoms during pregnancy, at least one-third are likely to have symptoms worsen over the course of gestation. Data suggest that continued and appropriate management of asthma throughout pregnancy results in optimal outcomes for both mother and infant [5].

Appropriate management of asthma and allergy in pregnancy requires adequate information on the safety and/or risks associated with specific treatments for the developing fetus. This information is essential for the prescribing clinician but also important for the pregnant woman. In the absence of strong and reassuring evidence on the safety of specific medication treatments, women may avoid needed medication or undertreat symptoms against advice due to fear of harming the pregnancy [6].

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Guidelines for asthma and allergy treatment are provided by professional practice groups and in general suggest that pregnant women should be treated the same as nonpregnant women [7]. However, the quantity and quality of human safety data for some specific medications can help inform treatment choices within those guidelines.

In this chapter, four topics will be reviewed: (1) current methods for studying medication safety in pregnancy and the strengths and weaknesses of each of these approaches, (2) the current level of safety data for selected commonly used medications to treat asthma and allergy conditions in women of reproductive age, (3) an overview of the changes to the pregnancy label section of the package insert for pharmaceutical products marketed in the USA and how these changes are being implemented, and (4) a list of resources that clinicians and their patients can use for current pregnancy safety data.

## Approaches to Studying Medication Safety in Pregnancy

The goal of pregnancy safety studies is to rule out, with a reasonable level of confidence, that a medication is a human teratogen, i.e., is causally related to adverse pregnancy outcomes including major birth defects in the prenatally exposed infant. Typically, known human teratogens, such as thalidomide, are associated with increased risks for patterns of adverse outcomes including clusters of specific birth defects.

Many human teratogens have been identified through a series of case reports linking prenatal use of a specific drug to an unusual birth outcome. However, observational studies are needed to demonstrate that the association is not coincidental (e.g., above the background risk of 3–5% for major birth defects) and to better understand the magnitude of the risk and critical period of susceptibility to that exposure in pregnancy. Observational studies are the primary source of safety data that guide clinical practice in pregnancy, as randomized clinical trials in pregnant women to evaluate medication safety are rarely conducted for ethical reasons. Currently in the USA, there is no universal systematic method for evaluating pregnancy safety for pharmaceuticals. Individual studies are conducted as required by regulatory authorities or as initiated by investigators.

There are four general observational study designs currently used for medication safety studies in pregnancy: pregnancy registry, cohort, case-control, and database/claims data studies. Pregnancy registries represent prospectively collected exposure and outcome data for a series of pregnancies exposed to a specific medication. Registries are often the first source of data available for a new drug. These studies are usually too small to detect anything but large effects for rare outcomes, such as specific major birth defects, but can identify early

"signals." Cohort studies are also prospective exposure investigations with an internal comparison group of pregnancies that are unexposed to the medication of interest. These studies can be larger in size, can be population-based, and can identify in some cases more moderate risks for adverse outcomes. Case-control studies focused on birth defects have the best statistical power to detect associations between medication exposures and specific major birth defects. Database or claims-based studies draw on existing medical data and repurpose these data to construct a type of historical cohort of exposed and unexposed pregnancies. Relying on certain assumptions regarding the quality of the data, database studies can involve large numbers of pregnancies and, depending on the frequency of use of a specific medication among pregnant women in that population, may have the ability to rule out more modest risks for some adverse birth outcomes.

Studies that attempt to account for the contribution of the mother's underlying condition, such as poorly controlled asthma, are preferred. Congruent evidence from more than one study and studies using different designs provide the strongest evidence for safety.

While it is not possible to prove that there is no risk associated with a specific medication, accumulated evidence that is of good quality should be viewed in the context of other relevant data such as bioavailability of the drug, timing of exposure in gestation, and preclinical studies in animals to support best clinical choices for treatment.

## Summary of Safety Data for Selected Asthma and Allergy Medications

Safety data for selected asthma and allergy medications by class of drug are summarized in Table 2.1. The references described are not exhaustive and do not include studies with sample sizes less than 50. However, the citations included are intended to be representative of the current state of knowledge about common medications used for asthma and allergy in pregnant women. For most medications used for any condition in pregnancy, there are often limited or no human data available, and asthma and allergy drugs are no exception [46]. Therefore, a caveat to be considered in reviewing the current scope of the literature is that few studies with adequate statistical power to rule out risks for even the most common specific major birth defects have been done. This is a goal for future research. In addition, chance and confounding by disease severity/control may explain many of the sporadic positive associations described in Table 2.1. Clinical recommendations for the treatment of asthma and other allergic diseases based on the data in Table 2.1 can be found in other chapters in this book.

**Table 2.1** Summary of human pregnancy safety data for selected asthma and allergy medications

| Medication | Major birth defects | Other birth outcomes |
|---|---|---|
| Systemic corticosteroids | Meta-analysis of cohort studies showed no overall increased risk for major birth defects in pooled 535 exposed pregnancies; meta-analysis of 4 case-control studies showed an increased risk of ~threefold for oral clefts [8]. However, most recent and largest case-control study from US National Birth Defects Prevention Study showed no increased risk for oral clefts with 1st trimester systemic steroid use for any indication in 2372 cases and 5922 controls [9] | Preterm delivery, low birth weight or reduced birth weight, preeclampsia, and gestational diabetes have all been reported to occur more frequently in women treated with systemic steroids in pregnancy; however, studies that attempted to control for underlying maternal disease and disease activity typically find the associated risks for these outcomes reduced or eliminated [10] |
| Any inhaled corticosteroids (ICS) including beclomethasone, budesonide, flunisolide, fluticasone, and triamcinolone | No increased risk for major birth defects in 396 exposed compared with the general population [11]. A meta-analysis of studies of inhaled steroids did not find an increased risk of major birth defects overall [12] | No increased risks for preterm delivery, low birth weight, or pregnancy-induced hypertension in 396 exposed or in meta-analysis [11, 12] |
| Budesonide | No increased risk for major birth defects overall or oral clefts among 2014 exposed in a population-based Scandinavian register [13] | No increased risks for preterm birth, reduced birth weight or length, or stillbirths in 2968 exposed in a population-based Scandinavian register [14] |
| Fluticasone | No increased risk for major congenital malformations overall in a cohort study of 1602 mother-infant pairs exposed to fluticasone compared to 3678 exposed to other ICS, stratified by severity [15] | No increased risk for low birth weight, preterm birth, or small for gestational age in a retrospective database study of infants of 3190 mothers exposed to fluticasone compared to 608 mothers exposed to budesonide [16] |

**Table 2.1** (continued)

| Medication | Major birth defects | Other birth outcomes |
|---|---|---|
| Cromolyn<br>Nedocromil | No increase in major birth defects overall in 296 pregnancies exposed throughout pregnancy [17]<br>No increase in major birth defects overall in 151 exposed pregnancies [18]. No overall increase in major birth defects in case-control study of 5124 malformed compared to 30,053 controls; 9 cases exposed to cromones; some suggestion of an increased risk for musculoskeletal malformations among the 9 cases but no specific pattern noted [19] | No increased risk for premature delivery or spontaneous abortion/stillbirth in 296 pregnancies exposed throughout pregnancy [17]. No increased risk for premature delivery, preeclampsia, or low birth weight in 243 women exposed anytime in pregnancy [18] |
| Montelukast | No increased risk for major birth defects overall in 74 and 180 exposed pregnancies [20, 21]. No increased risk in major birth defects overall or specific birth defects in 1164 exposed pregnancies in claims study [22]. No increased risk in major birth defects in 1827 exposed pregnancies in Danish register study [23] | No increased risk for reduced birth weight or shortened gestational age in 180 exposed when compared to other asthmatics [21]<br>No increased risk for preterm delivery, low birth weight, or preeclampsia in 1827 exposed compared to other treated asthmatics [23] |
| Omalizumab | No increased risk compared to the general population for major birth defects overall in 169 exposed pregnancies enrolled in a registry [24] | |
| Short-acting beta-agonists (primarily albuterol) | No increased risk for major birth defects over expected among 1090 albuterol-exposed pregnancies in a claims database [25]<br>No increased risk for major birth defects in 1753 albuterol-exposed pregnancies compared to other asthmatic pregnancies [26]<br>Modest increased risk for isolated cleft lip or cleft palate (odds ratios from 1.65 to 1.79) in albuterol-exposed pregnancies in case-control study of 2711 cases of oral clefts and 6482 controls [27]<br>Several additional studies have suggested modest increased risks (odds ratios <3) for specific birth defects such as any cardiac or gastroschisis, esophageal atresia, and omphalocele [28–30] | No increased risk for preterm delivery, low birth weight, or small for gestational age infants in 1828 pregnancies exposed to short-acting beta-agonists compared to other asthmatic pregnancies [26] |

(continued)

**Table 2.1** (continued)

| Medication | Major birth defects | Other birth outcomes |
|---|---|---|
| Long-acting beta-agonists | No evidence of increased risk for major birth defects in 65 salmeterol-exposed pregnancies [31]. In one analysis of a database, increased risks for major cardiac and major "other" birth defects were seen with first trimester exposure in 165 pregnancies [32]. However, in a later study from the same database, 841 pregnancies exposed to long-acting beta-agonists with low- or medium-dose inhaled corticosteroids showed no increased risk for major birth defects overall compared to pregnancies exposed to medium-to-high-dose inhaled corticosteroids alone [33] | No difference in low birth weight, preterm birth, or small for gestational age was noted in infants of mothers exposed to salmeterol versus formoterol in a retrospective database study [16] |
| Theophylline | No increase for major birth defects overall in 212, 292, and 273 pregnancies [18, 26, 34]. Three case reports of severe cardiac defects in exposed [35] | |
| Ephedrine | No increased risk for major birth defects in 373 exposed [36] | |
| Epinephrine | Increased risk for major and minor birth defects overall and specifically for inguinal hernia in 189 exposed [36] | |
| Metaproterenol | No excess in major birth defects noted in 361 exposed pregnancies from a database [25] | |
| Terbutaline | No increased risk for major birth defects in 149 exposed [25] | |
| Antihistamines | | |
| Brompheniramine | Increased risk for major birth defects overall in 65 exposed [36]. However, no increased risk for major birth defects in another study of 172 exposed [37] | |
| Cetirizine | No increased risk for major birth defects overall in 196 exposed [38] | No increased risks for preterm birth, reduced birth weight, or spontaneous abortion in 196 exposed [38] |

**Table 2.1** (continued)

| Medication | Major birth defects | Other birth outcomes |
|---|---|---|
| Chlorpheniramine | No increased risk for major birth defects overall in 1070 exposed but suggested increase in several specific defects [36]<br>No increased risk for major birth defects in another study of 61 exposed [25]<br>No increased risk for specific birth defects previously reported including the eye, ear, spina bifida, and cleft lip in case-control study; exploratory analyses identified associations with any neural tube defects and tetralogy of Fallot (odds ratios ranging from 2.6 to 3.1) [39] | |
| Dexchlorpheniramine | No increased risk for major birth defects overall in 1080 exposed [36] | |
| Diphenhydramine | No increased risk for major birth defects overall in 279, 549, or 1461 exposed [25, 36, 37]; however, an increased risk for oral clefts was found in a case-control study 599 cases and 599 controls [40]. In another case-control study, no associations were found for specific birth defects that had previously been suggested; however, in exploratory analyses associations were found for right ventricular outflow obstruction and D transposition of the great vessels (odds ratios 1.6–2.3) [39] | |
| Hydroxyzine | No increased risk for major birth defects overall in 50 and 828 exposed [25, 36] | |
| Loratadine | No increased risk for major birth defects overall in 161 and 1769 exposed [41, 42]. In a case-control study, no increased risk for selected specific birth defects, including hypospadias, was found [39] | |
| Triprolidine | No increase for major birth defects overall in 628 and 910 exposed [25, 37, 43] | |
| Oxymetazoline | No increased risk for major birth defects overall in 155 exposed [37] | |

(continued)

**Table 2.1** (continued)

| Medication | Major birth defects | Other birth outcomes |
|---|---|---|
| Phenylephrine | No increased risk for major birth defects overall in 1249 exposed; suggested increased risk for eye and ear defects and clubfoot [36]. No increased risk for major birth defects overall in 301 exposed [37]. In a case-control study of 12,734 malformed and 7606 controls, increased risks found for specific birth defects including pyloric stenosis, ear defects, and endocardial cushion defects (odds ratios 3.2–8.0) [44] | |
| Pseudoephedrine | No increased risk for major birth defects overall in 940, 865, and 665 exposed [25, 37, 43]. A large case-control study tested hypotheses regarding previously reported associations, such as gastroschisis, and explored other associations; there was no increased risk for gastroschisis; one association was found with modest increased risk for ventricular septal defects (odds ratio 1.3) [44] | |
| Intranasal corticosteroids | | |
| | No association of intranasal fluticasone ($n$ = 912) or mometasone ($n$ = 1127) with specific birth defects in a large cohort study, but triamcinolone ($n$ = 318) was associated with an increased risk for infant respiratory defects [45] | |

## Pregnancy and Lactation Labeling Rule (PLLR)

Assignment of pregnancy-risk letter categories, A, B, C, D, or X, was instituted by the US Food and Drug Administration (FDA) over 30 years ago to help clinicians interpret the human and animal data on pregnancy safety for an approved drug. However, in practice, there was concern about the unintended application of these letter categories as an oversimplified grading system and whether they conveyed the available information in a fair and nuanced manner.

To address the need for updated risk categories, in December of 2014, the FDA published a final rule entitled "Content and Format of Labeling for Human Prescription Drug and Biological Products: Requirements for Pregnancy and Lactation Labeling," which is also known simply as the "Pregnancy and Lactation Labeling Rule" or PLLR [47].

The PLLR requires changes to the content and format for information presented in prescription drug labeling in the Physician Labeling Rule (PLR) format to assist healthcare providers in assessing benefit versus risk and in subsequent counseling of pregnant women and nursing mothers who need to take medication. The PLLR removes the pregnancy letter categories A, B, C, D, and X for all drugs. The PLLR also requires the label to be updated when information becomes outdated.

The labeling changes went into effect on June 30, 2015. Prescription drugs and biologic products submitted for approval to the FDA after June 30, 2015, will use the new format immediately, while labeling for prescription drugs approved on or after June 30, 2001, will be phased in gradually.

As revised, the new format requires the following content:

- The Pregnancy Subsection (8.1) includes information for contacting a pregnancy exposure registry for the drug, if one is available. Next in the Pregnancy Subsection is an overall Risk Summary which summarizes the human, animal, and any pharmacological data regarding pregnancy risk in a brief but consistent form. This is followed by a Clinical Considerations section which addresses known information about risk of the underlying maternal disease and/or risks of undertreatment of that disease during pregnancy, any dosing or prescribing information that may differ in pregnancy, and information if relevant about labor and delivery and any known adverse maternal or infant reactions. The last portion of the Pregnancy Subsection provides more detailed information on the data supporting the Risk Summary and the Clinical Considerations statements.
- The Lactation Subsection (8.2) provides human data about using the drug while breastfeeding, such as the amount of drug in breast milk and potential effects on the breastfed infant. If no human data are available, then animal data may be presented here.
- The Females and Males of Reproductive Potential Subsection (8.3) includes information, when necessary, about the need for pregnancy testing, contraception recommendations, and information about infertility as it relates to the drug.

## Resources for Clinicians and Patients

There are several sources of information that may be useful resources for clinicians and patients for specific medications in pregnancy. They are listed in Table 2.2 below. Each has a different process for developing summary statements or recommendations and a different format for delivery of the information. However, each are periodically updated with new information on existing medications and any data on new medications.

**Table 2.2** Selected resources for clinicians and patients

| Resource | Format | Audience | Cost |
|---|---|---|---|
| *Drugs in Pregnancy and Lactation*, 11th edition, Wolters Kluwer, 2017<br>Authors: GG Briggs, RK Freeman, CV Towers, and AB Forinash | Hard cover book includes access to the interactive eBook version with complete content<br>Summary of animal and human literature with an overall pregnancy and breastfeeding recommendation for each medication | Clinicians | About $70 |
| *Reprotox*<br>An information resource developed and maintained by the Reproductive Toxicology Center; Literature reviews conducted by a team of specialists covering risks of exposures for fertility, pregnancy, lactation, and neonatal development<br>Reprotox.org | On line database with App; periodic updates<br>Summary of animal and human literature with a "Quick Take" summary for each medication | Clinicians | By subscription<br>About $200 for an individual; group membership available and may be offered through institutions<br>Free for students, residents, and fellows |
| *TERIS, Teratogen Information System* | Online database<br>Periodic updates | Clinicians | Subscription service |
| Systematic reviews conducted by an expert board of specialists covering exposures in pregnancy and risks for adverse infant or longer-term outcomes<br>http://depts.washington.edu/terisdb/contact.html | Summary of animal and human literature and a summary risk statement for each medication | | Individual $250 |
| *MotherToBaby*<br>National network of teratogen information specialists with expertise in reviewing the literature and providing individualized risk assessments; consultations in response to specific queries to the network specialist by clinicians and patients regarding medications during pregnancy and breastfeeding and infant/child outcomes<br>MotherToBaby.org | One-on-one consultation by telephone, email, live chat, or text<br>Summary fact sheets on specific medications available on website or via<br>App | Clinicians and patients | No cost to clinician or patient |

## Summary

Asthma and allergy are among the most common chronic conditions occurring in pregnancy. Women may be motivated to reduce medication use during pregnancy for fear of harming the developing fetus. However, particularly for asthma, data

strongly suggest that undertreatment that leads to poor symptom control and/or exacerbations during pregnancy increases risks for a wide range of adverse maternal and infant outcomes. Conversely, adequate management of maternal disease during pregnancy improves outcomes. To support appropriate treatment, clinicians and patients require reassurance that needed medications do not carry unnecessary risks. However, there are several challenges in conducting these studies. As a result, most medications, including those used to treat asthma and allergy, have not been comprehensively studied in human pregnancy. While more studies are needed, existing data for most currently used medications for asthma and allergy are reassuring. For assistance in accessing the most recent data and in synthesizing accumulated information, there are a number of trusted resources that clinicians can use for consultation and that patients can access for one-on-one assessments.

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# Chapter 3
# Asthma: Interrelationships with Pregnancy


**Vanessa E. Murphy, Megan E. Jensen, Linda E. Campbell, and Peter G. Gibson**

## Prevalence of Asthma During Pregnancy

Asthma is one of the most common medical conditions to affect pregnancy, with a prevalence that has been increasing in recent years. Asthma prevalence during pregnancy is similar to the background prevalence for adult women. In Australia, up to 12.7% of pregnant women had asthma [1]. American studies report a prevalence of asthma during pregnancy of 8.4% (in 2001) [2] and 7.8% (in 2007) [3], and in Sweden, 9.4% of mothers between 2006 and 2009 had asthma [4].

Evidence of rising prevalence comes from a large American study using the Healthcare Cost and Utilisation Project Database, covering over 7.7 million deliveries between 2003 and 2011, which found a steady increase in asthma prevalence from 1.9% in 2003 to 3.7% in 2011 [5]. While the overall prevalence of asthma in this report was low in comparison to previous studies, this is likely due to the data collection method, where data was collected from an inpatient hospital discharge database, and from the delivery visit only, which may have missed milder cases of asthma [5]. Another large population-based study from Denmark examined the prevalence of chronic diseases amongst women giving birth between 1989 and 2013 [6]. Chronic lung disease (including asthma) was the most frequent at 1.73%, ahead of thyroid disorders (1.5%) and anxiety and personality disorders (1.33%). Overall,

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there was a fourfold increase in maternal chronic diseases in 2009–2013, compared to 1989–1993. Specifically, for chronic lung disease, the prevalence increased from 0.53% (1989–1993) to 1.89% (1999–2003) to 3.19% (2009–2013) [6].

## Changes in Asthma Symptoms, Lung Function and Asthma Control During Pregnancy

Pregnancy is associated with variable changes in asthma symptoms, with one third of women having a worsening of symptoms, one third an improvement and one third no change [7]. Pregnancy itself can be associated with shortness of breath, and, as a result, evaluation of asthma control and lung function may be important to distinguish changes in disease from pregnancy-induced dyspnea. Advancing pregnancy leads to extra-pulmonary restriction which can mildly reduce ventilatory function. Previous studies which examined lung function are limited by small sample sizes, poor study design and the lack of a non-asthmatic control group [8, 9].

Studies examining asthma control during pregnancy have reported a high rate of uncontrolled asthma: 56% in a Brazilian study [10], 42% in a Danish study [11] and 16% with persistent uncontrolled asthma in an Australian study [12]. A recent study of 42 non-smoking pregnant women with diagnosed asthma and rhinitis in Portugal reported that 80% of women had poor control, as measured using the Control of Allergic Rhinitis and Asthma Test (CARAT), and 15% of participants had an $FEV_1$ <80% predicted [13]. Two assessments of lung function were conducted in 42 women (at a median of 18 and 28 weeks), while 22 had a third assessment (median 29 weeks) during pregnancy. The results showed that approximately 30% of women had abnormal pulmonary function tests, with the majority of these demonstrating mild obstruction.

Very little is known about the potential mechanisms by which pregnancy affects asthma symptoms. The role of maternal hormones, such as cortisol, estradiol or progesterone, has not been thoroughly investigated in the context of asthma control or exacerbations in pregnancy, with only one study investigating maternal serum progesterone and airway responsiveness in pregnancy, but finding no significant relationship [14]. Other hypotheses have been put forward regarding the influence of foetal sex (with inconsistent results) [15–17], the role of beta-2-adrenoreceptor responsiveness [18] or altered maternal immune function [19–21].

## Exacerbations of Asthma During Pregnancy

Exacerbations are a common clinical problem for women with asthma during pregnancy. We have previously shown that asthma exacerbations requiring medical intervention (either hospital admission, emergency department (ED)

visit, unscheduled physician visit or course of oral corticosteroids [OCS]) occurred in 33% [22] to 45% [23] of pregnant women with asthma who were recruited through a hospital antenatal clinic in Australia. An American study found that overall, 20% of women required medical intervention for exacerbations during pregnancy, with more exacerbations with increasing asthma severity [24].

Emergency department (ED) visits are common in pregnancy, and a recent study of privately insured American women (2010–2011) found that pregnant women with asthma were 2.5 times more likely to have any ED visit, compared to women without asthma (adjusted OR 2.46, 95% CI [2.32–2.62]) [25]. This was greater than the odds of ED visits for women with obesity (aOR 1.55), hypertension (aOR 1.49), diabetes (aOR 1.47) or gestational diabetes (a OR 1.13) [25].

Several risk factors for exacerbation have been previously reported in the literature, including cigarette smoking [12, 23], maternal anxiety [26], more severe asthma [22, 24], maternal overweight or obesity [27, 28] and, recently, excessive gestational weight gain [29]. A Danish cohort study examined the determinants of low-exacerbation risk pregnancies and found that women with stable asthma at enrolment, who had no history of pre-pregnancy exacerbations and were not prescribed controlled medication were less likely to have exacerbations in pregnancy [30].

Airway hyper-responsiveness is not generally measured during pregnancy; however, recently Ali et al. have described postpartum measures of AHR in relation to exacerbations during pregnancy [31]. Their study group was 50 women who were prescribed inhaled corticosteroids (ICS) and had been prospectively followed during their pregnancy, with further testing of lung function, airway inflammation, atopy and airway responsiveness to inhaled mannitol within 7-month postpartum. Thirteen of these women (26%) had one or more exacerbations (mild exacerbations in eight women and severe exacerbations requiring hospital admission, emergency department treatment and/or a course of oral corticosteroids in eight women) during pregnancy. A positive mannitol test was observed in 78% of participants, and those women who had had an exacerbation during pregnancy had significantly greater airway responsiveness, which was correlated with sputum neutrophil count. Women with exacerbations in pregnancy were less likely to have a positive skin prick test, and there were no associations between exacerbations and sputum inflammatory phenotype [31]. Previously, Stenius-Aarniala et al. reported a higher rate of exacerbation in pregnancy in women with non-atopic asthma [32]. Only one previous study has examined postpartum airway hyper-responsiveness, using methacholine [33]. In this study, 16 women had methacholine testing prior to conception, as well as during the second and third trimesters of pregnancy, and 1 month after delivery. Overall, there was a statistically significant improvement in airway responsiveness (twofold increase in $PC_{20}$) from preconception to the second trimester, with postpartum responsiveness similar to that prior to pregnancy. Interestingly, women with the most hyperresponsive airways prior to pregnancy had the greatest improvement in $PC_{20}$ during pregnancy [33].

## Asthma and Other Co-morbidities in Pregnancy

Pregnant women with asthma report many co-morbidities (Fig. 3.1). A population-based study of over 7.7 million deliveries reported that women with asthma were more likely to report diabetes, obesity, thyroid disease, hypertension and smoking compared to women without asthma [5]. A population-based study of over 243,000 deliveries similarly reported that mothers with asthma had higher rates of pre-existing diabetes, smoking, chronic hypertension, anaemia, fertility treatments, recurrent pregnancy loss and previous caesarean delivery than mothers without asthma [34]. Apart from complicating management of asthma in pregnancy, these conditions also independently contribute to the increased risk of adverse perinatal outcomes. Thus, women with asthma may benefit from multidisciplinary care during pregnancy if presenting with additional risk factors.

### *Gastro-oesophageal Reflux Disease (GERD)*

Dyspepsia from gastro-oesophageal reflux is a common complaint experienced by women during pregnancy, particularly as the pregnancy progresses, due to pathophysiological changes (i.e. progressively increased intra-abdominal pressure and alterations in oesophageal sphincter function and gastrointestinal (GI) transit). Although GERD is common in asthma, there are limited studies conducted in pregnant women with asthma. In a prospective Australian study of 42 pregnant women with a diagnosis of asthma and allergic rhinitis (AR), almost one in two (43%) reported an "acid taste in the mouth and regurgitation" on one or more days per week, especially in the third trimester; yet, none reported use of pharmacological

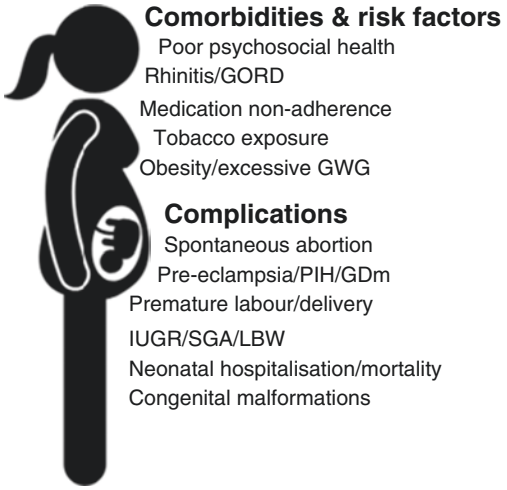


**Fig. 3.1** Pregnant woman with asthma are at increased risk of several co-morbidities, risk factors for exacerbation and complications of pregnancy. GORD gastro-oesophageal reflux disease, GWG gestational weight gain, PIH pregnancy-induced hypertension, GDm gestational diabetes mellitus, IUGR intrauterine growth restriction, SGA small for gestational age, LBW low birth weight

treatment for management [13]. In a cross-sectional study of 173 pregnant women in Iran (37% asthma; 27% probable asthma), GERD was determined to affect 81% of women [35]. In contrast to only 30% reporting acid regurgitation pre-pregnancy, 86% of women reported this symptom during pregnancy, with the majority reporting its onset from the first trimester [35]. In addition, 58% of women reported heartburn during pregnancy, while only 29% reported this for the pre-pregnancy period [35]. Although GERD was not observed to affect more women with asthma compared with those without asthma (75% vs. 80%), the severity of GERD was significantly worse in women with asthma (questionnaire score 2.69 vs. 2.25, $p = 0.02$); yet, there was no significant association between GERD frequency and severity with asthma control [35]. Management of GERD in pregnancy should begin with dietary changes and lifestyle modification, since many of the pharmacologic options have not been tested in RCTs in a pregnant population [36]. Antacids are considered first-line medical therapy, due to being nonsystemic and fast acting, and those containing calcium, aluminium and magnesium are considered to be safe in pregnancy [36].

## *Tobacco Exposure*

A longitudinal study of 172,305 births (6.7% with reported asthma) demonstrated that the prevalence of smoking has declined over a 10-year period from 1999 to 2008 in Australia, yet remained higher in asthmatic women compared to controls for each year assessed, with the overall smoking prevalence of 25% in pregnancies affected by maternal asthma vs. 17% in control pregnancies [37]. In smaller studies conducted in Australia, the prevalence of smoking amongst pregnant women with asthma has been reported to be 20–34% [12, 23, 38]. Conversely, a Danish case-control study conducted over 7 years reported a much lower prevalence of current smoking in their cohort of pregnant women, with a significantly lower prevalence in pregnancies affected by asthma (4.2%) vs. controls (7.2%) ($p < 0.01$) [39]. A second study from Denmark of 500 women with asthma found approximately 23% were classed as ex-smokers and 6% current smokers, with 13% reporting passive smoke exposure [11]. A cross-sectional Brazilian study of 103 pregnant women with asthma in Brazil also reported a comparatively low smoking prevalence of 9% [10]. These contrasts may represent differences in public health policies and social norms across countries.

In a study of 80 pregnant women with asthma, smoking was associated with a higher ACQ6 score during an exacerbation, compared with never smokers, after adjustment for multiple exacerbations, asthma severity and ICS use (coefficient 0.17, 95% CI 0.01–0.34, $p = 0.04$) [23]. Current smokers had a significantly higher cumulative exacerbation rate during pregnancy, compared with never smokers [23]. A second Australian study found self-reported smoking at enrolment (approximately 12-weeks gestation) was a significant risk factor for recurrent uncontrolled asthma during the pregnancy (RR 2.92, 95% CI 1.53–5.58) in their prospective

cohort of 189 women; however, there was no association with exacerbations requiring medical attention [12].

Furthermore, in a Danish study of 500 women with asthma, current and ex-smokers combined (ever smokers) had significantly lower $FEV_1$% and fractional exhaled nitric oxide (FENO) values compared with never smokers [11]. Notably, amongst never smokers, women exposed to passive smoke also had significantly lower FENO and $FEV_1$% values and used a higher ICS dose, compared to unexposed women [11]. Moreover, the incidence of ≥1 episode of partly/uncontrolled asthma during pregnancy was significantly higher amongst ever vs. never smokers (63% vs. 33%, $p < 0.0001$) [11]. This was also true amongst women exposed versus unexposed to passive tobacco smoke (55% vs. 28%, $p < 0.0001$), translating to an almost threefold increased odds of at least one episode of partly/uncontrolled asthma during pregnancy (OR 2.9, 95% CI 1.4–5.9, $p = 0.004$) [11]. The odds were even greater in women who were ever smokers, compared to women who were neither smokers nor exposed to passive tobacco smoke (OR 4.5, 95% CI 2.7–7.5, $p < 0.001$) [11].

Given the potential increased risk of poor asthma control and exacerbations during pregnancy, as well as the independent health deficits imposed by smoking on both mother and the developing foetus, tobacco smoke exposure is a significant health risk factor that requires attention in the management of pregnant women, both with and without asthma.

## *Psychosocial Factors*

A recent Australian prospective study, conducted in a socially disadvantaged area, examined the relationship between self-reported anxiety/depression and asthma control and exacerbations during pregnancy [40]. Of the 189 women included in the analysis, 45% self-reported a history of depression/anxiety (with 20% using anti-depressant medication) [40], a considerably higher proportion than reported in a recently published Australian clinical trial of 72 women, of whom 28% reported depression/anxiety as a co-morbidity at baseline [41]. Grzeskowiak et al. found that women with a history of depression/anxiety scored significantly higher on both the 12-week Antenatal Risk Questionnaire (ANRQ) and the Edinburgh Postnatal Depression Scale Score (EDPS) compared with women with no self-reported history of depression/anxiety; this translated to a significantly higher proportion of women classed as having a high ANRQ (88% vs. 27%, $p < 0.001$) and EDPS (19% vs. 4%, $p = 0.002$) score, respectively [40]. However, there was no group difference in the median State-Trait Anxiety Inventory (STAI-6) score, indicating no difference in anxiety levels between women with versus without a history of anxiety/depression [40]. Uncontrolled asthma (53% vs. 33%, $p = 0.005$) and recurrent uncontrolled asthma (24% vs. 10%, $p = 0.009$) was significantly more prevalent in women with a history of depression/anxiety versus no history [40]; however, there was no relationship

between maternal history of depression/anxiety and risk (adjRR 0.70, 95% CI 0.35–1.26) or incidence (adjIRR 0.66, 95% CI 0.35–1.26) of exacerbations during pregnancy [40].

In contrast, an earlier Australian study, in a similar sized cohort of pregnant women ($n = 175$) with predominantly mild asthma, found a significant association between both perceived asthma control (OR, 0.92, 95% CI 0.85–0.98, $p = 0.016$) and anxiety (OR, 1.05, 95% CI 1.01–1.08, $p = 0.008$), measured, respectively, using the Perceived Control of Asthma Questionnaire (PCAQ) and the STAI-6 at enrolment (20-weeks gestation), and the odds of a future exacerbation during the pregnancy, that is, a better perception of asthma control, reduced the odds, while higher levels of anxiety increased the odds of an exacerbation [26]. Notably, baseline asthma control (ACQ7) and ICS use were not related to exacerbation risk in this analysis [26]. In this prospective cohort of non-smoking pregnant women, anxiety was relatively low (median STAI-6 score, 26.7), and their PCAQ score (mean, 43.8) indicated a moderate-good perceived self-efficacy to cope with asthma symptoms/exacerbations [26].

Powell et al. also examined asthma-specific and general health quality of life (QoL) in a cross-sectional analysis of 125 pregnant women with predominantly mild asthma (19% smokers), using the Asthma Quality of Life Questionnaire-Marks (AQLQ-M) and the MOS 12-Item Short Form Health Survey version 1 (SF12v1), respectively [42]. The odds of uncontrolled asthma (ACQ score >1.5) was 38% lower for each unit decrease in the Brief Illness Perception Questionnaire emotions domain, that is, if women perceived their asthma to have a lower impact on their emotional state (OR 0.62, 95% CI 0.41–0.96, $p = 0.030$) [42]; however, asthma control was not related to asthma-specific or general health QoL [42]. On the other hand, Schatz et al. reported a significant association between asthma-related QoL, measured using Juniper's Asthma Quality of Life Questionnaire (AQLQ) at approximately 20-weeks gestation, and exacerbation risk in a secondary analysis of data from 310 women enrolled in a RCT [43]. Overall asthma-related QoL (AQLQ score 3.5 vs. 3.8, $p = 0.047$), and both the emotion (3.3 vs. 3.9, $p = 0.003$) and symptoms (3.5 vs. 3.9, $p- = 0.032$) AQLQ domains, was significantly lower in women who exacerbated during pregnancy versus those who did not [43]. In fact, the odds of an exacerbation during the pregnancy was decreased by more than 25% for each unit increase in total AQLQ score (adjOR 0.75, 95% CI 0.56–0.99, $p = 0.040$), as well as the emotion (adjOR 0.73, 95% CI 0.60–0.90, $p = 0.003$) and symptoms (adjOR 0.75, 95% CI 0.58–0.98, $p = 0.033$) AQLQ domain score at baseline, independent of baseline symptom frequency and $FEV_1$ [43].

Lastly, a recent study demonstrated that maternal chronic interpersonal trauma (assessed via the Revised Conflict Tactics Scale short form) increased the likelihood of active asthma (defined as self-reported asthma symptoms, asthma medication use or healthcare utilisation) during pregnancy, after adjustment for multiple factors including maternal age, race and education ($\beta = 0.59$, $p < 0.001$) [44]. Collectively, these studies implicate the need for monitoring of psychosocial factors and mental health in addition to symptoms and lung function in order to optimally manage asthma throughout pregnancy.

## *Nutrition, Obesity and Weight Gain*

Obesity is highly prevalent in women of child-bearing age, and rates appear even higher in those with asthma [4, 28, 38]. This is supported by several studies, with prevalence rates in pregnant women with asthma ranging from 11% to 43% across various countries [4, 10, 12, 27–29, 45–48]. However, few studies have examined the association between maternal weight status and exacerbation risk.

Earlier work by Hendler et al. reported a 30% increased odds of an asthma exacerbation requiring medical attention during pregnancy in an American cohort of obese versus nonobese women (adjOR, 1.3 [1.1–1.7]; $p = 0.01$); yet, there were no group differences in terms of the change in asthma severity during the course of pregnancy, asthma-related hospitalisations or OCS use [28]. Recent Australian data has also demonstrated a higher prevalence of asthma exacerbations in women who are either overweight or obese compared to healthy-weight women during pregnancy; in fact, approximately one in two women who were overweight/obese experienced an exacerbation requiring medical attention compared to one in four healthy-weight women [27]. Also associated with obesity was a higher ICS dose (after adjusting for non-adherence) in comparison to healthy-weight women [27]. Most recently, BMI has been reported as a significant predictor of asthma control status during pregnancy, with a 25% increase in the incidence rate of uncontrolled asthma with a BMI increase of 10 units/kg/m$^2$ [49]. Similarly, another recent study found that a BMI below 25 kg/m$^2$ was associated with a reduced exacerbation risk during pregnancy in a univariate analysis (OR 0.64, 95% CI 0.43, 0.98) [30].

The 2017 study by Murphy et al. also provided evidence to suggest that a potential mechanism of action explaining the relationship between exacerbations and weight status may be via macrophage activation [27], with the observation of increased levels of soluble CD-163 in obese versus healthy-weight pregnant women with asthma; this marker of macrophage activation was also associated with severe exacerbations, i.e. those requiring OCS treatment [27]. Pro-inflammatory markers, IL-6 and CRP, were also increased, which may be associated with the increased exacerbation risk observed in obese and overweight women [27]. In summary, the evidence to date indicates that overweight and obesity are highly prevalent in early pregnancy in women with asthma and may negatively affect the asthma course during pregnancy as well as increase the risk of adverse perinatal outcomes.

Another factor to consider is excessive gestational weight gain, which affects a large proportion of women regardless of pre-pregnancy BMI, and is associated with poorer maternal and infant outcomes, notably LGA and macrosomia [50]. In women with asthma, excessive GWG [i.e. above the Institute of Medicine recommendations] has been reported to affect at least 70% of women [27, 46]. In a recent Australian study of 164 pregnant women with asthma, ≥70% of women had excessive GWG over the second and third trimester, regardless of BMI category at enrolment (approximately 17-weeks gestation); however, excess GWG was not found to be associated with exacerbations, compared to GWG below/within guidelines for GWG [27]. This study was limited by the small sample size, with GWG data

available for only 70% of the group [27]. Likewise, Grezeskowiak et al. did not observe an association between GWG in the second and third trimester and asthma exacerbation risk in a sample of 189 Australian women [12]. However, the overall data highlight the need for weight management in both the prenatal and gestational period amongst women with asthma.

## Association of Asthma with Infertility

Women with asthma appear to have lower fertility rates, increased time to pregnancy (TTP) and a higher rate of spontaneous abortions. Of the few studies published in this area, a number originate from a group in Denmark. In a population-based twin study of 15,250 women ($n = 955$ (6.3%) with a self-reported history of asthma), maternal asthma was associated with a 25% increased odds of prolonged TTP (more than 12 months), following adjustment for BMI, smoking, age, age of menarche and socioeconomic status (OR 1.25; 95% CI 1.0–1.6) [51]. When examining a subgroup of women aged >30 years, the odds of prolonged TTP increased to 44% with maternal asthma (OR 1.44, 95% CI 1.10–1.88), highlighting that asthma has an even stronger effect on TTP in older women [51]. Although women with asthma who were untreated (OR 1.79, $p = 0.004$) or received daily ICS treatment (OR 2.34, $p = 0.003$) had a significantly greater odds of prolonged TTP compared to women without asthma, there was no statistically significant difference between these two asthma groups, suggesting that medication use does not explain the reduced fertility rates in women with asthma [51].

Results from a prospective study by the same group support these findings, with a significantly greater TTP in women with asthma ($n = 96$: 81 [84%] with current asthma, of which 37 were new diagnoses upon study entry), compared to women without asthma ($n = 149$); this was true for TTP from time of first unprotected intercourse (32.3 vs. 55.6 months; adjusted HR 0.52; 95% CI 0.35–0.77) and TTP from the time of first fertility treatment cycle (17.9 vs. 35.6 months; adjusted HR 0.66; 95% CI 0.44–0.98) [52]. In line with the group's previous work, maternal age had a significant impact on the association between asthma and TTP, with a longer TTP in women ≥35 years; however, no interaction effect upon fertility was detected between asthma and asthma-related variables (AHR, FENO, FEV1, atopy) [52]. Moreover, TTP did not differ between women with ICS-treated and untreated asthma (HR 1.13; 95% CI 0.60–2.15) [52], again supporting the suggestion that decreased fertility in asthmatic women may be independent of asthma control, severity or treatment. However, a recent multicentre, multi-national study has described significantly reduced fertility amongst women with current asthma who were using short-acting beta-agonists only, with the authors suggesting that the use of ICS/LABA may improve asthma control and reduce the systemic inflammation that may be causing the reduction in fertility [53].

In the Danish sample of 245 women with unexplained infertility, live births occurred at a lower rate in women with asthma, compared to controls (39.6 vs.

60.4%, $p = 0.002$); however, the rate of spontaneous abortions was similar between women with and without asthma (0.49 vs. 0.52, $p = 0.82$) [52]. In line with these findings, a small study by Sarkar et al. ($n = 180$/group) reported a similar prevalence of spontaneous abortions in women with asthma using montelukast, women with asthma using ICS and/or inhaled beta-agonists and women without asthma exposed to non-teratogens (11.1% vs. 9.4% vs. 10.5%, $p = 0.9$); however, this study likely lacked statistical power and did not control for potential confounders [54]. In contrast, four studies have reported a higher incidence/risk [55–58] of abortions in women with asthma; however, two of these studies did not report spontaneous and induced abortions separately [57, 58]. Both Blais et al. and Tata et al. differentiated between spontaneous and induced abortions in their analyses and also examined the impact of asthma control/severity [55, 56]. Both studies reported increased odds of spontaneous abortion associated with maternal asthma. The most recent study by Blais et al. examined data from a large cohort of women accessed via three databases/registries in Quebec, Canada ($N = 49{,}438$ pregnancies, of which $n = 15{,}107$ [31%] had asthma) [56], while the earlier study by Tata et al. examined data on 281,019 pregnancies from a UK national database, of which 13% were in women with asthma [55]. The overall incidence of spontaneous abortions in these two cohorts was 16% [56] and 13%, respectively [55], with Tata et al. reporting a 10% increased odds of spontaneous abortion with maternal asthma, after controlling for pre-pregnancy BMI, smoking status and maternal age [55], and Blais et al. reporting a 40% increased odds with maternal asthma after controlling for multiple factors including maternal age, receipt of social assistance, chronic hypertension, diabetes, previous spontaneous abortion(s) and use of teratogenic medications in the first trimester [56]. These results support maternal asthma as a strong risk factor for spontaneous abortions.

Furthermore, amongst women with asthma, uncontrolled asthma, but not asthma severity, in the year prior to the 20th week of gestation or termination, was associated with a 26% increased odds of spontaneous abortion, even after controlling for maternal age, previous spontaneous abortion(s), chronic hypertension, diabetes, use of teratogenic medications in the first trimester and use of intranasal steroids [56]. Tata et al. also reported a 24% greater odds of spontaneous abortion in pregnant asthmatic women who had at least one exacerbation recorded in the year preceding pregnancy and a 14% and 24% higher odds in women receiving SABA and ICS/LABA medications, respectively, compared to women without asthma [55]. Results from these large studies suggest optimal asthma management preconception and in the early stages of pregnancy is vital to improve the odds of foetus viability.

The mechanism behind this apparent reduced fertility/foetal viability in women with asthma is unclear, and, to date, minimal work has been conducted in this specific group. Findings from a small study in Denmark found that levels of endometrial-secreted vascular endothelial growth factor (VEGF) were lower in women with ($n = 23$) versus without ($n = 21$) asthma after adjustment for confounders, including fertility treatment [59]. This marker has been "implicated in endometrial receptivity" and may explain the reduced fertility observed in women with asthma. There was no effect of ICS treatment on VEGF levels in

women with asthma; however, lower VEGF concentrations were detected in those classed as non-atopic vs. atopic [59]. Additional work in larger sample sizes is required to elucidate the role of VEGF levels in fertility in women with asthma and examine any effect of asthma phenotype, control, severity and medications.

## Association of Asthma with Adverse Perinatal Outcomes

A systematic review and meta-analyses, first published in 2011, and updated for some outcomes up to 2012, indicated that maternal asthma is associated with an increased risk of many adverse perinatal outcomes, including low birth weight, preterm birth, pre-eclampsia [60], neonatal death and hospitalisation [61], as well as gestational diabetes, caesarean section delivery and placenta previa [62]. Active asthma management during pregnancy was associated with a reduced risk of some outcomes, including preterm birth [60], neonatal hospitalisation [61] and gestational diabetes [62], suggesting that the effects of maternal asthma on perinatal outcomes may be modifiable. Exacerbations were associated with a threefold increased risk of low birth weight (relative risk [RR] 3.02, 95% CI 1.87–4.89) and oral corticosteroid use with an increased risk of preterm birth (RR 1.51, 95% CI 1.15–1.98) [63]. The results reported in these meta-analyses are supported by more recent data.

A population-based study published in 2017 describes the differences in a range of perinatal outcomes, including some which have not been examined before, in pregnant women with and without asthma [5]. The extremely large sample size (223,236 women with asthma and approximately 7.5 million women without asthma) has allowed investigation of rare outcomes which have not previously been reported. Maternal death occurred in significantly more women with asthma (0.03%) than women without asthma (0.01%, adjusted OR 1.68 [95% CI 1.31–2.15]); however, the reasons for death were not reported. The publication also described increased risks of venous thromboembolism, including a 3.8-fold increased risk of pulmonary embolism and a twofold increased risk of deep vein thromboembolism, compared to pregnant women without asthma, after adjusting for maternal characteristics including age, income, obesity, smoking and other co-morbidities [5]. Women with asthma were more likely to have a hospital stay of 3 days or more, possibly due to the increased risk of poor delivery outcomes. Consistent with previous literature, maternal asthma was associated with increased risks for pregnancy-associated hypertension, pre-eclampsia [60], gestational diabetes [62], placenta previa [62], preterm birth [60], C-section delivery [62] and postpartum haemorrhage [62]. Few studies have examined chorioamnionitis amongst women with asthma, and although a previous meta-analysis did not find a significant risk with maternal asthma, the study from Baghlaf et al. examined more women with asthma than seven previous studies combined [62] and reported a significantly increased adjusted odds ratio [5]. After adjustment for maternal characteristics, hysterectomy

was not significantly increased in women with asthma. In addition to poor maternal outcomes, neonates whose mothers had asthma were also more likely to be small for gestational age, and to have congenital abnormalities [5], consistent with previous work [60, 61]. While several previous studies have reported the rates of stillbirth amongst women with asthma and meta-analysis found no significantly increased risk of this outcome compared to women without asthma [61], this study from Baghlaf et al. reported the novel finding that women with asthma were significantly less likely to experience intrauterine foetal death (aOR 0.85, 95% CI [0.79–0.91]), possibly due to increased surveillance as a result of increased risks for adverse outcomes [5]. Despite being a very large study, the prevalence of maternal asthma was low (2.9%), possibly limiting generalisability of these results to women with more severe asthma.

Rejno et al. conducted a population-based study of singleton births between 2006 and 2009 in Sweden and found that women with asthma had increased odds for several adverse pregnancy outcomes such as pre-eclampsia/eclampsia, antepartum haemorrhage, low birth weight, preterm birth and small for gestational age [4]. In a novel extension to this study, data from over one million Swedish pregnancies between 2001 and 2013 was examined, and a recent publication reports associations between maternal asthma and adverse pregnancy outcomes, both within the whole population (similarly to [4]) and within relatives (cousins and siblings) with and without asthma [64]. Overall, women with asthma had an increased risk for pre-eclampsia, placental abruption, instrumental delivery, emergency C-section and small for gestational age, in addition to a significantly lower mean birth weight (by 47 g) and a lower gestational age at delivery (by 0.12 weeks). When results were adjusted for familial factors using conditional logistic regression, associations with pre-eclampsia, instrumental delivery, emergency C-section, birth weight and gestational age at birth remained significant, suggesting that unmeasured genetic or environmental confounders shared by cousins or siblings do not explain the associations between maternal asthma and adverse perinatal outcomes [64].

An Israeli study has recently reported on pregnancy outcomes associated with maternal asthma over a 23-year period in a tertiary medical centre [34]. They found that compared to women without a diagnosis of maternal asthma, those with asthma had significantly higher rates of polyhydramnios (but not oligohydramnios), intrauterine growth restriction (IUGR), gestational diabetes, pre-eclampsia and pregnancy-induced hypertension (PIH), induction of labour (and failed induction of labour), placenta previa and C-section delivery. In addition, mothers were more likely to have pneumonia during pregnancy. At birth, neonates were more likely to be low birth weight; however, Apgar scores and rates of perinatal mortality were similar with neonates of non-asthmatic mothers. When confounders, including maternal age, ethnicity, diabetes, hypertension and gestational age at delivery, were taken into account, the odds ratios for preterm delivery (1.21, 95% CI [1.1–1.3]), pregnancy-induced hypertension (1.35, 95% CI [1.2–1.6]) and C-section delivery (1.27, 95% CI [1.2–1.4]) remained significant [34].

## Association of Maternal Asthma with Adverse Outcomes in Childhood

The effect of maternal asthma on offspring outcomes is not limited to those around the time of birth. There are studies which implicate the in utero environment in the development of many other health conditions and, in the context of maternal asthma, particularly asthma itself, other allergic diseases, such as rhinitis and atopic dermatitis [65], and developmental problems.

Children whose mothers have asthma are at high risk of both infant and preschool wheeze [66] as well as later childhood asthma [67], being twice as likely to wheeze by ages 2–3 years compared to children whose mothers do not have asthma [66] and 1.5 times more likely to develop asthma versus those whose fathers have asthma [67]. Children whose mothers experienced uncontrolled asthma or exacerbations in pregnancy are 50% more likely to develop asthma than children of mothers with mild controlled asthma [68], strongly suggesting a role for the in utero environment in programming future asthma risk. Strategies which reduce exacerbations and improve asthma control in pregnancy have potential for primary prevention of wheeze and asthma in this high-risk group.

There are some indications that children whose mothers had asthma have a higher likelihood of developmental delay and neurobehavioural co-morbidities. A recent systematic review has summarised the literature in this area with five studies providing inconclusive evidence for an association between asthma in pregnancy and atypical cognitive and behavioural development, while five studies provided evidence for no association [69]. In one of the earliest studies, Gordon and colleagues reported a high incidence of neurological anomalies (2.7%) amongst 1-year-old infants born to mothers with asthma, compared to a cohort born to mothers without asthma (1.7%) [70]. A study from Western Australia found that maternal asthma was more likely amongst children with mild to moderate intellectual disability (ID) compared to children without ID [71]. A more recent study from the same population confirmed a 25% increased risk of mild to moderate ID amongst children whose mothers had asthma and also found a significant association between maternal asthma and autism spectrum disorder (ASD) without ID [72]. The only prospective study in this area provided initial evidence that well-managed asthma during pregnancy results in improved child development, giving these infants a better start to life [73].

## Conclusion

Asthma is a highly prevalent condition in pregnancy, and women experience a range of changes in disease status with pregnancy which are unpredictable and vary from pregnancy to pregnancy. Optimal management of asthma during pregnancy is important for obtaining the best outcome for both mother and baby. Pregnancy is a

time when women's and/or health professional's attitudes towards medication use may hinder good control. Exacerbations are also highly prevalent and associated with poor perinatal outcomes and an increased risk of asthma in childhood. Achieving optimal asthma control, minimising exacerbations and ensuring a high level of care which considers the range of co-morbidities experienced by pregnant women with asthma have the potential to improve the health of the future generation.

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# Chapter 4
# Asthma: Management


**Jennifer A. Namazy**

## Introduction

Asthma is one of the most common potentially serious medical problems to complicate pregnancy, and asthma may adversely affect both maternal quality of life and perinatal outcomes. Optimal management of asthma during pregnancy is thus important for both mother and baby. This chapter reviews the general management of asthma during pregnancy including non-pharmacological aspects of gestational asthma management. Chapter 2 reviews specific information regarding the pharmacologic management of asthma during pregnancy.

Recent US national surveys report that the prevalence of asthma during pregnancy is about 8.8% [1]. This is supported by a recent study from the UK, which demonstrated that the prevalence of asthma during pregnancy was about 8.3% between 2000 and 2008 [2].

Treating asthmatic women requires understanding the effects of pregnancy on the course of asthma and, conversely, the effects of asthma on pregnancy outcomes. This information is covered in Chap. 3.

## Clinical Scenario

A 20-year-old woman G1P0 with a history of asthma presents to the clinic. She found out recently that she is pregnant and is at an estimated 8 weeks gestation. She has complaints of dyspnea, wheezing, and nighttime awakenings caused by cough. She is concerned about restarting her asthma medications. She is currently using an inhaled short-acting beta-agonist three to four times a day. She has been prescribed

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an inhaled corticosteroid in the past but is afraid to use the medication because of its possible effects on her unborn baby. In the last 2 years, she has had two ER visits for acute attacks of asthma. Triggers of asthma include cat exposure, tobacco smoke exposure, cleaning her house, and upper respiratory infections. On physical exam she has end-expiratory wheezes. Spirometry reveals an FEV1 of 75% of predicted value which increased to an FEV1 of 90% of predicted value after administration of an inhaled bronchodilator. On the basis of the frequency of her symptoms, their effect on sleep, her frequency of rescue therapy use, and her pulmonary function, her asthma was considered uncontrolled. She agreed to start inhaled budesonide. Her reluctance to use medications for fear of potential adverse effects on the fetus was acknowledged, but she was told that asthma exacerbations, and the risks of uncontrolled asthma, leading to maternal and fetal hypoxia, were more harmful to her and the baby compared to the risks of using inhaled corticosteroids during pregnancy.

## Review of Risks

Information should be given to the patient regarding asthma and allergies in general, effects of properly managed symptoms on pregnancy, possible effects of pregnancy on the symptoms, effects of carefully chosen medication on the baby, and anticipated course of labor and delivery.

Discussions may begin with a general overview of the effects pregnancy on asthma. Asthma course may worsen, improve, or remain unchanged during pregnancy, and the overall data suggest that these various courses occur with approximately equal frequency. Asthma also appears to be more severe or to worsen during pregnancy in women who have more severe asthma before pregnancy [3]. The course of asthma may vary by stage of pregnancy. The first trimester is generally well tolerated in asthmatic women, with infrequent acute episodes. Increased symptoms and more frequent exacerbations have been reported to occur between weeks 17 and 36 of gestation. In contrast, asthmatic women in general tend to experience fewer symptoms and less frequent asthma exacerbations during weeks 37–40 of pregnancy than during any earlier gestational period [4]. The mechanisms responsible for the altered asthma course during pregnancy are unknown. The myriad of pregnancy-associated changes in levels of sex hormones, cortisol and prostaglandins may contribute to changes in asthma course during pregnancy.

The discussion could continue with a discussion of the effect of controlled asthma on pregnancy. A meta-analysis from Murphy et al. derived from a substantial body of literature spanning several decades and including very large numbers of pregnant women (over 1,000,000 for low birth weight and over 250,000 for preterm labor) indicates that pregnant women with asthma are at a significantly increased risk of a range of adverse perinatal outcomes including low birth weight and preterm birth [5, 6].

This was supported by a more recent study from Sweden which reported an increased risk of preeclampsia, emergency cesarean section, and small for gestational age, even when controlled for familial confounding factors [7].

Uncontrolled asthma can lead to hypoxia and other physiologic abnormalities that could lead to decreased fetal blood oxygen and resulting abnormal growth and development of the fetus. A meta-analysis sought to investigate if asthma exacerbations, oral corticosteroid use, or asthma severity, all components of poor asthma control, are associated with prematurity and intrauterine growth restriction.

Data from this meta-analysis found a significantly increased risk of low birth weight infants of those subjects experiencing asthma exacerbation during pregnancy (RR 3.02 [1.87, 4.89]) and using oral corticosteroids during pregnancy (RR 1.41, 95% CI [1.04, 1.93]). Overall, the risk of low birth weight or early preterm delivery was not increased in women with moderate/severe asthma compared to women with mild asthma [8]. Murphy et al. reported in a meta-analysis an increased risk of low birth weight in women who had an asthma exacerbation during pregnancy (RR 2.54, 95% Ci 1.52–4.25) compared with women without asthma. This meta-analysis also reported a nonsignificant trend of increased preterm delivery in asthmatics with exacerbations during pregnancy (RR 1.54[0.89, 2.69]) and an increased relative risk of preterm delivery (RR 1.51, 95% CI [1.15, 1.98]) in those asthmatic women using oral corticosteroids during pregnancy [9]. Firoozi et al. investigated the effect of the severity of asthma during pregnancy on the risk of a small for gestational infants, low birth weight, and preterm birth. Their retrospective cohort study included over 13,000 subjects and demonstrated an increased risk of small for gestational age infants in the moderate and severe asthmatic groups. There was no increased risk of low birth weight or preterm delivery in these groups [10].

Dombrowski et al. found no significant effect of mild asthma or moderate/severe asthma on preterm delivery (at either <32 weeks or <37 weeks gestation), compared to controls without asthma. However, when the subgroup of women with severe asthma ($FEV_1$ <60% predicted and/or used oral steroids in the 4 weeks prior to study enrollment) was compared with controls, there was a significantly increased risk of preterm delivery (adjusted OR 2.2, 95% CI 1.2, 4.2) [11].

Stenius-Aarniala et al. compared data from 47 patients with an attack of asthma during pregnancy to data from 457 asthmatics with no recorded acute exacerbation and 237 healthy subjects. The authors found no increased incidence of congenital malformations in the infants of asthma women with exacerbations during pregnancy [12]. However, a more recent cohort of over 4000 pregnancies found an increased risk of total congenital malformations in the infants of pregnant asthmatic women who had an asthma exacerbation during pregnancy [1.48 (95% CI, 1.04–2.09) compared to infants of women who did not experience an exacerbation [13].

Stenius-Aarniala et al. did not find any increased risk of perinatal death in those women with an attack of asthma during pregnancy [12]. Similarly, a more recent study of 146 pregnant women with asthma exacerbations during pregnancy found that there was no increased risk of stillbirth in those women with severe exacerbations during pregnancy [14]. Two smaller retrospective studies also found that severe asthma was not associated with an increased risk of perinatal death compared

with mild asthmatics and controls [15, 16]. This was supported by a prospective study conducted at 16 centers of the Maternal-Fetal Medicine Units Network of the National Institute of Child Health and Human Development in over 2000 pregnant asthmatics. The authors found no increased risk of perinatal mortality when comparing moderate to severe asthmatics to those with milder disease [11]. One of the largest retrospective database studies in a cohort of 13,100 and 28,042 single pregnancies in women with and without asthma found that there was an increased risk of perinatal mortality (OR 1.35, 95% CI 1.08–1.67) in infants of asthmatic women [17]. In follow-up, the authors used a two-stage sampling cohort design and found that the increased risk of perinatal mortality did not remain significant after adjusting for cigarette smoking (OR 1.12,95% CI 0.87–1.45) [18].

A large prospective cohort study that specifically examined the effect of asthma severity on preeclampsia found that women with moderate to severe symptoms during pregnancy were at increased risk of preeclampsia, suggesting a role of active maternal inflammation [19]. A study from Schatz et al. found a significant association between hypertension during pregnancy and lower $FEV_1$ after adjustment for covariates. The mean percent predicted $FEV_1$ was lower, and the proportion of women with $FEV_1$ <80% was higher, in women with hypertension during pregnancy compared to those without hypertension [20].

Data from a case control study which investigated the relationship between maternal asthma, preeclampsia, and preterm delivery did not indicate a greater risk of preeclampsia among women with physician-diagnosed asthma [21]. However, there was a significant association between preeclampsia and asthma among a subgroup of women who experienced symptoms during pregnancy and had received their diagnosis more than 10 years earlier [21]. Findings from other studies have shown that women with asthma exacerbations during pregnancy, a marker of poor control, had similar risk of preeclampsia to women with asthma who did not have exacerbations in pregnancy [9, 22]. These data suggest that inherent asthma severity, rather than control or exacerbations, may be related to the increased risk of preeclampsia in asthmatic women. This would support a common pathogenesis theory for this increased risk, which is supported by two types of observations. First, preeclampsia has been associated with airway hyperresponsiveness. When measurements were made in postpartum women, those who had preeclampsia during pregnancy had significantly increased airway hyperresponsiveness compared to women with previously normotensive pregnancies. This was observed even in non-asthmatic women, and the authors suggested that a possible explanation for the association between preeclampsia and asthma was mast cell infiltration of the smooth muscle in both the lungs and myometrium [23]. Another mechanism which has been proposed to contribute to preeclampsia in women with asthma is vascular hyperreactivity leading to changes in uteroplacental blood flow which have been observed in vitro in placentae from women with moderate and severe asthma [24] and women with preeclampsia [25].

In summary, one can review with the pregnant asthmatic patient the above data which suggest a relationship between asthma, particularly more severe asthma, and various adverse perinatal outcomes. The data also suggest that better controlled

asthma, as assessed by symptoms, pulmonary function, or exacerbations, is less likely to be associated with adverse perinatal outcomes, especially prematurity and reduced fetal growth, than poorly controlled asthma [7–10, 13, 20, 26–28] attached, which may be duplicates of what you have).

## Diagnosis and Monitoring

In a patient without a previous diagnosis of asthma, asthma must be differentiated from a number of other potential causes of respiratory symptoms during pregnancy. The most common differential diagnosis is dyspnea of pregnancy, which may occur in early pregnancy in approximately 70% of women. This dyspnea is usually differentiated from asthma by its lack of association with cough, wheezing, or airway obstruction. Other important masqueraders of asthma include vocal cord dysfunction, panic attacks, hyperventilation, and cough due to postnasal drip, laryngopharyngeal reflux, or angiotensin-converting enzyme (ACE) inhibitor therapy. All of these can coexist with asthma. Even when these conditions coexist with asthma, their diagnosis and appropriate therapy usually reduce the patient's respiratory symptoms.

Wheezing, chest tightness, cough, and associated shortness of breath are common symptoms of asthma. The diagnosis is ideally confirmed by the demonstration of reversible airways obstruction, which most commonly is an increase in forced expiratory volume in 1 s (FEV1) by 12% or more and of at least 200 mL after an inhaled short-acting bronchodilator. In nonpregnant patients with normal pulmonary function, asthma can be confirmed by means of methacholine challenge testing. However, this type of testing is not recommended in pregnant patients. Airway responsiveness to mannitol and nonatopic state appears to characterize women at an increased risk of asthma exacerbations during pregnancy [29]. In contrast, characteristics of patients with a lower risk of asthma exacerbations during pregnancy were no history of prepregnancy exacerbations, no controller medication, and clinically stable asthma prior to pregnancy. This information could be considered helpful in discussions with pregnant asthmatics or patients undergoing family planning.

Several biomarkers for asthma have been studied in the pregnant population as well. Hyaluronic acid, which has been shown to be a marker of systemic inflammation, was recently evaluated as a screening tool for asthma control during pregnancy [30]. In that study, hyaluronic acid values could discriminate patients with ACT total score >20 (controlled patients) and <20 (uncontrolled patient) (AUC 0.78, 95% CI 0.65–0.92). Further studies are necessary to confirm these observations.

While osteopontin increases during pregnancy irrespective of asthma severity, clusterin appears to correlate with lung function [31]. Recent studies suggest that an elevated FENO can be used in pregnant women to follow asthma similar to its use in nonpregnant patients [32]. Thus, an elevated FENO would likely support the diagnosis of asthma in pregnant patients. If FENO is normal or unavailable, thera-

peutic trials of asthma therapy, such as 2–4 weeks of regular inhaled corticosteroids, may be used during pregnancy in patients with possible but unconfirmed asthma. A recent double-blind, parallel-group, controlled study by Powell et al. tested the measurement of fraction of exhaled nitric oxide (F(E)NO) to guide management of pregnant asthmatics. The primary outcome was total asthma exacerbations. The authors found that the exacerbation rate was lower in the group using F(E)NO to adjust asthma therapies [33]. Further studies in other populations are necessary to confirm these findings.

Once the diagnosis of asthma is confirmed, the next step is the assessment of asthma severity (in patients not already on controller therapy) or assessment of control (in patients already on controller therapy) (Table 4.1). Patients with intermittent asthma have short episodes and use rescue therapy less than or equal to two times per week, nocturnal symptoms less than or equal to two times a month, and normal pulmonary function between episodes. Patients with more frequent symptoms or who require daily asthma medications should be considered to have persistent asthma. Validated questionnaires are used in nonpregnant patients to assess asthma control, and the pregnancy Asthma Control Test (p-ACT) has recently been shown to be valid and reliable to monitor asthma control during pregnancy [34]. CARAT or "Control of Allergic Rhinitis and Asthma Test" is a brief self-administered questionnaire to quantify the degree of control of allergic rhinitis and asthma. It was recently validated in a study of 42 pregnant asthmatics [35]. Based on the control and severity of asthma, as well as spirometry, ACT and FeNO a controller medication might be considered. Chapter 2 will review in detail the safety of commonly used medications during pregnancy. Step therapy for pharmacologic management of asthma is similar to that of the nonpregnant asthmatic (Table 4.2). The caveat is that for step 3 there is a choice. One might choose to increase to a medium-dose inhaled corticosteroid, or, since more data available regarding the safety of long-acting bronchodilators during pregnancy, a low-dose inhaled corticosteroid/long-acting bronchodilator may be appropriate.

**Table 4.1** Classification of asthma severity in pregnant patients

| Asthma severity | Symptom frequency | Nighttime awakening | Interference with normal activity | $FEV_1$ or peak flow (predicted percentage of personal best) |
|---|---|---|---|---|
| Intermittent | 2 days per week or less | Twice per month or less | None | More than 80% |
| Mild persistent | More than 2 days per week, but not daily | More than twice per month | Minor limitation | More than 80% |
| Moderate persistent | Daily symptoms | More than once per week | Some limitation | 60–80% |
| Severe persistent | Throughout the day | Four times per week or more | Extremely limited | Less than 60% |

Data from Schatz and Dombrowski [49]
*Abbreviation:* $FEV_1$ forced expiratory volume in the first second of expiration

**Table 4.2** Steps in asthma therapy during pregnancy

| Step | Preferred controller medication | Alternative controller medication |
|---|---|---|
| 1 | None | – |
| 2 | Low-dose inhaled CS | LTRA, theophylline, or cromolyn |
| 3 | Medium-dose inhaled CS or low-dose inhaled CS plus LABA | Low-dose inhaled CS plus LTRA or theophylline |
| 4 | Medium-dose inhaled CS plus LABA | Medium-dose inhaled CS plus either LTRA or theophylline |
| 5 | High-dose inhaled CS plus LABA | Medium-dose inhaled CS plus LABA plus tiotropium |
| 6 | High-dose inhaled CS plus LABA plus oral prednisone | Omalizumab for allergic patients<br>Anti-IL5 biologic for patients with eosinophilic asthma |

Data modified from Schatz and Dombrowski [50]
*Abbreviations: CS* corticosteroid, *LABA* long-acting β-agonist, *LTRA* leukotriene receptor antagonist

## Non-pharmacological Management

### *Barriers to Control*

Based on the data presented thus far, control of maternal asthma is essential to reduce the risk of perinatal complications. There are several factors that remain barriers to asthma control in this group of patients. They include psychological state, smoking, obesity, adherence, physician undertreatment, and viral infections.

Pregnancy represents a time of psychological vulnerability, even for healthy women. Most women feel emotionally labile and ambivalent regarding the pregnancy. Changes in body image, the physical symptoms accompanying normal pregnancy, and various fears regarding the pregnancy and the developing infant cause additional stress. In the pregnant woman with asthma or allergic disease, psychological stresses may be especially important. First, in women whose symptoms tend to worsen with stress, the stress of normal pregnancy may exacerbate symptoms. Furthermore, the morbidity associated with asthma or allergic symptoms, especially if the symptoms interfere with sleep, may add substantially to the stress of normal pregnancy. The following principles of optimal psychological management during pregnancy can help the asthmatic or allergic patient (Table 4.3).

It comes as no surprise that pregnant women are hesitant about continuing asthma medications during pregnancy for fear of causing untoward effects on their unborn baby. *A recent* cohort study of 115,169 pregnant asthmatics in South Korea reported that women tended to rapidly reduce their asthma medication use during the beginning of their pregnancy. This led to a greater number of exacerbations in a small part of the study population [36]. Another study found that about one-third of pregnant asthmatics discontinued asthma medications during pregnancy, often without consulting their physicians [37]. Another study by Lim et al. [38] examined the reasons for nonadherence in this particular population of patients. Data were

**Table 4.3** Principles of optimal psychological management during pregnancy

| |
|---|
| *Vocalization*<br>Allowing the patient ample opportunity to express her fears and concerns is therapeutic in itself |
| *Education*<br>Information should be given to the patient regarding asthma and allergies in general, effects of properly managed symptoms on pregnancy, possible effects of pregnancy on the symptoms, effects of carefully chosen medication on the baby, anticipated course of labor and delivery, inheritance of asthma and allergic diseases (see Chap. 2), and possible methods of decreasing the likelihood of allergy in the infant (see Chap. 13). Such knowledge provides a sense of mastery over the unknown and reduces anxiety |
| *Support*<br>Although most patients have a social-familial support network, the physician managing the asthma or allergic disease should be an important additional source of support. Regular visits and easy accessibility to the physician for unanticipated problems should significantly reduce anxiety |
| *Reassurance*<br>If the patient knows she can express her concerns to a knowledgeable and caring professional, if she understands the educational information presented, and if she has regular visits and easy accessibility to the physician, she will be reassured with a sense of confidence and security. In addition, the pregnant woman should be specifically reassured that the physicians will work with her as a team to optimize maternal and neonatal outcomes<br>Although most pregnant women with asthma or allergic disease will require no additional psychological intervention, an occasional patient with unusual stress or impoverished coping mechanisms may require psychiatric consultation |

Modified to table from Schatz et al. [51]

obtained from interviews with pregnant asthmatic women. Concerns about medication use, specifically steroid use, overshadowed concerns about the potential risk of uncontrolled asthma. Many women appeared content to rely on their reliever therapy, and many decreased their preventive therapy without consulting their doctors. Interestingly, the majority of participants complained about the lack of information available regarding asthma during pregnancy. Lack of support was also a common complaint. Many women felt that the information they were receiving from their pharmacists, nurses, and doctors was contradictory, leading them to make their own choices about medication management. As a result, many of the participants decreased or discontinued their asthma medications or withheld doses during pregnancy. According to the studies' authors, it was clear from the interviews that women felt it would have been helpful if asthma had been brought up more by their healthcare professionals, providing opportunities for pursuing more reliable information.

A disappointing fact is that medical professionals can provide incorrect information. A recent study found that over a quarter of family physicians would instruct their patients to decrease or discontinue asthma medication during pregnancy when asthma was well controlled by current therapy [39]. Another study by Cimbollek et al. surveyed 1000 physicians, almost half of whom were respiratory medicine specialists/allergy specialists and the other half were primary care physicians. Almost 30% of physicians would not perform spirometry in pregnant asthmatic

patients, and only 64% reported that they followed the asthma guidelines in the management of pregnant asthmatic patients [40].

Physician reluctance to treat may also affect the course of asthma during pregnancy. One study identified 51 pregnant women and 500 nonpregnant women presenting to the emergency department with acute asthma. Although asthma severity appeared to be similar in the two groups based on peak flow rates, pregnant women were significantly less likely to be discharged on oral corticosteroids (38% vs. 64%). Presumably related to this undertreatment, pregnant women were three times more likely than nonpregnant women to report an ongoing exacerbation 2 weeks later [41, 42].

Uninformed decisions by pregnant asthmatic patients or those managing their asthma may lead to exacerbations of asthma during pregnancy and potentially adverse perinatal outcomes. Therefore, asthma education is a critical component in the management of the pregnant asthmatic. One successful approach was recently reported in the multidisciplinary approach to management of maternal asthma study or MAMMA. Subjects were randomized to either receive a pharmacist-led intervention (consisting of self-management strategies, such as proper inhaler technique, adherence support, monthly Asthma Control Questionnaire (ACQ) assessments, FEV1, and action plans) or usual care. There was communication between the pharmacist, family physician, midwife, and the patient. At the end of 6 months, there was a significant reduction in ACQ (improved asthma control) compared to the group that received usual care [43].

Obesity has been shown to be an inflammatory state that may play an important role in asthma initiation and control. Obesity during pregnancy has been associated with adverse perinatal outcomes including gestational diabetes, preeclampsia, thromboembolic disorders, postpartum hemorrhage, large for gestational age, fetal death, and congenital anomalies. Higher BMI and gestational weight gain have been associated with an increased risk for asthma exacerbations in both nonpregnant and pregnant women [44]. The mechanisms leading to these outcomes are thought to be due to a heightened inflammatory response and are reviewed in Chap. 3.

Population-based studies have shown a relationship between smoking and airway hyperresponsiveness [11], implying that smoking is a risk factor for asthma. The relationship between gestational asthma and smoking is also reviewed in Chap. 3. The potential for maternal smoking to both increase the risk of uncontrolled asthma and to directly adversely affect pregnancy suggests that discontinuation of smoking should be a high-priority goal during pregnancy.

Infections during pregnancy can certainly affect the course of gestational asthma and be a barrier to asthma control. Some degree of decrease in cell-mediated immunity may make the pregnant patient more susceptible to viral infection, and upper respiratory tract infections have been reported to be the most common precipitants of asthma exacerbations during pregnancy [14]. Sinusitis, a known asthma trigger, has been reported to be six times more common in pregnant compared to nonpregnant women [45]. In addition, pneumonia has been reported to be greater than five times more common in asthmatic than non-asthmatic women during pregnancy [46].

Pregnant women with asthma have been shown to have more common colds during pregnancy than pregnant women without asthma. In one study, the severity of cold symptoms was also increased in women with asthma. In addition, among women with asthma, having a laboratory-confirmed viral infection was associated with poorer maternal health, with 60% of infections associated with uncontrolled asthma and a higher likelihood of preeclampsia. Viral infections may be complicated by bronchitis, bacterial pneumonia, and bacterial sinusitis, all of which may have adverse effects on both mother and baby. More research is needed on the prevention of viral-induced asthma exacerbations during pregnancy. Pregnant women are at increased risk of severe influenza during pregnancy, which may also lead to asthma exacerbations. *Therefore, vaccination for influenza for the pregnant asthmatic is an important part of management* [47].

A recent study tried to determine whether a diagnosis of upper respiratory infection or sinusitis was more common during pregnancy and whether pregnant women were more likely to receive a prescription for antibiotics. This study did not confirm the prior finding that sinusitis or antibiotic use for upper respiratory infections is increased in pregnancy. The report did find that respiratory comorbidities, such as asthma, increased the risk of antibiotic use during pregnancy [48].

More clinical trials are needed addressing the non-medication aspects of asthma management, including assessment and monitoring, self-management education, and adherence. Related to adherence, one of the most important needs for the future is the availability of additional safety information for asthma medications used during pregnancy that can also account for asthma control.

Another priority for future research is developing methods for overcoming barriers to asthma control during pregnancy. As discussed above, these barriers include major modifiable risk factors such as cigarette smoking, clinician undertreatment, patient nonadherence, and viral infections which have been shown to be associated with asthma exacerbations. Optimal smoking cessation strategies, clinician education, effective patient education and support, and means of preventing viral infections or at least reducing their adverse effect on asthma should increase the likelihood of adequately controlled gestational asthma.

## Medication Management

The medical management of asthma during pregnancy is not unlike that of the nonpregnant asthmatic. Therapy is divided into long-term control medications and rescue therapy. Long-term control medications are used for maintenance therapy to prevent asthma manifestations and include inhaled corticosteroids, cromolyn, long-acting beta-agonists, leukotriene receptor antagonists, and theophylline. Controller therapy should be increased in steps (Table 4.1) until adequate control is achieved. Rescue therapy, most commonly inhaled short-acting beta-agonists, provides immediate relief of symptoms. Oral corticosteroids can either be used as a form of rescue therapy or as chronic therapy for severe persistent asthma.

Because pregnant women are generally excluded from clinical trials, there is a lack of adequate prospective efficacy or safety information for most medications taken during pregnancy, especially newer medications, as well as biologics and sublingual immunotherapy. Moreover, the existing observational data are often limited by the lack of information regarding asthma control as mentioned above. Similarly, more studies are needed to better define the effect of asthma severity and control on perinatal outcomes in general and as a potential confounder in the medication data.

Specific safety data on commonly used asthma and allergy medications during pregnancy is covered in greater detail in Chap. 2.

## Conclusion

Asthma is a common medical problem that may worsen during pregnancy. In addition to affecting maternal quality of life, uncontrolled asthma may lead to adverse perinatal outcomes. Awareness of proper treatment options for asthma during pregnancy is important for clinicians who care for pregnant patients in order to optimize maternal and infant health.

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# Chapter 5
# Rhinitis and Sinusitis


**Michael P. Carroll Jr., Adeeb A. Bulkhi, and Richard F. Lockey**

## Normal Anatomy of the Nose and Sinuses

The nose is an orifice for breathing that filters, moisturizes, and regulates the temperature of air as it enters the nose, pharynx, and lung and provides for olfaction. It is divided into two compartments by a nasal septum. Short, somewhat stiff, sensitive hairs, located at the nasal entrance, allow for enhanced tactile stimuli which can result in nasal itching and sneezing. The superior, middle, and inferior turbinates extend from the lateral walls of each side of the nose and occupy much of the free space within the nasal cavity. They overlie the superior, middle, and inferior nasal meatus, respectively, and can become edematous with various forms of rhinitis and rhinosinusitis and subsequently obstruct airflow [1, 2]. The middle meatus is important because it contains three convoluted and narrow ostiomeatal pathways which drain the anterior ethmoid, frontal, and maxillary sinuses.

Several kinds of epithelial cells line the nasal cavity and sinuses. Stratified squamous epithelium is located at the distal vestibule of the nose and is continuous with the facial skin. The nasal cavity, sinuses, and respiratory tract are lined by respiratory epithelium which contains various cell types including ciliated columnar and goblet

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cells. Goblet cells, located within the epithelium, produce mucus which is mobilized and cleared by ciliated columnar epithelial cells. Specialized olfactory ciliated epithelium is located in the superior aspect of the nose. The epithelial lining of the nasal cavity is in constant contact with the external environment and is regularly exposed to changes in the ambient temperature and humidity, allergens, infectious agents, pollutants, and other airborne substances.

The amount of blood reaching the nose and nasal pharynx is controlled by the constriction and dilation of small arteries and arterioles, depending on physiologic and environmental influences. Subepithelial capillaries are fenestrated, making them capable of responding rapidly to the administration of intranasal medications. The olfactory nerve and branches of the trigeminal nerve, the ophthalmic and maxillary branches, innervate the nasal cavity. Sympathetic and parasympathetic nerve fibers cause vasoconstriction and vasodilatation, respectively, when appropriately stimulated [2].

The paranasal sinus cavities contain air and communicate with the nasal cavity via ostia, which are approximately 2–6 ml in diameter. Goblet cells lining the sinuses produce nitric oxide, which has both vasodilatory and antimicrobial properties. The exact function of the sinuses remains unknown [2], but each pair of sinuses depends on their respective ostiomeatal complex for ventilation and mucus drainage. Obstruction of these complexes can result in an increase or decrease in sinus pressure and place the affected subject at risk to develop acute or chronic rhinosinusitis [3]. Pneumatization of the sinuses begins at birth and is not complete until adolescence. The degree of pneumatization varies [3]. The sphenoid and frontal sinuses are the last to develop, and up to 10% of normal individuals do not have frontal sinuses.

The anterior and posterior ethmoid sinuses are situated medially to the orbits, bilaterally, and drain into the middle and superior meatus, respectively. The maxillary sinuses lie lateral to the nose on each side of the face between the maxilla and the orbits and drain into the middle meatus. The paired frontal sinuses arise within the frontal bone and drain into the middle meatus. The sphenoid sinuses lie posterior to the ethmoid cells and drain into the sphenoethmoidal recesses on either side of the posterior nasal septum [3], superior to the superior nasal concha (Fig. 5.1).

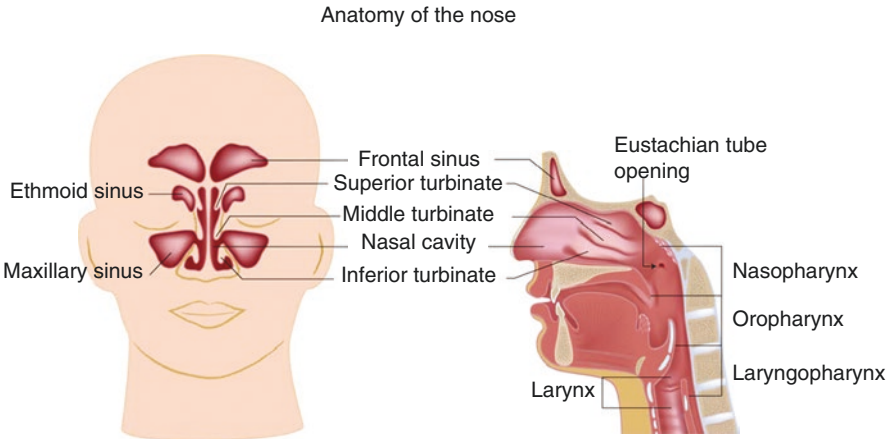


**Fig. 5.1** Anatomy of nasal cavity and sinuses. (With permission from Dreamstime LLC)

## Effects of Nasal and Sinus Disease on Asthma and General Health

Subjects with chronic diseases of the nose and sinuses, such as rhinitis, are at risk for other diseases. For example, with allergic rhinitis, subjects are three times more at risk to develop asthma [4, 5]. It is also a comorbid condition of this disease and "as goes the nose (i.e., in allergic rhinitis), so goes asthma." Treatment of symptomatic allergic rhinitis improves asthma outcomes.

Allergic rhinitis, especially when not appropriately managed, can result in an increased incidence of otitis media, infectious rhinosinusitis, and other upper airway diseases [6, 7]. Infectious rhinosinusitis is also a comorbid condition of asthma. Allergic rhinitis and infectious rhinosinusitis often coexist [3]. Therefore, it is essential that they be diagnosed and managed correctly.

## Pathophysiology of Atopic Diseases

The primary function of the upper airway epithelium is to warm, cool, and humidify the air and to defend the host against noxious agents, including pollutants, allergens, and infectious agents. Allergic rhinitis is caused by an allergic immune response in which specific IgE antibody combines with an allergen to which a subject is allergic and causes a hypersensitivity reaction. This reaction is also referred to as a type I hypersensitivity reaction [8]. Atopic subjects have a family history of atopic eczema, allergic rhinoconjunctivitis, and allergic asthma and therefore are genetically predisposed to develop these diseases.

IgE, the principle mediator of the immediate hypersensitivity reaction, attaches to mast cells present in blood vessels of connective tissues and mucosal membranes. Nonatopic subjects also produce IgE and have mast cells; however, because of their genetic predisposition (family history) and allergen exposure, atopic subjects become sensitized to specific allergens. When exposed to an allergen to which they are allergic, they develop an immediate hypersensitivity reaction, causing acute and chronic allergic rhinosinusitis and allergic asthma. Viral infections and environmental pollutants are thought to play a role in the sensitization process.

An example of an allergic reaction is a cat-allergic subject who develops allergic rhinitis when exposed to cat allergens. When aerosolized cat saliva and pelt proteins, sources of cat allergens, are inhaled, these allergens are absorbed onto mucosal surfaces, in this case, in the nose. Two IgE molecules located on a mast cell are bridged by the cat allergen, triggering the mast cell to release stored and newly generated vasoactive amines, such as histamine and proteases. They also generate and secrete products of arachidonic acid, such as prostaglandins and leukotrienes, and cytokines, such as tumor necrosis factor (TNF). These mediators cause an inflammatory response, vascular dilation, increased vascular permeability, and the recruitment of eosinophils, neutrophils, and Th2 cells (Fig. 5.2a, b). They also cause smooth muscle contraction in the bronchi, responsible for the bronchial constriction

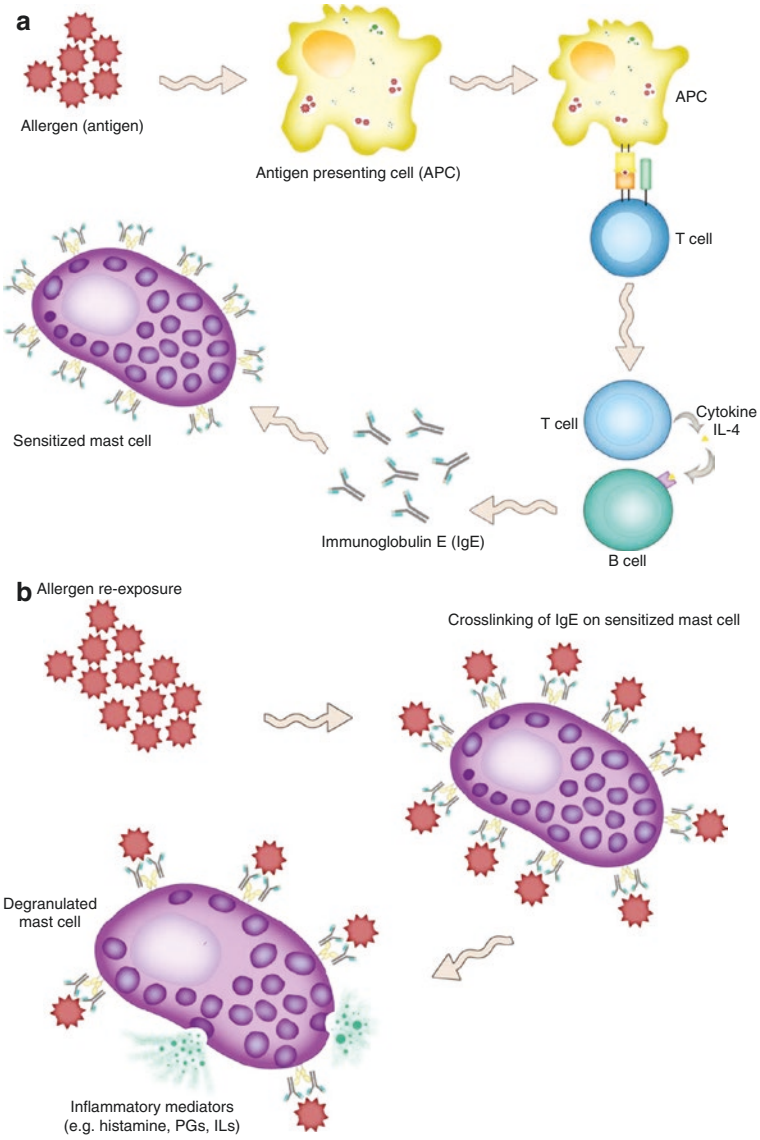


**Fig. 5.2** (**a**) An allergen (antigen) is introduced via inhalation and is processed by the antigen-presenting cell (APC). The allergen is degraded into small amino acid chains and subsequently displayed on the major histocompatibility complex II (MHC II) for specific T-cell receptor (TCR) recognition. Once the specific TCR recognizes the processed allergen on MHC II, a series of events occur leading to T-cell activation. Activated T cells interact with specific B cells and become activated. Activated B cells, with the help of interleukin 4 (IL-4), undergo immunoglobulin class switching. Class-switched B cells become plasma cells and begin producing immunoglobulin E (IgE) specific to the allergen. Secreted IgE coat mast cells. (**b**) Upon re-exposure to an identical allergen, IgE attaches to mast cells via high-affinity IgE receptors (FcεRI) and recognizes the allergen, which cross-links IgE molecules. This cross-linking leads to mast cell degranulation and the secretion of stored and newly formed inflammatory mediators, e.g., histamine, heparin, prostaglandins (PGs), and various cytokines. These mediators are responsible for the early- and late-phase signs and symptoms of IgE-mediated allergic diseases

in allergic asthma. This inflammatory cascade triggers the symptoms of allergic rhinitis which includes sneezing, nasal itching, rhinorrhea, and nasal congestion; with asthma, this inflammation causes cough, wheezing, and shortness of breath. The inflammatory process can ultimately damage the epithelial tissues of the nose, sinuses, and lung.

## Rhinitis or Rhinosinusitis During Pregnancy

The symptoms of rhinitis and rhinosinusitis can change during pregnancy. Some subjects improve, some worsen, and others remain the same [9]. One out of five pregnant women may be affected by allergic rhinitis, allergic asthma, or atopic eczema or a combination thereof [10]. In addition, the incidence of other types of rhinitis, for example, nonallergic rhinitis, may increase due to the physiologic and hormonal changes associated with pregnancy. Pregnancy-associated hormones effect nasal blood flow and mucosal glands causing edema and hyperemia of the nasal mucosa [10]. This can result in "rhinitis of pregnancy," epistaxis, and worsening of underlying types of rhinitis and rhinosinusitis, which may be present before pregnancy or which occur during pregnancy. These topics are discussed below.

## Rhinitis

Rhinitis is characterized by the presence of one or more of the following nasal symptoms: congestion, anterior or posterior rhinorrhea, sneezing, and pruritus [7]. It is often confused with rhinosinusitis, a term usually synonymous with sinusitis (Table 5.1). Poorly controlled rhinitis is a significant cause of impaired quality of life because of its associated facial discomfort, fatigability, cognitive impairment, and sleep disturbance [7, 11–13]. Appropriate management of rhinitis is also essential to optimally control asthma and sleep apnea. Various common types of rhinitis (Table 5.2) are caused by inflammation of the epithelial lining of the nasal cavity, such as occurs with allergic or infectious rhinitis [7]. Other forms of rhinitis include rhinitis of pregnancy, atrophic rhinitis, rhinitis medicamentosa, and rhinitis associated with systemic diseases, such as granulomatosis with polyangiitis (historically known as Wegener's granulomatosis) or eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome). These diseases can also present while a subject is pregnant and should be considered, especially with severe symptoms, in the differential diagnosis.

**Table 5.1** Summary and comparison of rhinitis and sinusitis subtypes

| | **Allergic rhinitis** | **Nonallergic rhinitis (e.g., vasomotor, hormonal)** | **Infectious rhinitis (common cold)** | **Rhinosinusitis (sinusitis)** |
|---|---|---|---|---|
| **Duration** | Varies | Varies | 3–10 days; up to 2 weeks in smokers | Acute <4 weeks<br>Subacute: 4–12 weeks<br>Chronic: >3 months |
| **Frequency** | Allergen exposure | Perennial/varies | Acute | |
| **Fever** | _ | Absent | +<br>Low grade | + |
| **Nasal discharge** | Watery | Prominent watery | Clear (viral)<br>Purulent (bacterial) | + |
| **Pruritus** | + | Absent | – | – |
| **Sneezing** | + | Absent | +/– | +/– |
| **Nasal congestion** | Prominent in late phase | Prominent | + | + |
| **Facial pain/ pressure** | – | +/– | +/– | + |
| **Pain in upper teeth** | – | +/– | +/– | + |
| **Headache** | – | +/– | +/– | + |
| **Cough** | +/– | – | + | + |
| **Malaise** | – | – | +/– | + |
| **Notes** | Seasonal | See subtypes | Pharyngitis | |

Legend: + is present; +/– is present or not present; – is not present

**Table 5.2** Type and causes of rhinitis

| Common types and etiologies of rhinitis |
|---|
| Allergic rhinitis |
| Seasonal |
| Perennial |
| Nonallergic rhinitis |
| Pregnancy rhinitis |
| Vasomotor rhinitis |
| Gustatory rhinitis |
| Nonallergic rhinitis with eosinophilia syndrome (NARES) |
| Atrophic rhinitis |
| Mixed |
| CPAP-associated rhinitis (continuous positive airway pressure) |
| Rhinitis medicamentosa |
| Nasal decongestant sprays |
| Intranasal cocaine |
| Systemic medication-induced rhinitis |
| Oral contraceptives |

**Table 5.2** (continued)

| Common types and etiologies of rhinitis |
|---|
| Erectile dysfunction drugs |
| Alpha-blockers |
| Some hypertensives |
| Aspirin and other NSAIDS |
| Some antidepressants |
| Some benzodiazepines |
| Systemic diseases |
| Hypothyroidism |
| Granulomatosis with polyangiitis (Wegener's granulomatosis) |
| Midline granuloma |
| Sarcoidosis |
| Cystic fibrosis |
| Immotile cilia syndrome (Kartagener) |

Adapted from Peden [14]

## *Allergic Rhinitis*

### Etiology

Allergic rhinitis affects up to 60 million people in the United States, approximately 20% of all children and adults [15–18], including up to one-third of women of childbearing age [10, 19]. It becomes worse in approximately one-third of affected pregnant subjects [20]. It is characterized by symptoms which begin within minutes of allergen exposure often followed by a late-phase response 4–8 hours later. Early-phase symptoms include nasal congestion, sneezing, rhinorrhea, and pruritus. Eighty percent of subjects can also have allergic conjunctivitis which causes itching, redness, and tearing of the eyes. Congestion of the nose dominates the late-phase reaction [7]. Continuous allergen exposure results in chronic symptoms. When both the nose and eyes are affected, it is referred to as allergic rhinoconjunctivitis.

### Diagnosis

A detailed history focusing on seasonal and perennial environmental exacerbations and exposures which triggers symptoms (pollen, cat and dog emanations, dust mites, fungi) and responses to medications, such as antihistamines and intranasal corticosteroids, is essential. A complete physical examination with emphasis on the head, eyes, ears, nose and oral pharynx, skin, and chest should follow. The nasal mucosa membranes are usually edematous, pale with clear mucus, all consistent

with the suspected diagnosis. The affected conjunctiva is often injected with accompanying chemosis (edema of the bulbar conjunctiva). Appropriate prick-puncture and intradermal skin tests or in vitro-specific IgE tests can help confirm historical suspected causative allergens associated with the disease [7], with in vitro tests preferred during pregnancy.

## Treatment

Management of the pregnant versus nonpregnant subject does not significantly differ. Non-pharmacologic strategies, such as allergen and irritant avoidance, are important [21]. Data on the safety of rhinitis medications during pregnancy are reviewed in detail in Chap. 2. Nonsedating second-generation antihistamines, such as cetirizine and loratadine, are considered safe and are first drugs of choice. Montelukast is also considered safe to use during pregnancy, but it is not very effective. For more persistent symptoms, an intranasal corticosteroid can be utilized [19, 21], such as mometasone, beclomethasone, fluticasone, and others. Although the safety of nasal decongestants, such as phenylephrine and oxymetazoline, has not been studied directly, they appear to be safe with short-term use (less than 3 days), particularly after the first trimester. However, oral decongestants have been associated with birth defects, when used in the first trimester [19] (Table 5.3).

Allergen immunotherapy is another treatment modality by which allergen-sensitized subjects receive allergen vaccines to which they manifest allergy either by subcutaneous allergen immunotherapy (SCIT) or sublingual allergen immunotherapy (SLIT). SCIT is more often prescribed when multiple allergens are involved in the pathogenesis of the disease, i.e., allergy to tree, grass, and weed pollen, dust mites, cat, dog, and other allergens. SLIT is primarily employed when the number allergens to which an individual is limited, e.g., only grass pollen, ragweed pollen, and/or dust mites. When given over time, such therapy induces clinical tolerance to the allergens to which an individual is allergic. Such therapy does not usually begin during pregnancy. Allergen immunotherapy, depending on the risk/benefit, can be continued or discontinued during pregnancy [22]. For SCIT, the dose of allergen vaccine and the interval between injections are usually halved to decrease the potential of inducing a systemic allergic reaction which can affect the welfare of the fetus and mother [23]. SLIT is similar to SCIT except that the allergen vaccine or tablet for SLIT is delivered under the tongue and absorbed locally, not by the subcutaneous route. Information about SLIT safety during pregnancy is insufficient, but animal studies show no risk to the fetus. In general, allergen immunotherapy can be continued if tolerated before but should not be initiated during pregnancy [24].

**Table 5.3** Summary of medications used in rhinitis management

| Medication | Mechanism of action | Dosage | Pregnancy implications | Side effects |
|---|---|---|---|---|
| Intranasal cromolyn (NasalCrom®) | Acts locally to reduce calcium influx which decreases histamine degranulation from mast cells | Instill one spray (5.2 mg) in each nostril three to four times daily; may be increased up to six times daily | Based on available studies, cromolyn may be used for the treatment of allergic rhinitis in pregnant women | Burning sensation of the nose, nasal mucosa irritation, sneezing, stinging sensation of the nose, headache, unpleasant taste, cough, hoarseness, postnasal drip |
| Chlorpheniramine | Competes with histamine for H1-receptor sites on effector cells in the gastrointestinal tract, blood vessels, and respiratory tract | Immediate release: 4 mg every 4–6 h (not exceed 24 mg/24 h) Extended release: 12 mg every 12 h (not exceed 24 mg/24 h) | Based on available studies, cromolyn may be used for the treatment of allergic rhinitis in pregnant women | Drowsiness (slight to moderate), thickening of bronchial secretions, dizziness, excitability, fatigue, headache, nervousness, abdominal pain, diarrhea, increased appetite, nausea, xerostomia, urinary retention |
| Cetirizine (Zyrtec®) | Competes with histamine for H1-receptor sites on effector cells in the gastrointestinal tract, blood vessels, and respiratory tract | 5–10 mg once daily, depending upon symptom severity | Maternal use of cetirizine has not been associated with an increased risk of major malformations. Cetirizine may be used for the treatment of allergic rhinitis during pregnancy | Drowsiness, headache, insomnia, fatigue, malaise, dizziness, abdominal pain, xerostomia, diarrhea, nausea, vomiting, pharyngitis, epistaxis bronchospasm |
| Loratadine (Claritin®) | Long-acting tricyclic antihistamine with selective peripheral histamine H1-receptor antagonistic properties | 10 mg daily once daily or 5 mg twice daily | Maternal use of loratadine has not been associated with an increased risk of major malformations. Loratadine may be used for the treatment of allergic rhinitis during pregnancy | Headache, drowsiness, fatigue, malaise, xerostomia, stomatitis |

(continued)

**Table 5.3** (continued)

| Medication | Mechanism of action | Dosage | Pregnancy implications | Side effects |
|---|---|---|---|---|
| Montelukast (Singulair®) | Selective leukotriene receptor antagonist that inhibits the cysteinyl leukotriene receptor | 10 mg once daily (in the evening) | Based on available data, an increased risk of teratogenic effects has not been observed with montelukast use in pregnancy | Headache, dizziness, fatigue, dyspepsia, gastroenteritis, toothache, pyuria increased serum AST and ALT, weakness, nasal congestion, epistaxis |
| Budesonide (Rhinocort®) | Controls the rate of protein synthesis; depresses release and activity of endogenous chemical mediators of inflammation (kinins, histamine, liposomal enzymes, prostaglandins) and the migration of polymorphonuclear leukocytes, fibroblasts; reverses capillary permeability and lysosomal stabilization at the cellular level to prevent or control inflammation | One spray (32 mcg) in each nostril once daily (64 mcg/day) | Studies of pregnant women using intranasal budesonide have not demonstrated an increased risk of abnormalities. Intranasal corticosteroids are recommended for the treatment of rhinitis during pregnancy; the lowest effective dose should be used | Epistaxis, pharyngitis, bronchospasm, cough, nasal mucosa irritation |
| Mometasone (Nasonex®) | | Two sprays (100 mcg) in each nostril once daily (200 mcg) | Intranasal corticosteroids, including mometasone, beclomethasone, and fluticasone, may be acceptable for the treatment of rhinitis during pregnancy when used at recommended doses. Pregnant women adequately controlled on mometasone, beclomethasone, and fluticasone may continue therapy; if initiating treatment during pregnancy, use of an agent with more data in pregnant women may be preferred | Headache, viral infection, pharyngitis, cough, epistaxis |
| Beclomethasone (Qnasl®) | | Two inhalations (160 mcg) in each nostril once daily (320 mcg daily) | | Nasopharyngitis, dizziness, headache, altered sense of smell, anosmia, adrenal suppression (at high doses or in susceptible individuals), hypercorticoidism(at high doses or in susceptible individuals) |
| Fluticasone (Flonase®) | | Two sprays (50 mcg/spray) per nostril once daily (200 mcg/day) | | Headache, dizziness, generalized ache, nausea and vomiting, abdominal pain, diarrhea, Pharyngitis, epistaxis, acute asthma, cough, pharyngolaryngeal pain |

**Table 5.3** (continued)

| Medication | Mechanism of action | Dosage | Pregnancy implications | Side effects |
|---|---|---|---|---|
| Phenylephrine (Neo-Synephrine®) | Potent, direct-acting alpha-adrenergic agonist with virtually no beta-adrenergic activity; produces local vasoconstriction resulting in nasal decongestion | Instill 2–3 sprays in each nostril no more than every 4 h for ≤3 days | Decongestants are not the preferred agents for the treatment of rhinitis during pregnancy. Short-term use (<3 days) of intranasal phenylephrine or oxymetazoline may be beneficial to some patients, although its safety during pregnancy has not been studied. Should be avoided in the first trimester of pregnancy | Burning, nasal discharge, sneezing, stinging |
| Oxymetazoline (Afrin®) | | 2–3 sprays into each nostril twice daily for ≤3 days (2 doses/24 h) | | Dry nose, nasal congestion (rebound; chronic use), nasal mucosa irritation (temporary), sneezing |
| Pseudoephedrine (Sudafed®) | Directly stimulates alpha-adrenergic receptors of respiratory mucosa causing vasoconstriction; directly stimulates beta-adrenergic receptors causing bronchial relaxation, increased heart rate and contractility | Immediate release, 60 mg every 4 to 6 h; extended release, 120 mg every 12 h or 240 mg every 24 h | Oral pseudoephedrine should be avoided during the first trimester. There is risk of gastroschisis, small intestinal atresia, and hemifacial microsomia due to pseudoephedrine's vasoconstrictive effects | Cardiac arrhythmia, chest tightness, hypertension, palpitations, tachycardia, ataxia, dizziness, drowsiness, excitability, fatigue |
| Ipratropium (Atrovent®) | Local application to nasal mucosa inhibits serous and seromucous gland secretions | Two sprays (21 mcg/spray) in each nostril two or three times daily (total dose, 168–252 mcg/day) | Adverse events have not been observed in animal reproduction studies | Headache, dysgeusia, xerostomia, diarrhea, nausea, upper respiratory tract infection, epistaxis, pharyngitis, dry nose, nasal mucosa irritation, nasal congestion |

(continued)

**Table 5.3** (continued)

| Medication | Mechanism of action | Dosage | Pregnancy implications | Side effects |
|---|---|---|---|---|
| Azelastine (Astelin®) | Competes with histamine for H1-receptor sites on effector cells and inhibits the release of histamine and other mediators involved in the allergic response | One or two sprays (0.1% solution) in each nostril twice daily or two sprays | Data related to the use of azelastine in pregnancy is limited; if treatment for rhinitis in a pregnant woman is needed, other agents are preferred | Bitter taste, headache, drowsiness, rhinitis, dysesthesia, dizziness, fatigue, epistaxis, burning sensation of the nose, pharyngitis, nasal discomfort, sneezing, nasal mucosa ulcer, pharyngolaryngeal pain |

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## *Hormonal Rhinitis*

### Etiology

Pregnancy rhinitis (also called rhinitis of pregnancy) and menstrual cycle rhinitis are both examples of hormonally induced rhinitis. Pregnancy rhinitis is associated with nasal congestion usually beginning after the 2nd month of pregnancy [25] and occurs in approximately 30% of randomly selected women [26]. Its principle cause is an increase in prolactin, vasoactive intestinal peptide, placental growth hormone, progesterone, and estrogen which affect the nasal vasculature, resulting in vascular engorgement and increased mucosal gland activity [19]. Pregnancy rhinitis usually abates 2 weeks postpartum.

### Diagnosis

The diagnosis is made clinically by an adequate history and physical examination. Other forms of rhinitis should be excluded.

### Treatment

The treatment of hormonal rhinitis is similar to other nonallergic rhinitis syndromes and includes the avoidance of aggravating irritants. Some women can tolerate the symptoms of pregnancy rhinitis without medical management [2]; however, rhinitis in pregnancy is associated with increased snoring, possibly placing the mother at risk for sleep apnea and exacerbating hypertension associated with pregnancy.

This also may be a factor in the development of preeclampsia [27]. Treatment may include exercise, head of bed elevation, nasal alar dilatation, and nasal saline rinses. When these measures fail, intranasal corticosteroids, such as budesonide, can be administered, although intranasal fluticasone was not effective for pregnancy rhinitis in one study [28]. Decongestants such as oxymetazoline and pseudoephedrine may be used with caution with an appropriate risk-benefit discussion [7, 19, 29, 30]; however, they should not be administered until after the first trimester [2] as they may be associated with teratogenicity.

## *Infectious Rhinitis*

### Etiology

Infectious rhinitis, associated with an upper respiratory tract infection (URI) or common cold, is an acute inflammatory disease of the upper airway. URIs are primarily caused by an acute viral infection [31–35]. Common viruses include rhinovirus (30–50%), coronavirus (10–15%), influenza virus (5–15%), respiratory syncytial virus (5%), parainfluenza virus (5%), adenovirus (<5%), and enterovirus (<5%) [36] (Fig. 5.3). The incubation period is usually 24–72 h with symptoms persisting for 3–10 days [36, 37]. Symptoms include nasal congestion, clear to mucopurulent nasal discharge, a sensation of discomfort and pressure in the face, headache, olfactory disturbances, cough, and postnasal drip. A secondary bacterial infection sometimes occurs necessitating additional therapy. A bacterial etiology should be considered when the symptoms persist beyond 7–10 days or when symptoms worsen after transient improvement [7].

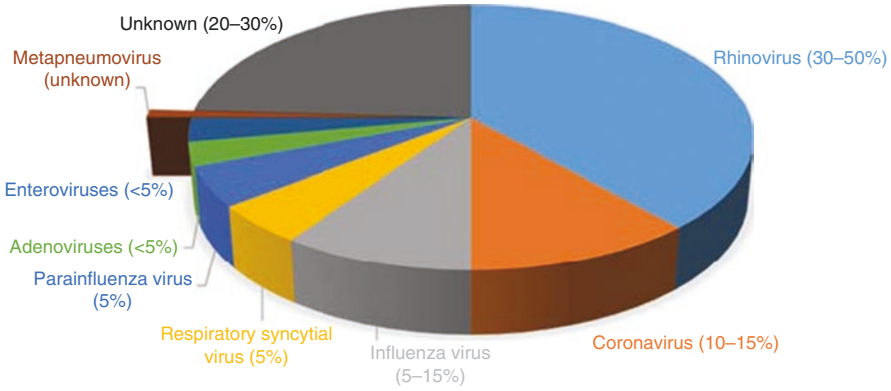


**Fig. 5.3** Viral etiology of the common cold. (Adapted from Kirkpatrick [37])

### Diagnosis

Infectious rhinitis is diagnosed clinically and is based on the history and physical examination [6, 7]. A culture of nasal secretions is usually not indicated because it does not accurately reflect the organisms in the sinuses causing the infection.

### Treatment

Treatment of a viral URI during pregnancy is identical to that of the nonpregnant subject. Subjects are usually observed for 7–10 days with anticipated spontaneous resolution. Antibiotics are usually not necessary unless a primary or secondary bacterial infection is suspected [7, 32]. Decongestants should be used cautiously, particularly in the first trimester [19].

Antibiotics to be considered for a primary or secondary bacterial sinus infection include penicillin derivatives, including those that contain sulbactam/clavulanate and cephalosporins, erythromycin, and azithromycin [19]. Clindamycin can also be used when other antibiotics fail. Clarithromycin, fluoroquinolones, aminoglycosides, sulfonamides, tetracyclines, and vancomycin should not be considered first line, especially during the first trimester, due to potentially greater side effects. Appropriate antibiotic use is necessary until the subject's symptoms have resolved.

## *Nonallergic Rhinitis*

### Etiology

Nonallergic rhinitis, also referred to as vasomotor or idiopathic rhinitis, is thought to be vagally mediated. It is occasionally associated with gustatory rhinitis, i.e., rhinorrhea exacerbated by eating [7]. Subjects with nonallergic rhinitis appear to have heightened sensitivity to nociceptive stimuli such as aerosolized irritants, spicy foods, environmental temperature changes, alcohol ingestion, cold dry air, and even exercise [7, 38–41]. Symptoms are variable and consist mainly of nasal obstruction and rhinorrhea, both anteriorly and into the posterior pharynx (postnasal drip). Sneezing and pruritus are less common.

### Diagnosis

Nonallergic rhinitis is diagnosed primarily after other types of rhinitis have been excluded. It is based on the characteristic history and physical findings, mainly nasal mucosal edema, and by the triggers which exacerbate the disease.

### Treatment

Many women experience this type of rhinitis during pregnancy and it can be confused with pregnancy rhinitis. Symptomatic therapy includes elevating the head of the bed, avoiding irritants, and using intranasal saline. When such measures fail and symptoms persist, pharmacologic intervention can be considered. Intranasal ipratropium bromide is primarily used to treat excessive nasal secretion or rhinorrhea, which can occur both anteriorly and posteriorly, and is especially effective for gustatory rhinitis. Intranasal corticosteroids are the drugs of choice for eosinophilic nonallergic rhinitis (see below) and can be tried in other subjects with nonallergic rhinitis. Oral and topical antihistamines, such as azelastine, can also be considered, although their safety during pregnancy has not been studied. The topical antihistamine azelastine also is efficacious [7, 15, 42, 43], but has not been studied in human pregnancy. These are sometimes used along with the cautious use of nasal decongestants, which preferably should be avoided especially during the first trimester. Oxymetazoline drops or spray, with no more than one or two sprays in each nostril twice daily, ideally for no more than 3 days in a row, may be helpful in subjects with substantial nasal obstruction. Intranasal corticosteroids have been reported to protect against rhinitis medicamentosa [44, 45]; therefore, patients should be maintained on intranasal corticosteroids if oxymetazoline or its equivalent is used long term.

## *Nonallergic Rhinitis with Eosinophilia Syndrome (NARES)*

### Etiology

Nonallergic rhinitis with eosinophilia syndrome (NARES) is a nonallergic inflammatory form of rhinitis. Subjects have perennial symptoms including sneezing, watery rhinorrhea, nasal pruritus, congestion, and intermittent decreased olfactory sensation [46, 47]. Its prevalence and etiology are unknown. The characteristic association is the eosinophilia found on nasal smear of greater than 5% [7, 48–51] and a lack of demonstrable allergy as determined by skin or in vitro allergen testing [7].

### Diagnosis

The diagnosis of NARES is supported by the history and physical exam examination, greater than 5% eosinophilia on nasal smear and the lack of positive in vivo or in vitro allergy tests.

### Treatment

Conservative treatment should include the aforementioned nonallergic rhinitis strategies. These include avoiding aggravating irritants, such as smoke and other pollutants. Some cases may respond to exercise, head of bed elevation, and nasal alar dilatation [7]. The pharmacologic treatment of NARES includes topical intranasal corticosteroids such as budesonide [7, 52, 53]. Intranasal ipratropium is effective to reduce symptoms of rhinorrhea [7, 15].

## *Occupational Rhinitis*

### Etiology

Occupational rhinitis, either allergic or nonallergic, is caused by allergens or irritants, respectively, that are encountered in the workplace. Examples of substances that can induce allergic rhinitis include animal and food emanations. Detergents, such as those containing chlorine or ammonia, can be associated with nonallergic occupational rhinitis. Occupational asthma may accompany rhinitis.

### Diagnosis

The diagnosis of occupational rhinitis, like other forms of rhinitis, is based on the history and physical exam. IgE sensitization can be demonstrated by in vivo or in vitro tests, with in vitro tests again preferred during pregnancy. Nasal allergen challenge can be useful to determine the suspected cause of symptoms [7, 54, 55] but would usually be deferred to postpartum. Eosinophils, basophils, eosinophilic cationic protein, and tryptase are biological markers that are increased on nasal lavage following an allergen challenge in IgE-dependent sensitization.

### Treatment

The ideal treatment of occupational rhinitis is to avoid the aggravating substances causing the symptoms. Site visits may be beneficial, which can be both diagnostic and allow for planning of site-specific changes. In addition, the Occupational Safety and Health Administration (OSHA) requires employers to keep on-site reports of potential substances which should be reviewed. When conservative measures fail and symptoms persist, intranasal corticosteroids can be considered. Decongestants such as oxymetazoline and pseudoephedrine may be used after the first trimester with appropriate risk-benefit ratio [7, 19, 29, 30]. See discussion above about the concomitant use of intranasal corticosteroids with long-term oxymetazoline.

## *Drug-Induced Rhinitis and Rhinitis Medicamentosa*

### Etiology

Drug-induced rhinitis is caused by a variety of different medications, some of which include ACE inhibitors [56], alpha-receptor antagonists [57], phosphodiesterase inhibitors [58], beta-blockers, and calcium channel blockers. Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDS) can exacerbate rhinitis associated with aspirin-exacerbated respiratory disease [7, 59, 60], a phenotype of asthma associated with nasal polyps, asthma, and severe intolerance to NSAIDS.

Rhinitis medicamentosa develops from the prolonged use of topical alpha-adrenergic agents such as oxymetazoline and phenylephrine. Symptoms are caused by hypertrophy of the nasal mucosa, loss of nasociliary structures, and goblet cell hyperplasia with subsequent rebound nasal obstruction from the repeated use of these medications. It can develop in as little as 3 days, but often at much longer intervals of use. Nasal septal perforation can result as a complication. The use of intranasal cocaine can similarly cause rhinitis medicamentosa. Subjects may develop tachyphylaxis and the need for more frequent dosing to achieve adequate decongestion.

### Diagnosis

The diagnosis of topical drug-induced rhinitis is obtained by detailed history and physical examination. The nasal mucosa can appear inflamed with mucosal membrane ulcerations, bleeding with minimal mucus, which is especially true with the use of topical/intranasal adrenergic agents and illicit drug use. The rhinitis associated with most oral medications is primarily nasal mucosal edema and nasal congestion.

### Treatment

The ideal treatment of oral drug-induced rhinitis is to stop the medication(s) causing the problem [7]. If the medication primarily causing nasal congestion cannot be discontinued, symptomatic therapies of various forms can be tried. Management also includes elevating the head of bed, nasal dilatation, and the use of intranasal corticosteroids.

Rhinitis medicamentosa is treated by stopping the offending agent and the use of intranasal corticosteroids. It is important to inform subjects with rhinitis medicamentosa that the symptoms may worsen temporarily once the offending agent is discontinued. A short burst of oral corticosteroids can be helpful but should be used with caution, due to potential risk of low birth weight, premature birth, preeclampsia, and possibly birth defects with first trimester use.

### *Atrophic Rhinitis*

#### Etiology

Atrophic rhinitis or "empty nose syndrome" is caused by nasal mucosal atrophy, resulting in nasal erosion and crusting, blood and blood clots, and dryness and sometimes a foul odor. The etiology of primary idiopathic atrophic rhinitis is unknown. However, this disease is also associated with recurrent and chronic infection, chronic granulomatous disease (such as tuberculosis), repeated surgery, or radiation therapy. Secretions may be purulent [7, 61]. Superinfection, if suspected, is commonly due to *Pseudomonas aeruginosa* and *Staphylococcus aureus* [61].

#### Diagnosis

The history and physical examination are essential to make the diagnosis. The nasal mucosal membranes are usually dry, ulcerated, and covered by crusty exudates. Nasal cavities may appear to be larger than usual because of underlying bone resorption. Nasal septal perforation can result in a "saddle nose" deformity [62].

Secondary atrophic rhinitis can be suspected if any two or more of the following criteria are present: subject-reported recurrent epistaxis or episodic anosmia, clinician-documented nasal purulence, crusting, the presence of a chronic inflammatory disease such as sarcoidosis, granulomatosis with polyangiitis (Churg-Strauss syndrome), or two or more sinonasal surgeries [61, 63]. The diagnosis is clinical, but a computerized tomography (CT) scan may be helpful to evaluate the subject for an underlying systemic disease. Nasal biopsy can help confirm a diagnosis.

#### Treatment

Primary should be distinguished from secondary atrophic rhinitis, wherein the underlying disease should be treated. Treatment of primary atrophic rhinitis consists of nasal saline washes to remove crusty exudates and debris from the nose, topical mupirocin, and if secondary infection is present, appropriate antibiotics [7]. Mupirocin has not been studied in pregnancy.

## Rhinosinusitis

Acute or chronic rhinosinusitis is characterized by purulent rhinorrhea, postnasal discharge, anosmia, nasal congestion, facial discomfort, headache, fever, and cough (Table 5.1). It is common in pregnancy [63–65]. The term rhinosinusitis indicates that the nose and the sinuses are affected. Typically, infectious rhinitis secondary to a viral upper respiratory tract infection (URI) precedes infectious rhinosinusitis associated with inflammation of the nasal cavity and the sinuses. It is classified

based on symptom duration [66]: acute rhinosinusitis is defined as symptoms lasting less than 4 weeks, subacute rhinosinusitis as symptoms lasting 4–12 weeks, recurrent acute rhinosinusitis as four or more episodes of rhinosinusitis per year, and chronic rhinosinusitis, as symptoms lasting for greater than 12 weeks. All forms of sinusitis are primarily medical and not surgical problems just as is any chronic inflammatory disease. The diagnosis is made clinically and by rhinoscopy. A CT scan should only be obtained when a complication or surgery is contemplated. An abnormal CT scan does not confirm the diagnosis, as mucosal thickening and air fluid levels can occur with a URI and can take several weeks to resolve. These findings can also occur with allergic rhinitis and rhinosinusitis. Mucosal thickening, cysts, and polyps present in the sinuses are mostly incidental findings.

## *Acute and Subacute Rhinosinusitis*

### Etiology

Acute rhinosinusitis (ARS) is classified based on its etiology, being either viral or bacterial, and thus termed acute viral rhinosinusitis (AVRS) or acute bacterial rhinosinusitis (ABRS), respectively. Symptoms of both overlap but include those listed above. AVRS can lead to ABRS, which is characterized by symptoms persisting for more than 10 days with objective confirmation of purulent discharge from the nares or posterior pharynx. Most cases of acute rhinosinusitis are of viral origin, with approximately 0.5–2.0% progressing to ABRS, typically caused by secondary infections with *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Staphylococcus aureus* [67, 68] (Fig. 5.4).

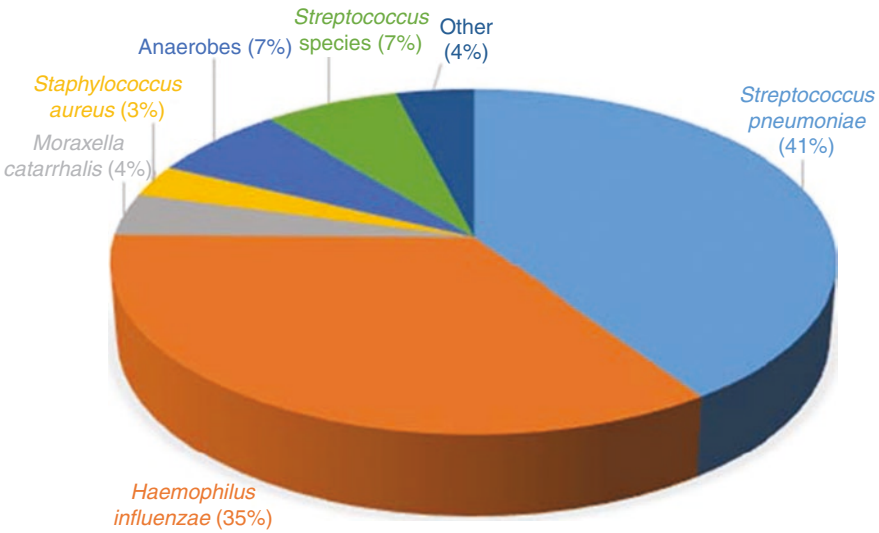


**Fig. 5.4** Pathogens which cause acute bacterial rhinosinusitis. (Adapted from Chow et al. [67])

## Diagnosis

The diagnosis of ARS is based on the history and physical with clinical symptoms lasting for several weeks or less. Of considerable concern is the individual who develops a secondary bacterial infection manifested by a fever associated with purulent nasal discharge and facial discomfort or pain, again, usually following a viral respiratory tract infection. Rhinoscopy may be necessary to confirm the diagnosis. Indication for referral are subjects who are not responding to antibiotics or who have persistent fever, periorbital edema and erythema, cranial nerve palsies, abnormal extraocular muscle function, proptosis, vision changes, severe progressive headaches, altered mental status, or signs of meningeal inflammation [3, 69]. Presentation of acute rhinosinusitis and subacute rhinosinusitis are similar and are solely differentiated by the duration of illness.

## Treatment

Treatment of AVRS is conservative. An intranasal corticosteroid, such as budesonide, is a treatment of choice. Double-blind controlled studies indicate efficacy for acute viral rhinosinusitis. Intranasal decongestants, such as oxymetazoline, may also be used for nasal mucosa edema, preferably after the first trimester, but should only be used temporarily and then discontinued unless used in conjunction with intranasal corticosteroids. Other medications such as antihistamines and oral decongestants may also be helpful.

The treatment of ABRS is similar; however, antibiotics are necessary. Intranasal corticosteroids plus amoxicillin, amoxicillin-clavulanic acid, or a second- or third-generation cephalosporin are first-line drugs. In penicillin-allergic subjects, a macrolide, such as azithromycin, is recommended. When necessary, trimethoprim-sulfamethoxazole (TMP-SMX), particularly in penicillin-allergic subjects, may also be utilized, but its use has been associated with folate deficiency in the mother and neural tube defects in the newborn. Duration of therapy is variable but should be continued until the subject is well and clear of discolored nasal discharge for up to 5 days. Sinus puncture and saline irrigation may be helpful to both diagnose and treat the disease as it has few side effects and may help reduce discomfort or pain [2].

## Risk of Disease Versus Treatment

The main complication of untreated AVRS is the progression to ABRS. Some complications of ABRS include orbital cellulitis, preseptal (periorbital) cellulitis, intracranial or epidural abscess, osteomyelitis of the surrounding bones, and meningitis [3, 68]. AVRS usually resolves on its own with or without supportive treatment such as antihistamines, decongestants, and intranasal corticosteroids.

## *Recurrent Acute Rhinosinusitis*

### Etiology

Recurrent acute rhinosinusitis (RARS) is diagnosed when four or more episodes of ABRS occur over a year with resolution of symptom between infections. Symptoms of RARS are similar to ABRS.

### Diagnosis

The diagnosis is made clinically. Nasal endoscopy and occasionally imaging studies should be considered to rule out any underlying abnormalities in the soft tissue or boney structure which could predispose to RARS, such as bony abnormalities of the ostiomeatal complex and sinus cavities. These are uncommon.

### Treatment

Treatment of RARS is identical to ABRS. In addition, an underlying etiology must be ruled out. Various forms of rhinitis, particularly allergic rhinitis, may predispose to all types of rhinosinusitis. One study indicates that the chronic use of antibiotics or intranasal corticosteroids is not beneficial in reducing the number of episodes per year [66]. Subjects with recurrent acute rhinosinusitis should be evaluated for a primary or secondary immunodeficiency and other predisposing illnesses such as cystic fibrosis, ciliary dysfunction, and anatomical abnormalities [3]. A referral to a competent allergist/immunologist is helpful for this purpose.

## *Chronic Rhinosinusitis*

### Etiology

Chronic rhinosinusitis (CRS) is an inflammatory condition involving the paranasal sinuses lasting for more than 3 months. It may begin with an acute viral respiratory tract infection that fails to resolve. Symptoms and signs vary in prevalence and severity, including nasal congestion; anterior and posterior mucopurulent discharge; facial discomfort, pressure, or fullness; headaches; and olfactory disturbance. Fatigue, malaise, cough, and sleep disturbances can also be present. Subtypes of CRS include CRS with nasal polyposis (CRS with NP), CRS without nasal polyposis (CRS without NP), and allergic fungal rhinosinusitis (AFRS). Mucosal remodeling can occur as it occurs in severe asthma, potentially resulting in irreversible chronic upper airway disease [3, 66].

## Diagnosis

The presence of two or more symptoms and signs for greater than 3 months is suggestive of CRS. These include (1) mucopurulent discharge, (2) nasal obstruction or congestion, (3) facial pain, (4) pressure or fullness in the face, and (5) decreased sense of smell. It also ideally requires documentation of inflammation by means of one or more of the following: (1) purulent discharge or edema in the middle meatus or anterior ethmoid region (rhinoscopy), (2) nasal polyps (rhinoscopy), or (3) radiographic imaging consistent with the clinical diagnosis of chronic sinusitis [3, 66, 70]. Subjects with chronic sinusitis, particularly when associated with chronic infection, should be evaluated for a primary or secondary immunodeficiency and other predisposing illnesses such as cystic fibrosis, ciliary dysfunction, and anatomical abnormalities [3]. A referral to a competent allergist/immunologist is helpful for this purpose.

- *CRS with Nasal Polyposis* (CRS with NP)
  CRS with NP accounts for 20–33% of CRS and is characterized by the presence of nasal polyps usually emanating from the middle meatus, gradual worsening nasal congestion, a feeling of fullness and pressure in the face, anterior and posterior pharyngeal purulent drainage, and anosmia. Fever and facial discomfort are usually absent. Translucent, yellow-gray or white, and often glistening polyps are usually visible with anterior rhinoscopy. Edematous nasal turbinates are often mistaken for polyps, the former of which are pink, sensitive to touch, and appear similar to surrounding mucosa [3, 66, 70].
- *CRS without Nasal Polyposis* (CRS Without NP)
  CRS without NP is the most common form of CRS accounting for approximately 60–65% of cases. Differentiating CRS without NP and RARS may be difficult. The former has persistent and the latter intermittent symptoms and signs. Symptoms and signs include facial fullness, discomfort or pain, anterior/posterior purulent change, and fatigue. An elevated temperature is rare. The pathophysiology of this disease is not completely understood [3, 66, 70].
- *Allergic Fungal Rhinosinusitis*
  Allergic fungal rhinosinusitis (AFRS) accounts for 5–10% of all CRS and is usually caused by the colonization of the mucosal membranes of the upper airway and sinuses with a noninvasive fungus, the most common of which is *Aspergillus fumigatus*, and a subsequent allergic response. Subjects with AFRS often have asthma, NP, and allergic rhinitis, and it occurs in immunocompetent subjects. The signs and symptoms are similar to that of CRS with NP. Subjects with AFRS, however, usually have a pathognomonic "peanut butter" appearing mucus drainage from the nares or posteriorly into their oral pharynx [3, 66, 70].

## Treatment

Appropriate treatment of CRS reduces the signs and symptoms of the disease and improves the quality of life. It primarily involves controlling mucosal inflammation and edema, improving sinus tract ventilation and drainage, treating the

microorganisms involved, and trying to reduce the frequency of exacerbations. This is accomplished by ruling out an underlying immunodeficiency disease, by treating the underlying allergic disease when present, and by administering appropriate immunizations [70].

Medical management of CRS typically involves topical corticosteroids which reduce inflammation, antibiotics to treat the offending microorganisms, and nasal irrigation to promote sinus drainage [66]. Systemic corticosteroids are sometimes indicated to decrease inflammation but usually only for a short period of time. Evidence-based medicine is lacking for most forms of treatment. Intranasal corticosteroids, such as budesonide, versus systemic corticosteroids are preferred especially during pregnancy. If indicated [65, 66, 70], an antibiotic regimen such as amoxicillin-clavulanate acid is usually the first drug of choice. Others include a macrolide, such as erythromycin, or clindamycin or metronidazole, although the latter medication is contraindicated in the first trimester. Other antibiotics to consider include cefuroxime, cefdinir, cefpodoxime, azithromycin, or TMP-SMX (in penicillin-allergic only) [2, 71]. Antifungals have not been proven to be helpful but are sometimes utilized; however, they have not been shown to be safe to use during pregnancy.

## Conclusion

Allergic diseases and other forms of rhinitis and rhinosinusitis affect approximately one-third of women in the childbearing age [9, 19]. When poorly controlled, they affect the quality of life and could potentially harm the mother and fetus [13]; therefore, they require a proper diagnosis and effective treatment.

Sleep-disturbed breathing is one of the most common symptoms reported with untreated rhinitis and rhinosinusitis in both pregnant and nonpregnant subjects [70, 72]. Other sequelae include generalized malaise, cognitive and psychiatric problems, impaired exercise tolerance, decreased self-esteem, depression, and decreased work productivity [72]. Specifically, among pregnant subjects suffering from these diseases, the quality of life in the third versus the second trimester appears worse.

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# Chapter 6
# Anaphylaxis in Pregnancy


**Christopher W. Calabria and Christopher A. Coop**

## Introduction

Anaphylaxis, as defined by an international group of experts, is a serious allergic reaction that is rapid in onset and can cause death [1, 2]. Worldwide, definitions commonly utilized include "a serious, life-threatening generalized or systemic hypersensitivity reaction" [1, 2]. Overall, the incidence seems to be increasing but is likely under-recognized or underdiagnosed. The overall lifetime prevalence of anaphylaxis 0.05–0.2% is based on international studies [3], and the lifetime risk of symptoms suggestive of anaphylaxis in the general population as reported by the general public is at least 1.6% [4].

While hospital admissions for anaphylaxis increased in the USA from 1999 to 2009 (annual percentage change 2.2%), there were decreased case fatality rates among emergency department and hospitalized patients (annual percentage change −2.35%). Overall mortality rates ranged from 0.63 to 0.76/million population, equating to 186–225 deaths/year, and were stable in the decade studied [5]. Similar findings of increased hospitalizations (615%) but no increase in fatalities were found over a 20-year period in England and Wales [6]. Admissions and fatality rates for drug- and insect-sting-induced anaphylaxis were highest in those 60 years and older, while there is a marked peak in the incidence of food-induced anaphylaxis admissions and fatalities during the second and third decades of life. In a review of 2458 fatalities from 1999 to 2010, drugs were the most common etiology (58.8%) followed by unspecified inducers (19.3%), venoms (15.2%), and foods (6.7%) [7].

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During pregnancy, anaphylaxis can be catastrophic to both the mother and the fetus, causing hypoxic-ischemic encephalopathy, permanent central nervous system damage, or even death. In pregnancy, the true incidence of anaphylaxis is unknown, with most data gleaned from case reports and reviews of the literature. Given the nearly four million childbirths/year in the United States (USA) alone (CDC stats accessed Jan 13, 2018) [8], with a 0.1% incidence of anaphylaxis during pregnancy, there would be an estimated 4000 cases of pregnancy-related anaphylaxis every year in the USA. In an epidemiologic study of postpartum women discharged from Texas hospitals in 2004 to 2005 with a diagnosis of anaphylaxis, 19 cases of anaphylaxis *during labor and delivery* were reported (2.7 cases per 100,000 deliveries) [9].

This chapter reviews the literature on anaphylaxis during pregnancy, as well as labor and delivery, and is intended for allergists, primary care physicians, obstetricians, and other healthcare professionals who care for pregnant patients.

## Etiologies

During pregnancy, the etiologies of anaphylaxis are the same as for nonpregnant patients. These etiologies include foods, medications, insect stings, latex, and physical triggers including exercise and cold.

More specifically, food triggers include peanut, tree nuts, fish, shellfish, milk, egg, wheat, and soybean, but theoretically any food can trigger anaphylaxis. Food triggers also have geographic variation with more peach allergy in some European countries and sesame being a more common trigger in the Middle East. Recent discoveries include a delayed mammalian meat allergy. This involves a novel IgE response against a mammalian oligosaccharide epitope galactose-alpha-1,3-galactose (i.e., alpha-gal), which often presents with delayed urticaria and angioedema 3–6 h after eating beef, pork, or lamb. IgE against alpha-gal in the USA is initially formed after tick bites from *Amblyomma americanum* [10].

Medications that trigger anaphylaxis most commonly include antimicrobials/antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), chemotherapeutic agents (carboplatin, etc.), and biologic agents to include cetuximab, rituximab, infliximab, and rarely omalizumab. Diagnostic agents that are relatively common triggers of anaphylaxis include radiocontrast media and medical dyes such as fluorescein. Perioperative anaphylaxis can be triggered by neuromuscular-blocking agents (suxamethonium, rocuronium, etc.), hypnotics (thiopental, propofol), opioids, antimicrobials, protamine, chlorhexidine, latex, and colloid plasma expanders such as dextran [1].

Insects that trigger anaphylaxis are stinging insects (order Hymenoptera) which include honey bee, yellow jackets, hornets, wasps, and imported fire ants. Mastocytosis is a rare disorder characterized by increased mast cell

proliferation and accumulation in organs and is broadly separated into two subgroups: cutaneous and systemic mastocytosis. While there is limited information on the impact of mastocytosis on pregnancy (and vice versa), a recent review summarizes the management of mastocytosis during pregnancy [11].

Hormonal changes can also be a factor during pregnancy. Rapid change in progesterone during the second and third trimesters may be implicated rarely as a cause of anaphylaxis that improves with delivery [12]. Additional risk factors and cofactors for anaphylaxis will be discussed later and include exercise, NSAIDs, alcohol, and beta-blocker and ACE inhibitor usage.

*During labor and delivery*, the most common etiology of anaphylaxis is prophylactic penicillin or cephalosporin utilized to prevent maternal infection after cesarean delivery or to prevent neonatal group B streptococcal infection [9, 13–21]. Additional etiologies which have been implicated include other antibiotics, oxytocin, and perioperative agents including neuromuscular blockers, epidural medications, general anesthetics, latex, and chlorhexidine [13, 22–31]. In the aforementioned study by Mulla et al., beta-lactams were responsible for 11 of 19 cases, other antibiotics in 2/19, oxytocic agents in 2/19, and a single case each of an antiemetic, antihypertensive, antirheumatic agent and radiocontrast media in the remainder [9].

Additionally, the exertion of labor has been reported to cause reactions in those with exercise-induced anaphylaxis [32]. In the first few postpartum days, breastfeeding anaphylaxis has been reported and may be amplified in some women concurrently using NSAIDs [33–35]. A possible pathophysiologic explanation is that the sharp decrease in progesterone after childbirth coupled with the rise in prolactin leads to mast cell degranulation.

## Clinical Diagnosis and Differential Diagnosis

Anaphylaxis is diagnosed clinically by the acute onset and rapid progression of characteristic symptoms, which typically involve more than one organ system [1, 2, 36]. Based upon case series of all patients with anaphylaxis, skin and mucosal involvement is present in 80–90% of cases, respiratory tract involvement in up to 70%, cardiovascular involvement in up to 45%, and central nervous system involvement in up to 15% [36]. Signs and symptoms include acute onset of generalized urticaria, angioedema, itching, and/or flushing. Additional features of anaphylaxis are respiratory symptoms to include dyspnea, wheezing, and stridor. Cardiovascular features of anaphylaxis are hypotension/reduced blood pressure, chest pain, dysrhythmias, and cardiac arrest. Persistent gastrointestinal symptoms such as crampy abdominal pain and vomiting may also be associated with anaphylaxis. Anaphylactic symptoms specific to pregnancy can include intense

**Table 6.1** Signs and symptoms of anaphylaxis

| |
|---|
| *Cutaneous/skin* |
| Urticaria (hives), flushing, itching, edema, erythema |
| Ocular: periorbital itching, erythema, and edema; conjunctival erythema, tearing |
| Oral: itching of the lips, tongue, palate, external auditor canals; swelling of the lips, tongue, uvula |
| *Respiratory* |
| Nasal: congestion, runny nose, sneezing, pruritus |
| Throat: itching, swelling, tongue swelling, hoarseness, stridor |
| Lungs: shortness of breath, chest tightness, deep cough, wheezing/bronchospasm |
| Cyanosis and respiratory distress/arrest |
| *Gastrointestinal* |
| Abdominal pain, cramping, vomiting, nausea, diarrhea |
| *Cardiovascular* |
| Hypotension, feeling faint, chest pain, tachycardia, palpitations, arrhythmias, shock |
| *Neurological/central nervous system* |
| Altered mental status, sense of impending doom, dizziness, confusion, tunnel vision, throbbing headache |
| *Other* |
| Metallic taste, uterine cramping, urinary and fecal incontinence |
| *More unique to pregnancy* |
| Intense itching in vaginal/vulvar regions, uterine cramps, low back pain, fetal distress, preterm labor |

vulvar and vaginal itching, low back pain, uterine cramps, fetal distress, and preterm labor [1, 2, 13] (see Table 6.1).

The diagnosis of anaphylaxis is based primarily upon a detailed history of the episode. Information should be obtained about all exposures and events in the hours preceding onset of symptoms, including new prescription, nonprescription or recreational drugs, exercise, time and contents of last meal/food eaten, ethanol use, acute infection such as a cold, increased emotional stress, and any insect bites/stings [1].

## Physiologic Considerations

When evaluating a pregnant patient for possible anaphylaxis, it is important to remember that normal vital signs change in late pregnancy. The respiratory rate increases by 10% and the pulse increases by 15%. Systolic blood pressure does not change but diastolic blood pressure decreases by 15%. Supine hypotension syndromes occur in >10% of pregnant women, due to compression of the inferior vena cava by the gravid uterus [37].

Pregnancy, labor, and delivery can lead to cardiovascular decompensation in patients with coexisting heart disease. Intravascular fluid volume increases by 35%, and cardiac output increases by about 40% and can increase an additional 30–45%

during labor and delivery, leading to congestive heart failure and pulmonary edema. Many cardiac conditions can place the mother at increased risk of decompensation, including cardiomyopathy, myocarditis, acute coronary syndrome, mitral valve disorders, primary pulmonary hypertension, and others [37].

## Differential Diagnosis of Anaphylaxis and Hypotension in Pregnancy

The differential diagnosis of anaphylaxis during pregnancy (prior to labor and delivery) is similar in pregnant and nonpregnant patients. Common examples include fainting/syncope, acute urticaria, acute angioedema, acute asthma attacks, and panic attacks/anxiety.

During labor and delivery, the differential diagnosis includes various causes of maternal respiratory and cardiovascular distress, including amniotic fluid embolism, pulmonary embolism, pulmonary edema, acute coronary syndrome, cerebrovascular accident, and laryngeal obstruction.

Amniotic fluid embolism (AFE) is a life-threatening obstetric emergency characterized by sudden cardiorespiratory collapse and disseminated intravascular coagulation.

AFE occurs in 2–8 per 100,000 deliveries and is responsible for between 7.5% and 10% of the maternal mortality in the USA [38]. AFE presents with profound hypotension, cyanosis, dyspnea, respiratory distress, hemorrhage, DIC, and altered mental status. The presence of bronchospasm and the absence of coagulopathy and large-volume blood loss suggest anaphylaxis rather than AFE [39]. Management of AFE is complex and multidisciplinary (OB/GYN, intensivists, anesthesia, respiratory therapy) and includes stabilization measures using high-quality CPR and ACLS measures, immediate delivery of viable pregnancies, prompt fluid replacement to treat hypotension, inotrope utilization to manage concomitant right ventricular and later left ventricular failure, and aggressive management of DIC.

A unique cause of laryngeal obstruction in labor is laryngopathia gravidarum (LG), which presents immediately before parturition in women with preeclampsia. In patients with LG, the onset of laryngeal symptoms is slower than in those with anaphylaxis. Typical concomitant symptoms include hypertension, peripheral edema, urinary abnormalities, and a history of preeclampsia. Predelivery management of preeclampsia includes blood pressure control, fluid restriction, and seizure prophylaxis in those with severe clinical features; definitive cure of preeclampsia is delivery.

When evaluating a pregnant woman with hypotension, you must distinguish hypotension associated with anaphylaxis from more common causes of hypotension during pregnancy which include hemorrhage, spinal block, and local anesthetic administration [40]. Anaphylaxis should be suspected if there is the sudden onset of itching, urticaria, angioedema, wheezing, or stridor in association with hypotension.

## Risk Factors for Severe/Fatal Anaphylaxis and Cofactors that Amplify Anaphylaxis

There are multiple patient risk factors that increase the risk of severe or fatal anaphylactic episodes. These include age-related factors, concomitant respiratory disease such as asthma [41], cardiovascular disease [42], mastocytosis or clonal mast cell disorders [43], and severe atopic disease. Some concurrent medications, including beta-adrenergic blockers and angiotensin-converting enzyme inhibitors, may also increase the risk [44]. Recent research also implicates elevated baseline levels of tryptase [44], bradykinin (because of low serum ACE activity), and platelet-activating factor (PAF; because of low serum PAF acetylhydrolase activity) [45].

## Pathophysiology and Mechanisms

Classically, anaphylaxis is induced by antigen cross-linking of antigen-specific IgE that has bound to the high-affinity IgE receptor (FceRI) on mast cells and basophils. This cross-linking of IgE and its receptor triggers a signaling cascade resulting in mast cell degranulation of preformed mediators including histamine, tryptase, chymase, proteoglycans, and carboxypeptidase A3. It also results in synthesis and secretion of newly generated mediators including leukotrienes, prostaglandins, and platelet-activating factor. Finally an array of cytokines and chemokines are produced and released, including IL-6, IL-33, and TNF-α [36].

However, the clinical definition of anaphylaxis has also evolved to a more mechanistic description based on precision medicine into phenotypes with underlying endotypes supported by diagnostic biomarkers [46]. Phenotypes are defined by clinical presentation into classic type I-like reactions noted above, cytokine storm-like reactions, and mixed reactions. Endotypes underlying these phenotypes include IgE- and non-IgE-mediated mechanisms, cytokine release, mixed reactions, and direct activation of immune cells [47].

Several clinical observations and extrapolations from experimental evidence in mice support the importance of non-IgE-mediated or IgG-mediated anaphylaxis in humans. This has been reported in transfused and IVIG-treated IgA-deficient subjects (who had IgG anti-IgA antibodies) [48], in subjects treated with chimeric, humanized, and even fully human monoclonal antibodies [47, 49], after von Willebrand factor infusion [50], and in subjects treated with dextran [51] or aprotinin [52]. Chimeric IgG mAbs, such as rituximab, can induce release of tryptase and histamine in the context of hypotension and cytokine storm-like symptoms, suggesting the potential role of IgG in patients with anaphylaxis.

Cytokine storm-like reactions are caused by release of pro-inflammatory mediators such as TNF-α, IL-1B, and Il-6, and the target cells include monocytes, macrophages, mast cells, and other immune cells with FcγR. Triggers for these reactions include chimeric, humanized, and human mAbs and chemotherapy, including

oxaliplatin [47]. These reactions are characterized by chills, fever, and generalized malaise followed by hypotension, desaturation, and cardiovascular collapse [47].

Mixed reactions with features of type I- and cytokine storm-like reactions can be seen with monoclonal antibodies and chemotherapy in which pruritus, hives, and swelling are associated with chills, fever, hypotension, and desaturation.

Direct activation of mast cells and other immune cells can occur with vancomycin, contrast media, and through complement activation by highly charged chondroitin sulfate glycosaminoglycans, with generation of the anaphylatoxins C3a and C5a which can bind to complement receptors [53]. The resulting release of histamine, leukotrienes, and prostaglandins can induce flushing, hives, hypoxia, vasodilation, and hypotension [47]. Other examples of direct mast cell activators include opioids, cold air, ethanol, and exercise.

In recent years, PAF has also been studied as a marker of anaphylaxis and is generally considered more strongly associated with further evidence of the existence of IgG-mediated anaphylaxis. Several reports demonstrated that serum PAF levels are higher in patients experiencing anaphylaxis than in controls and serum PAF acetylhydrolase, the enzyme that breaks down PAF, correlates inversely with anaphylaxis severity [45, 54].

Taken together, anaphylaxis should not be viewed as a simple IgE-mediated process anymore. Clinical phenotypes may vary and different mechanisms are involved depending on the trigger involved.

## Effects of Anaphylaxis on Fetal Oxygenation

Anaphylaxis has a potentially devastating effect on fetal oxygenation. Fetal oxygenation is directly compromised by maternal hypoxemia and indirectly compromised by maternal hypotension or vasoconstriction leading to reduced uterine blood flow [55]. Each volume of blood passing through the uterus and placenta gives up an amount of oxygen reflecting the Po2 difference between fetal and maternal circulation, known as the Fick principle. Total oxygen delivery is a function of blood flow multiplied by the quantity of oxygen delivered by 1 mL of blood. High uterine blood flow rate (942 ml/min at 36 weeks gestation) is needed for normal fetal oxygenation to compensate for placental inefficiencies and high oxygen consumption. Arterial Po2 in the fetus is approximately one third to one fourth that of arterial Po2 in the mother.

With any decreased blood flow, the fetus compromises by means of redistricting blood to vital organs (brain, heart, placenta, adrenal glands), increased oxygen update and tissue oxygen extraction, and decreased body movements. When these mechanisms fail, the fetus is at risk of hypoxic-ischemic encephalopathy and central nervous system damage and death. Maternal cardiac arrest mandates immediate cesarean delivery. While 90% of infants delivered within 5 min of arrest are neurologically intact, <60% of those delivered within 15 min are likely to be neurologically intact [37].

## Diagnostic Evaluation and Testing

An elevated serum total tryptase (level > 11.4 ng/mL) may be useful in the diagnosis of anaphylaxis during pregnancy. Elevated tryptase levels provide evidence of mast cell activation and support the diagnosis of anaphylaxis. Serum tryptase levels peak between 60 and 90 min after the beginning of anaphylaxis, and the tryptase levels may remain elevated for up to 5 h or longer [56]. Some patients do not experience an elevated tryptase associated with anaphylaxis; therefore a normal tryptase level cannot be used to refute the diagnosis of anaphylaxis [57]. Elevated tryptase levels have also been reported in patients with amniotic fluid embolisms and myocardial infarctions [58–60].

Plasma histamine can be elevated with anaphylaxis. Plasma histamine levels peak within 5–10 min after the onset of anaphylaxis and decline quickly such that levels typically return to baseline by 15–30 min. Other laboratory tests associated with anaphylaxis are histamine metabolites (N-methylhistamine and N-methylimidazole acetic acid), prostaglandin D2, 11-beta-prostaglandin F2-alpha, and leukotriene C4 and leukotriene E4 [61, 62]. These laboratory tests are typically measured in a 24-h urine sample. Elevated platelet-activating factor levels have been associated with patients with severe anaphylaxis [54].

## Management

The acute management of anaphylaxis in pregnancy is similar to the management of patients that are not pregnant; however there are some exceptions. There should be a written emergency action plan for the treatment of anaphylaxis in pregnant patients. The pregnant patient should rapidly be assessed including the maternal circulation, the airway, the respiratory function, the mental status, and the body weight. If there is an apparent trigger of anaphylaxis, this trigger should be removed immediately. An example of an apparent trigger is an intravenous medication that could be stopped if it is suspected of causing anaphylaxis. Additionally, help from a resuscitation team should be summoned as soon as possible. Ideally, the resuscitation team should include an anesthesiologist, an obstetrician, and a neonatologist [37, 63].

Epinephrine is the initial drug of choice for anaphylaxis. It should be injected intramuscularly in the mid outer thigh at a dose of 0.3 mg (0.3 mL) of a 1 mg/mL (1:1000) solution. The epinephrine dose can be repeated every 5–15 min [1, 2, 11]. Epinephrine stops the mast cell mediator release responsible for inducing anaphylaxis. H1 and H2 antihistamines and glucocorticoids can be administered as well to the gravid patient, but epinephrine is the first drug of choice. Albuterol via a nebulizer may be helpful if the anaphylactic patient is experiencing wheezing and bronchospasm.

Epinephrine has been implicated in some studies as a cause of fetal malformations; however there is some evidence that it is safe for use in anaphylaxis during pregnancy. A case reported showed the successful use of continuous intravenous epinephrine for 3.5 h in a pregnant patient with refractory anaphylaxis during labor [64].

In addition to epinephrine, supplemental oxygen up to 100% (6–8 L/min) should be administered to the pregnant patient through a face mask or oropharyngeal airway. The patient should be placed on her left side and her extremities should be elevated. The left-sided placement prevents the gravid uterus from compressing the inferior vena cava and obstructing the venous return of blood to the heart. The patient should not sit or stand up because these maneuvers could cause cardiac arrest from an empty inferior vena cava or empty ventricle syndrome [37, 63].

Intravenous access should be established with two 14–16 gauge catheters, especially for the gravid patient that does not respond rapidly to the initial dose of epinephrine. Large amounts of intravenous fluid may be needed for the anaphylactic hypotensive patient. Continuous monitoring of the vital signs of the pregnant patient is recommended. Maternal systolic blood pressure should be maintained at a minimum of 90 mm of mercury (Hg). The fetal heart rate should be monitored as well. If needed, cardiopulmonary resuscitation should be performed. Chest compressions should be started at a rate of 100 per minute, and the depth of the chest compressions should be 1.5–2 in. Chest compressions are given prior to two rescue breaths [65]. Ultimately an emergency cesarean section delivery can be performed at any time for anaphylaxis refractory to medical management [37, 63].

For patients with recurrent idiopathic anaphylaxis or mast cell disorders refractory to high-dose antihistamines and leukotriene blockers, one may consider utilizing omalizumab, which has demonstrated clinically significant benefit in several case reports and small case series [66].

## Prevention

Prevention of anaphylaxis in the pregnant patient is paramount. It is important that the patient strictly avoid allergens that may induce anaphylaxis. Typically this involves avoiding relevant foods, stinging insects, medications, latex, or other allergens which have caused anaphylaxis in the patient previously. The patient should be provided with a written anaphylaxis action plan on how to avoid their pertinent trigger(s). Allergy skin testing during pregnancy should be avoided; however serum-specific IgE testing to foods, venom, latex, and aeroallergens is available and is considered safe during pregnancy [67].

Venom and aeroallergen immunotherapy generally is not started during pregnancy; however if the patient is on the maintenance dose and receiving good benefit

from immunotherapy, then the patient may continue with maintenance immunotherapy [68, 69]. If the patient is in the early buildup phase of immunotherapy, then it is best to stop immunotherapy until after pregnancy; one may consider holding the dose if they are in the latter parts of the buildup phase. Anaphylactic reactions to immunotherapy generally occur more frequently during the buildup phase. Sublingual immunotherapy has been reported to be safe during pregnancy, but more studies are needed to confirm this safety [70].

A penicillin allergy is another potential trigger of anaphylaxis in pregnant women. Penicillin skin testing should generally be avoided during pregnancy but could be accomplished prior to pregnancy in women with a history of a penicillin allergy. Specific IgE testing to penicillin is not sensitive and is not recommended [71]. For those pregnant patients with a penicillin allergy and positive group B streptococcus genital cultures, alternative antibiotics such as clindamycin or vancomycin should be considered based on antimicrobial sensitivity testing [72]. In such patients, penicillin skin tests are also an alternative, depending on availability and individual patient benefit-risk considerations.

Finally, for those pregnant patients with a latex allergy, latex avoidance should be practiced. Currently healthcare providers and hospitals are very aware of the potential of latex allergy and hospitals are able to be latex safe [73]. During pregnancy, specific IgE testing to latex is acceptable; however skin testing to latex should be avoided. Additionally, latex skin testing is not standardized or commercially available and may not be an ideal method for testing.

## Conclusions/Summary

Clinicians including allergist/immunologists, obstetricians, and primary care providers can play an integral role in the prevention of anaphylaxis during pregnancy. Clinicians should do a prepregnancy risk assessment for anaphylaxis in all women of childbearing age and implement risk reduction strategies. This includes performing appropriate skin testing, challenge tests, and implementing immunotherapy prior to pregnancy if at all possible. Once pregnancy occurs, management of pregnant patients is often appropriately conservative to reduce the rates of iatrogenic anaphylaxis. Reducing anaphylaxis rates during pregnancy is even more paramount as anaphylaxis during pregnancy, labor, and delivery can be catastrophic for the infant and the mother. Written communication between the allergist/immunologist, obstetrician, and other personal physicians is imperative. A personalized anaphylaxis emergency action plan should be developed, medical alert jewelry/identification should be worn, and injectable epinephrine should be prescribed and be available at all times. Prospective studies of anaphylaxis during pregnancy and following women at risk for anaphylaxis (i.e., such as those with known food, drug, latex, and insect sting allergies) are needed to help further advance optimal management strategies.

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# Chapter 7
# Atopic Dermatitis and Allergic Contact Dermatitis in Pregnancy

**Stephanie L. Mawhirt and Luz Fonacier**

## Abbreviations

| | |
|---|---|
| ACD | Allergic contact dermatitis |
| AD | Atopic dermatitis |
| AEP | Atopic eruption of pregnancy |
| PT | Patch test or patch testing |

## Immunologic Changes in Pregnancy

The normal immunologic changes in pregnancy ensure a balanced state so that the maternal immune system may continue to defend against infections while also maintaining a state of immune tolerance in regard to the developing fetus. Pregnancy manifests an overall T-helper type-2 (Th2) lymphocyte immune state with a concomitant, reciprocal decrease in T-helper type-1 (Th1) lymphocyte cytokine production, in order to prevent rejection of the fetus which essentially represents a semi-allograft to the mother [1–3]. Specifically, the cytokines IL-4 and IL-13 are upregulated by placental growth factor which are integral to the promotion of the Th2 pathway [4]. There are several physiological changes in the skin which occur during pregnancy; however, it is unknown if there are cutaneous-specific immunologic alterations that may account for the development of new AD, worsening of pre-existing AD in pregnancy, or increased susceptibility to ACD.

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## Atopic Dermatitis Overview

Atopic dermatitis, commonly referred to as eczema, is a chronic, relapsing inflammatory and cell-mediated allergic skin disease that has historically represented a pediatric diagnosis but is increasingly recognized in adults [5]. Patients afflicted with AD may also suffer from other atopic diseases such as allergic asthma and/or allergic rhino-conjunctivitis. Essential in the diagnosis of AD is an acute, subacute, or chronic pruritic eczema that is overall chronic and relapsing with age-specific morphological patterns (infants/children: face, neck, extensor; any age group – current/previous flexural lesions with general sparing of the groin and axilla) [6]. Atopic dermatitis has a major impact on the patient's quality of life, including missed days from work and/or school, associated depression and anxiety, as well as impaired sleep quality due to the relentless nature of the disease, especially if it is not well controlled.

## Pathophysiology

### *Filaggrin Gene Mutation*

The pathophysiology of AD is complex and multifaceted. There are several genes which encode for proteins involved in epidermal barrier function, but the most common genetic defect in AD is a loss-of-function mutation in the filaggrin (FLG) gene [5]. Filaggrin protein normally functions to prevent trans-epidermal water loss and maintain the epidermal barrier through pH regulation and natural moisturization. Approximately 50% of patients with moderate-to-severe AD have a FLG gene mutation; it is also associated with persistent disease in adulthood [7]. It is unknown if the expression of filaggrin is altered during pregnancy [8]. However, a recent Danish study concluded that women with FLG mutations maintained an increased risk of AD flares during pregnancy [9].

### *Th2 Cell-Mediated Immune Predominance*

Similar to normal pregnancy, AD is also associated with an exaggerated Th2 immune response. In regard to the immunopathology of AD, there is an upregulation of Th2 and Th22 lymphocyte subsets along with their respective inflammatory cytokines such as IL-4, IL-5, IL-10, and IL-13 [5]. These cytokines are responsible for the downregulation of skin barrier proteins and subsequent epidermal hyperplasia observed in AD. Cytokine IL-4 is the major driver of Th2 predominance associated with acute exacerbations of AD. There is also

evidence to suggest that cutaneous-residing mast cells may be in part responsible for the Th2 effects exhibited in AD [2, 10].

### *Immunologic Triggers and Hormonal Influences*

Besides emotional stress as a major trigger of AD flares and the itch-scratch cycle in adult patients, other triggers include aeroallergen exposure and *Staphylococcus aureus* bacterial skin colonization [5]. Dust mite antigen is an aeroallergen relevant to AD, particularly since dust mite-associated proteases may further disrupt the skin barrier. Sensitized patients may demonstrate improvement in their AD following subcutaneous immunotherapy with dust mite antigen [11]. Toxins produced by *Staphylococcus aureus* result in cytokine production and subsequent inflammation via superantigen activation pathways, resulting in AD exacerbation. There is some evidence to suggest that estrogen-progesterone hormonal changes have an effect on AD, and studies have shown menstrual cycle and pregnancy-associated clinical worsening of AD [12–14]. Hormonal influences which occur during pregnancy certainly affect the skin integrity (i.e., increased vascularity and/or edema, stretching, and thinning). These changes may translate to increased skin susceptibility to allergens and irritants, leading to an exaggerated inflammatory response and thus worsened AD in pregnancy.

## Clinical Features and Diagnosis

Atopic dermatitis represents a clinical diagnosis based on the presence of certain key features, with intense pruritus being the principal component. Major features of AD include pruritus, a chronic/relapsing course, and typical, morphological lesions involving a flexural body distribution in adult patients; these and other features are listed in Table 7.1. The flexural regions classically include the antecubital and popliteal fossae, as well as the intertriginous armpit folds and the anterior neck. Different phases of AD exhibit varying skin findings. In the acute phase, AD is characterized by erythematous papules and plaques with or without excoriations and vesicles with serous exudate. Chronic AD is characterized by lichenified skin thickening, fibrotic papules, and marked xerosis. Prurigo nodules may result from repeated rubbing of the affected skin [5]. Figures 7.1 and 7.2 demonstrate the characteristic skin findings in the acute and chronic phases of AD, respectively. Although there are currently no definitive biomarkers for AD, up to 80% of patients may demonstrate an elevated total serum IgE level, and some patients may display mild-to-moderate peripheral eosinophilia (defined as an absolute eosinophil count ranging from 500 to 5000 cells/microliter). These parameters are not specific to AD and therefore are

**Table 7.1** Essential, important, and associated features defining atopic dermatitis

| Essential criteria (must be present) | Important criteria (supports diagnosis) | Associated criteria (nonspecific) |
|---|---|---|
| **Pruritus**<br>**Eczema** (acute, subacute, chronic)<br>**Morphology**<br>Age-specific patterns<br>*Infants/children: f*ace, neck, extensor<br>*Any age group:* current or previous flexural lesions; sparing groin and axilla<br>**History** (chronic or relapsing) | **Early age of onset**<br>**Atopy** (personal and/or family history)<br>**IgE** (elevated total or specific IgE levels)<br>**Xerosis** | Atypical vascular responses (facial pallor, delayed blanching response, white dermatographism)<br>Keratosis pilaris/pityriasis alba/hyperlinear palms/ichthyosis<br>Ocular/periorbital changes<br>Other regional findings (perioral/periauricular lesions, nipple, perifollicular accentuation, lichen simplex chronicus/prurigo |

Adapted from Eichenfield et al. [6]

**Fig. 7.1** Acute atopic dermatitis with excoriation and infection

**Fig. 7.2** Chronic atopic dermatitis with lichenification

not required for diagnosis. Skin biopsy for histopathology is also not required but may be utilized to exclude other disorders when the diagnosis remains unclear.

## Atopic Dermatitis in Pregnancy

Studies have shown that AD represents the most common dermatologic disease of pregnant women, accounting for upward of half of all dermatoses in pregnancy [8, 15, 16]. The overall prevalence of AD in pregnant women in the United States is not known [8]. A large study in Norway found an AD prevalence of about 4% in pregnant patients spanning the years 1991–2003 [17]. It has been estimated that approximately 20–40% of patients have a pre-existing history of AD [15, 16]. For those patients with pre-existing AD, approximately 52% experience worsening of their disease, while 24% demonstrate improvement, and 24% remain unchanged; this was among a total of 88 patients who carried their pregnancies to term [14]. Atopic dermatitis severity tends to deteriorate later in the second or third trimester, although disease exacerbation may occur at any stage of the pregnancy [12, 14, 15]. Approximately 10% of patients suffer worsened disease during the postpartum period [8].

### *Atopic Eruption of Pregnancy*

Based on a 2006 retrospective review of more than 500 patients over a 10-year period, the classification of atopic eruption of pregnancy (AEP) was introduced [16]. Overall, AEP represents an umbrella term including several entities with clinical features similar to AD which occur during pregnancy. These include eczema of pregnancy, prurigo of pregnancy, and pruritic folliculitis of pregnancy, which together account for approximately 50% of all pregnancy-specific dermatoses [16, 18, 19]. Eczema of pregnancy or AEP is clinically similar to AD in nonpregnant patients. The majority of patients who develop AEP have prior atopic disease history (i.e., atopic dermatitis, asthma, allergic rhinitis/conjunctivitis). Only about 21% of patients with AEP do not have atopy prior to conception [16]. Atopic eruption of pregnancy is considered a self-limited condition which may occur during any trimester of pregnancy and may also recur in subsequent pregnancies [16, 19]. There are two main types of AEP: (1) eczematous type which is classified by eczematous skin changes affecting classic AD body sites in adults and (2) prurigo type which constitutes an erythematous papular rash located on the trunk as well as prurigo nodules which are typically distributed on the arms and distal lower extremities [19]. Approximately 71% of patients have elevated total IgE (median 156 kU/L), but an elevated level is not required for diagnosis [16]. Dermato-histopathology findings in the eczematous type of AEP demonstrate a perivascular lymphohistiocytic infiltrate with eosinophils and epidermal changes such as spongiosis,

epidermal hyperplasia, or parakeratosis [20]. Additional studies are required to elucidate if AEP represents a clinical exacerbation of pre-existing AD or perhaps an increased susceptibility for AD due to the Th2 cell-mediated predominant state of the pregnancy itself.

## Management and Treatment Principles

The treatment of AD should be individualized and involves coordination of care with an allergist-immunologist and/or dermatologist, especially for moderate-to-severe or recalcitrant cases. Treatment principles revolve around avoidance of known triggers, improved skin barrier function, resolution of inflammatory lesions, and relief of pruritus without compromising maternal and/or fetal outcomes. In consideration of the pregnant patient, the general treatment approach is to attain optimal control of the disease, ideally prior to conception. Definitive consensus guidelines for the use of several AD therapies during pregnancy are lacking. Mild disease during pregnancy may be well controlled with generally considered safe therapies such as low- to mid-potency topical corticosteroids. Moderate-to-severe and recalcitrant atopic dermatitis is more difficult to treat given the limitation of medications which the practitioner may utilize with absolute safety. Several therapeutic options are contraindicated (i.e., methotrexate, mycophenolate mofetil, azathioprine) given their known teratogenic properties. Outlined below are pharmacological treatments which may be prescribed to the pregnant patient afflicted with AD based on published literature. Table 7.2 depicts medications used for AD and their relevance to the pregnant patient.

### *Skin Hydration, Moisturization, and Other Conventional Therapies*

Standard AD therapy focuses on skin hydration along with the use of moisturizers or emollients. Skin rehydration via bathing can help to restore the water content of the epidermis. Patients should soak in a warm water bath for approximately 15 minutes on a daily basis. Upon exiting the bath, patients should drip-dry and immediately apply a moisturizer or a topical corticosteroid known as a soak and seal method. Moisturization is an integral part of the management of AD since it restores the skin barrier. Lotions, creams, and ointments are different moisturizing vehicles. Lotions tend to contain preservatives and fragrances which may be irritating, and they also have a higher water and/or alcohol content, potentially resulting in a drying effect upon evaporation from the skin surface. On the other hand, ointments are the most occlusive type of moisturizer but may be the least cosmetically appealing. It is important to provide patient education on the different vehicles available for skin

**Table 7.2** Pharmacologic treatments for atopic dermatitis and relevance to pregnancy

| | Potential human maternal adverse effects | Potential human/ animal[&] fetal adverse effects | FDA pregnancy labeling and lactation rule | Use in atopic dermatitis in pregnant patients |
|---|---|---|---|---|
| **Topical corticosteroids** | | | | |
| *Class 1: super potent* | Skin atrophy; striae; telangiectasias; hyper- and hypopigmentation | Risk for intrauterine fetal growth restriction; possible teratogenic potential | [a, b] | Avoidance recommended; consider lower potency topical corticosteroid |
| Fluocinonide 0.1% | | | | |
| Clobetasol propionate 0.0% | | | | |
| Betamethasone dipropionate 0.05% | | | | |
| Diflorasone diacetate 0.05% | | | | |
| Halobetasol 0.05% | | | | |
| *Class 2: high potency* | | | | |
| Amcinonide 0.05–0.1% | | | | |
| Desoximetasone 0.05%, 0.25% | | | | |
| Fluocinonide 0.05% | | | | |
| Halcinonide 0.05%, 0.1% | | | | |
| Clocortolone 0.1% | | | | |
| Betamethasone valerate 0.1% | | | | |
| Betamethasone dipropionate 0.05% | | | | |
| *Class 3: upper mid-potency* | | Risk for intrauterine fetal growth restriction | | Use with caution; consider lower potency topical corticosteroid; consider lowest amount and shortest duration of application |
| Triamcinolone acetonide 0.5% | | | | |
| Triamcinolone diacetate 0.025–0.1% | | | | |
| Betamethasone valerate 0.12% | | | | |
| Betamethasone dipropionate 0.05% | | | | |
| Fluticasone propionate 0.005% | | | | |
| Mometasone furoate 0.1% | | | | |
| *Class 4: mid-potency* | | | | |
| Desoximetasone 0.05% | | | | |
| Hydrocortisone butyrate 0.1% | | | | |
| Desonide 0.05% | | | | |
| Fluocinolone | | | | |
| *Class 5: lower mid-potency* | | | | |
| Flurandrenolide 0.05% | | | | |
| Fluticasone propionate 0.05% | | | | |
| Hydrocortisone valerate 0.2% | | | | |
| Prednicarbate 0.1% | | | | |
| *Class 6: low potency* | | | | Use with caution; low potency may not be effective in moderate-to-severe cases |
| Alclometasone dipropionate 0.05% | | | | |
| *Class 7: least potent* | | | | |
| Hydrocortisone 1%, 2.5% | | | | |

(continued)

**Table 7.2** (continued)

| | Potential human maternal adverse effects | Potential human/animal[&] fetal adverse effects | FDA pregnancy labeling and lactation rule | Use in atopic dermatitis in pregnant patients |
|---|---|---|---|---|
| **Systemic corticosteroids** | | | | |
| Prednisone | Hypertension; preeclampsia; eclampsia; gestational diabetes; adrenal suppression; immunosuppression; steroid myopathy; steroid psychosis | Teratogenic; cleft lip and cleft palate defects (especially in first trimester); risk for intrauterine fetal growth restriction | [a, b] | Caution advised (especially in first trimester); only use lowest effective dose for shortest duration for severe-recalcitrant cases; potential for dermatitis flare/rebound after discontinuation; recommended to use ≤20 mg/day |
| **Topical calcineurin inhibitors** | | | | |
| Pimecrolimus 1% cream<br>Tacrolimus 0.03% ointment<br>Tacrolimus 0.1% ointment | Burning at application site during initial use | No data on topical formulation | [a, c] | Considered after topical steroid therapy has failed; avoid use on nipple while breastfeeding |
| **Topical phosphodiesterase-4 inhibitor** | | | | |
| Crisaborole 2% ointment | Burning at application site during initial use | No human data<br>No teratogenic effects observed[&], [54] | [d] | No available human data |
| **Systemic immunosuppressant therapy** | | | | |
| Cyclosporine A | Systemic immunosuppression; hypertension; renal dysfunction; preeclampsia; eclampsia; gestational diabetes | Limited human data; risk for premature birth/low birth weight for gestational age<br>Embryo and fetal toxicity at maternally toxic doses[&], [55] | [a, b] | Avoidance recommended; only to be considered after other first-line treatments have failed; requires drug and side effect monitoring |

**Table 7.2** (continued)

| | Potential human maternal adverse effects | Potential human/animal[&] fetal adverse effects | FDA pregnancy labeling and lactation rule | Use in atopic dermatitis in pregnant patients |
|---|---|---|---|---|
| Mycophenolate mofetil | Systemic immunosuppression | Teratogenic; increased risk of congenital malformations and spontaneous abortion | [e] | Avoidance recommended; known teratogenic effects based on human data |
| Azathioprine | Systemic immunosuppression; antimetabolite effect | | [e] | Avoidance recommended; rarely used for atopic dermatitis treatment |
| Methotrexate | Systemic immunosuppression; anti-metabolite effect; folate depletion; impaired fertility | | [e] | Contraindicated; rarely used for atopic dermatitis treatment; known teratogenic effects based on human data |
| **Monoclonal antibody therapy** | | | | |
| Dupilumab | Herpes viral infection/reactivation; blepharitis; serum sickness-like reaction | No observed teratogenic effects[&], [56] | [d] | Avoidance recommended; no human data during pregnancy |
| Rituximab | B-lymphocyte depletion | Limited human data; possible B lymphocytopenia | [d] | Avoidance recommended; rarely used for atopic dermatitis treatment |
| | | B lymphocytopenia; no observed teratogenic effects[&], [57] | | |

[a]No adequate and well-controlled studies in pregnant women
[b]Should be used only if the potential benefit justifies the potential risk to the fetus
[c]Use in pregnant women is too limited to permit assessment of safety of its use during pregnancy
[d]No data available in pregnant women to inform on any associated drug risk
[e]Use can cause fetal harm when administered during pregnancy and should be avoided whenever possible
[&]Available animal data

moisturization as this increases compliance. Patients must also avoid potential irritants; mild personal products including detergents, cleansers, and soaps are preferred. Other basic measures include avoidance of skin contact with abrasive materials such as wools and other rough fabrics. In patients with known dust mite sensitization, specific reduction measures (i.e., carpet removal, dust mite-proof covers, washing the bedding sheets and pillow cases in 120-degree Fahrenheit water) should be implemented, if feasible.

## *Topical Corticosteroids*

For acute or chronic AD, topical corticosteroids represent a mainstay of treatment as they decrease the underlying inflammatory pathophysiology and help to relieve pruritus. The severity of AD (mild, moderate, severe, or recalcitrant) dictates the potency required for effective treatment. There are seven potency classes of topical corticosteroids (displayed in Table 7.2). Topical corticosteroid absorption is dependent on the following: (1) potency of the product, (2) application site, (3) amount used and duration of use, (4) vehicle of administration, and (5) degree of occlusion. Cutaneous side effects of topical corticosteroids include the development of skin atrophy, striae, purpura, hyperpigmentation, hypopigmentation, and/or telangiectasias with prolonged use. Caution to avoid application of potent corticosteroids to the face and intertriginous body areas (i.e., axilla, inguinal region) must be advised to the patient.

Although considered a pregnancy category C in previous nomenclature, topical corticosteroids are generally considered first line for the treatment of AD in pregnancy [8, 21–25]. There are no well-controlled studies of topical corticosteroid use in pregnant women. There are recommendations in the literature that high-potency (Class 2) and super-potency (Class 1) topical steroids should be avoided in the pregnant patient due to their teratogenic potential [22]. Based on British and American guidelines, low- to mid-potency topical corticosteroids may be preferably used in the pregnant patient; however, higher-potency preparations should be used with caution in limited duration and quantity or avoided completely [24, 25]. Potent topical corticosteroid use during the third trimester has been linked to fetal growth restriction [24]. In one case report, intrauterine fetal growth restriction was observed in a woman who had used topical triamcinolone at an estimated dose of 40 mg per day during weeks 12–29 of gestation [26]. In case studies, there have been no definitive associations of orofacial cleft malformations or preterm delivery with topical corticosteroid use [21, 27, 28]. It should also be noted that the use of topical corticosteroids potentiates the risk for stretch marks, particularly when applied in areas prone to striae development in pregnancy (i.e., abdomen and breasts). Overall, based on the limited available data regarding topical corticosteroid use in pregnancy, these medications appear to be generally safe and should be used at the lowest effective potency, amount, and duration for appropriate treatment of AD.

### *Systemic Corticosteroids*

Systemic corticosteroids are not routinely used for the management of AD due to their multiple and significant adverse effects and potential for rebound dermatitis. As a therapy for AD exacerbations, they are considered relatively safe to use in the pregnant patient during the third trimester for severe or recalcitrant disease [23]. Prednisone is the preferred corticosteroid due to its relatively limited passage across the placenta [29]. Cleft lip and palate defects have been observed with oral systemic corticosteroid administration in the first trimester, and pregnant patients should be advised on this potential fetal adverse effect [22, 30]. There are several studies which suggest associations of systemic corticosteroids with intrauterine fetal growth restriction, gastroesophageal reflux, and increased risk of cerebral palsy; however, it is difficult to ascertain if these adverse fetal outcomes are secondary directly to maternal corticosteroid administration or due to underlying maternal disease [8, 31–33]. Well-established maternal adverse effects of systemic corticosteroid use in pregnancy include hypertension, preeclampsia, and gestational diabetes, all of which can negatively affect fetal outcomes (i.e., intrauterine growth restriction, macrosomia, intrauterine fetal demise). Overall, for these reasons, systemic steroids should be avoided in pregnancy but, if used, must be prescribed at the lowest effective dose with the general consensus of less than or equal to 20 mg per day of prednisone for severe, recalcitrant cases of AD for a limited period of time [19, 34].

### *Immunomodulators and Systemic Immunosuppressants*

Pimecrolimus 1% cream and tacrolimus 0.03% and 0.1% ointment are indicated for the treatment of mild-to-moderate and moderate-to-severe AD, respectively. These agents act by inhibiting calcineurin which in turn prevents the transcription of T cell-mediated cytokines. Both agents are effective and safe nonsteroidal options for the treatment of AD, but data regarding the safety of these drugs in pregnancy remains rather limited. There are no well-controlled studies of topical calcineurin inhibitor use during pregnancy, and therefore information is lacking on their safety. Burning upon initial application is a common side effect which resolves after a few days of consistent use. In their systemic formulation, calcineurin inhibitors have been associated with premature birth [22]. However, topical preparations of tacrolimus have limited systemic absorption and may be used in limited amounts over affected body areas as steroid-sparing therapy for AD in pregnancy that does not respond to standard moisturization and/or topical corticosteroids [22, 23]. Despite the maintained black-box warnings of an increased risk of lymphoma, post-surveillance marketing has not demonstrated any such increased incidence with topical calcineurin inhibitors [35].

Cyclosporine, a systemic immunosuppressant which decreases T-lymphocyte function, is used for patients with severe, recalcitrant AD. Cyclosporine (at higher

doses compared to that for AD) has been associated with premature birth in pregnant women receiving it for transplant rejection [36]. Due to its extensive side effect profile, including hypertension and nephrotoxicity, it is generally not recommended in pregnancy as these side effects can potentiate other complications such as gestational hypertension and diabetes, preeclampsia, and eclampsia. There are no strong recommendations for the use of cyclosporine for AD in pregnancy, and it should only be seriously considered after other modalities have failed [23]. If prescribed, patients must be monitored with appropriate laboratory testing such as complete blood count, renal and liver function, as well as blood pressure readings and urinalysis.

Mycophenolate mofetil is a systemic immunosuppressant that enzymatically inhibits the proliferation of T and B lymphocytes which may be considered for severe, refractory AD but is contraindicated during pregnancy. Post-marketing surveillance has demonstrated that mycophenolate mofetil is associated with an increased risk of spontaneous abortion during the first trimester as well as congenital malformations such as cleft lip and/or cleft palate, microtia, external auditory canal atresia, and additional abnormalities of the heart, esophagus, and kidneys [37].

Azathioprine and methotrexate are other immunosuppressants rarely used for the treatment of severe AD. Due to their antimetabolite effects, interfering with RNA and DNA production, they harbor significant side effects (i.e., bone marrow suppression, congenital anomalies) to the developing fetus and therefore are contraindicated in the pregnant patient with AD. Methotrexate also has abortifacient properties. Moreover, patients on methotrexate considering pregnancy should be taken off of this medication at least 3 months prior to attempting conception.

## *Monoclonal Antibody Therapy*

Dupilumab is a novel monoclonal antibody, administered as a subcutaneous injection, against the alpha subunit of the interleukin-4 (IL-4) receptor which drives Th2 cell-mediated immunity. Dupilumab was approved for adult patients with moderate-to-severe AD in 2017. As an IgG monoclonal antibody, it theoretically has the capability to cross the placenta and reach the developing fetus. In animal studies of monkeys, there were no fetal adverse effects observed when mothers were given ten times the maximum recommended human dose throughout the duration of pregnancy. There are currently no data available on dupilumab use in pregnant women to inform on any associated maternal and/or fetal risk. Additionally, there is risk of herpes virus reactivation with dupilumab use which is an important consideration in the pregnant patient.

Although not considered a standard therapy, rituximab, a monoclonal antibody against CD20 on B lymphocytes, has been unknowingly administered for persistent, severe AD during the first trimester of pregnancy with no observed adverse effects

to the mother or twin infants [38]. Nevertheless, rituximab may adversely affect B-cell development in the fetus and should be avoided under general circumstances. Omalizumab is a recombinant, humanized monoclonal antibody which binds freely circulating IgE, thus blocking its binding to receptors on basophils and mast cells, preventing their activation and degranulation. A 2016 systematic review and meta-analysis comprising 103 pediatric and adult patients from 1 randomized, placebo-controlled trial and 12 case series investigated the efficacy of omalizumab in AD. The authors concluded overall that there was a lack of substantial evidence for the effectiveness of omalizumab for treatment in AD [39]. There are no published case reports on the use of omalizumab for AD in pregnancy.

### *Subcutaneous Immunotherapy to Dust Mite Antigen*

Patients with allergic asthma or rhinosinusitis and sensitization to dust mite may demonstrate improvement in their AD with the administration of subcutaneous immunotherapy to dust mite antigen [11, 40]. During immunotherapy, there are two general phases: (1) buildup in which the patient is administered increasing doses of allergen and (2) maintenance during which the clinically effective dose is achieved and continued. Patients who become pregnant while on immunotherapy should remain at their previously administered immunotherapy dose if their current phase has demonstrated therapeutic efficacy.

### *Other Therapies and Alternative Medicine*

Antihistamines do not have an impactful role in the relief of pruritus associated with AD as the primary process is a cell-mediated inflammatory reaction. Narrow-band ultraviolet B (UVB) phototherapy can be considered in moderate-to-severe cases of AD which do not respond to standard therapy. Phototherapy works by inhibiting antigen-presenting cell function and interrupting the cytokine production from keratinocytes. Narrow-band UVB therapy is overall considered a safe therapy in pregnancy; however, at high doses it has been associated with decreased maternal serum folate levels which may cause neural tube defects in the fetus during the first trimester [41]. Crisaborole 2% topical ointment was approved in 2016 for the treatment of mild-to-moderate AD. It acts as a phosphodiesterase-4 inhibitor, suppressing cytokines involved in inflammation. There are no available data on the use of crisaborole during pregnancy. There is a paucity of data regarding the effectiveness of alternative medicine for the treatment of AD. In a small Korean case series, three pregnant patients were treated with a combination of acupuncture, herbal medicines, and herbal wet dressing, resulting in improvement in their AD without any noted adverse maternal or fetal effects [42].

## Maternal-Fetal Considerations

### *Maternal and Fetal Outcomes*

No data exist to suggest that the disease pathophysiology of AD negatively affects maternal or fetal outcomes such as fertility, spontaneous abortion, or birth defects [8]. A retrospective cohort study conducted in Norway which included 66,535 mothers with AD showed that there was a decreased risk of stillbirth and neonatal death compared to mothers without atopic disease [17]. A Finnish study demonstrated that AD was weakly associated with low infant birth weight (<1000 g) [43]. Moreover, in a small American cohort of 225 pregnant patients with AD, there were no stillbirths recorded, and the rate of spontaneous abortion was comparable among all 2592 pregnancies of mothers without AD [44]. It has been proposed that the immune system shift to a Th2 predominance in AD may offer an additional protective effect against adverse fetal outcomes [17]. As in AD, there are no adverse fetal outcomes associated with AEP. Maternal outcomes in AEP are favorable, and the overwhelming majority of women experience disease resolution in the postpartum period [16, 19].

### *Herpes Simplex Viral Infection*

Due to the impaired epithelial skin barrier function, patients with AD are susceptible to coinfections with various microorganisms such as herpes simplex virus type 1 or 2 (HSV-1/HSV-2). The healthcare practitioner must maintain a heightened awareness particularly for HSV infection as an extremely rare but complicating feature of AD in the pregnant patient [45–47]. The immunosuppressed state of pregnancy can predispose to eczema herpeticum gravidarum, subsequently resulting in disseminated herpes infection. Timely recognition and treatment with acyclovir is imperative; hospitalization may be required.

### *Other Infections*

The impaired skin barrier function in AD also contributes to colonization and coinfections of other organisms, including methicillin-resistant *Staphylococcus* aureus (MRSA), Malassezia-type fungi, and molluscum contagiosum. In fact, more than 90% of eczematous lesions in AD are colonized by *Staphylococcus aureus* bacteria [5]. Impetiginization is the process by which eczematous areas become acutely infected by the bacteria, thus leading to additional inflammation, pain, and erythema, as well as impetigo-like oozing or crusting. *Staphylococcus* infection of AD lesions requires appropriate treatment with dicloxacillin or cephalexin for non-methicillin-resistant strains. Infection with MRSA requires broad-spectrum antibiotic therapy.

### *Dermatitis of the Hands, Nipple, and Vulvovaginal Regions*

Patients with AD may manifest a nonspecific irritant hand dermatitis which tends to become aggravated by repeated handwashing and/or wetting. This is relevant in regard to infant care in the postpartum period. Special care should be taken to prevent excessive water exposure and drying of the hands. Frequent moisturization and emollient protection can help prevent hand dermatitis. Eczematous dermatitis of the nipple and areola region may manifest in up to 2% of breastfeeding mothers in the postpartum period; 50% of these cases will be related to exacerbations of AD [8, 48]. Patients with AEP also display a tendency to develop hand and nipple dermatitis [20]. Successful breastfeeding can become an issue due to nipple eczematization. General moisturization in addition to low- to mid-potency topical corticosteroids may be used for AD of the nipple and areola but should be sufficiently removed each time before breastfeeding the infant. Atopic dermatitis may also affect the *labia minor* and majora in pregnant women, manifesting as ill-defined erythematous plaques with or without desquamation and/or lichenification. Many cases are difficult to treat, but topical corticosteroids remain the therapy of choice. Bager et al. found that filaggrin mutations were associated with increased risk of problems related to perineal trauma endured during childbirth, including epidermal healing and urinary incontinence [9].

## Allergic Contact Dermatitis Overview

Allergic contact dermatitis (ACD) is an inflammatory skin reaction due to external contact exposures and manifests as pruritic, erythematous skin lesions which may be maculopapular, vesicular, or lichenified. There exist thousands of substances and chemicals found in a myriad of consumer products which may act as contact allergens. Identification and avoidance of clinically relevant contact allergens is the mainstay of treatment. Patch testing (PT) is the diagnostic test of choice to identify a patient's contact allergens. However, PT to identify such potential contact sensitizers and allergens is not recommended in the pregnant patient.

## Pathophysiology

Contact dermatitis may be due to an irritant or allergic cause. Irritant contact dermatitis (ICD), accounting for 80% of contact dermatitis, develops on sites exposed to irritant agents causing direct skin damage which subsequently activates the innate immune system. Allergic contact dermatitis represents a type IV, cell-mediated hypersensitivity reaction caused by skin contact with haptens, or nonprotein contact allergens. In the sensitization phase, allergen contact with the skin induces an innate

immunity cascade, with release of IL-1α, IL-1β, TNF-α, GM-CSF, and IL-8 and activation of Langerhans cells (LCs) and dermal dendritic cell (dDCs) [49]. The hapten is engulfed by LCs or dDCs, and the hapten-peptide complexes migrate to the regional lymph nodes, where they prime T cells (Th1, Th2, Th17, Treg cells) that proliferate and then circulate in the blood. On second exposure, the elicitation phase occurs where the hapten is recognized by the now-sensitized, hapten-specific T cells that trigger an inflammatory cascade of cytokines and cellular infiltrates and further stimulate keratinocytes to produce the manifestations of ACD.

## Clinical Features and Diagnosis

Allergic contact dermatitis should be suspected in patients with chronic eczematous or noneczematous dermatitis with ill-defined borders or in a particular recognizable diagnostic distribution [50]. Based on the location of allergen contact with the skin, ACD may theoretically manifest in any area of the body; however, common documented sites include a scattered or generalized distribution, as well as the hands and face. Other commonly observed regions include the scalp, eyelids, lips, and neck [50]. The rash of ACD may occur in different stages depending on the frequency and duration of contact allergen exposure. Pruritus is a prominent feature. Acutely affected areas appear as erythematous macules/papules, vesicles, or bullae. Chronic ACD may be associated with scaling, fissures, and lichenification. Photos of acute and chronic ACD are depicted in Figs. 7.3 and 7.4. Systemic contact dermatitis (SCD) refers to a skin condition where an individual sensitized to an allergen

**Fig. 7.3** Acute allergic contact dermatitis to fragrance

**Fig. 7.4** Chronic contact dermatitis of the hands

subsequently reacts to that same allergen or a cross-reacting allergen via the systemic route (oral, intravenous, intramuscular, inhalational, transmucosal, or transcutaneous) through type IV immune-mediated mechanisms.

The diagnosis of ACD relies on a comprehensive clinical history including a full review of the patient's work and/or home exposures, hobbies, and personal product use. Patch testing remains the gold standard for the diagnosis of ACD [50]. As previously mentioned, thousands of contact sensitizers and allergens have been implicated in ACD. Some of the most common ones include but are certainly not limited to the following: metals (nickel, chromate, cobalt, gold, mercury), cosmetics and personal hygiene products (fragrances, balsam of Peru, preservatives (formaldehyde, parabens), lanolin, organic dyes (p-phenylenediamine), surfactant (cocamidopropyl betaine), rubber chemicals (mercapto compounds, carbamates), topical medications (corticosteroids, neomycin, bacitracin), and plastic resins (epoxies, acrylics, formaldehyde resins) [50]. Patch testing involves placing an occlusive panel of contact allergens on the patient's back for a period of 48 hours, followed by its removal and subsequent clinical reading at specific time points for any observed positive reactions. The PT reexposes the patient to the culprit allergen for possible identification. Although there are no formal recommendations or consensus guidelines against performing PT in pregnant patients, it should generally be avoided [51]. PT results may be affected by the immunological changes induced by pregnancy. Furthermore, in any patient undergoing PT, there is a risk, although minimal, for systemic ACD. Another method of testing is known as the repeat open application test (commonly abbreviated as ROAT) in which a substance containing a suspected contact allergen, typically a personal product, is applied to the antecubital fossa twice daily. This is done at home by the patient for 1 week during which time a clinical reaction may be observed. This may identify the product the patient may react to but may not identify the specific chemical or allergen component.

## Allergic Contact Dermatitis in Pregnancy

There is limited information regarding ACD specifically in the pregnant patient. A case report of ACD manifesting as scalp pruritus and severe facial angioedema due to hair dye in a second trimester pregnant woman who suffered no complications has been previously described [52]. As PT is usually deferred during pregnancy, there is limited information on the prevalence and diagnosis of ACD during pregnancy.

## Management and Treatment Principles

The definitive mainstay of treatment of ACD involves identification and avoidance of contact with the offending allergen(s). If the allergen is known, it can be entered into a database (Contact Allergen Management Program (CAMP; www.contactderm.org) or Contact Allergen Replacement Database (CARD; www.AllergyFreeSkin.com)), thus generating a product list which does not contain the contact allergen for patient reference. Supportive measures include fragrance-free moisturization. Antihistamines do not offer significant relief of pruritus. Topical corticosteroids are considered a first-line treatment modality for ACD. For the thinnest skin on the body (i.e., face, eyelids), the lowest, effective potency topical corticosteroids may be used with maintained caution and for a limited duration. More potent topical steroids are usually needed in order to appropriately treat chronic, lichenified lesions [50]. As in AD, treatment principals for topical steroid use during pregnancy remain the same: low- to mid-potency topical corticosteroids may be safely used, while higher-potency steroids should be used in limited amount and duration with caution or avoided, if possible. Systemic corticosteroids should be avoided as treatment for ACD, especially in pregnancy, and should only be used for severe, systemic cases in the smallest effective dose for a limited duration.

## Maternal-Fetal Considerations

### *Allergic Contact Dermatitis of the Hands, Nipple, and Vulvovaginal Regions*

Hand and nipple ACD may occur in the postpartum period from products such as moisturizers and gels used either on the newborn or to relieve pain or irritation secondary to breastfeeding. Lanolin, a well-described contact sensitizer and allergen, is found in many preparations for the prevention and treatment of diaper rash and in creams or gels for relief of sore and/or cracked nipples in breastfeeding mothers. Low- to mid-potency topical corticosteroids may be used for nipple dermatitis

which should be applied after breastfeeding and thoroughly washed off and removed prior the next nursing session [8]. Other substances which may act as relevant contact allergens include alcohols found in a variety of products such as cleansing wipes and hand sanitizers. Methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) or MI alone have become increasingly recognized contact allergens and are found in cosmetic and industrial products, including baby wipes. Allergic contact dermatitis of the vulvovaginal region may present in the postpartum period due to local anesthetic benzocaine application, lanolin, or sanitary pad use [53]. Vulvovaginal region ACD manifests with burning, pruritus, and erythema and can be extremely uncomfortable or painful for the patient. Treatment involves discontinuation of culprit product(s) which may contain relevant contact allergens.

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# Chapter 8
# Urticaria and Angioedema


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## Introduction

Urticaria and angioedema can manifest throughout pregnancy with an impact ranging from a decline in one's quality of life to a potentially life-threatening situation in some cases of hereditary angioedema. Management should be tailored for each patient based on her history, personal priorities, severity of disease, and potential complications. As medication use is typically avoided in pregnancy if possible, due to actual or perceived risks to the fetus, women are often undertreated. In women with pre-existing chronic urticaria/angioedema, a thorough conversation between the clinician and patient should take place, ideally prior to conception, on the risks and benefits of therapy throughout pregnancy and lactation.

Urticaria are erythematous, blanchable, pruritic wheals which develop as a result of mast cell and basophil activation, leading to the release of vasoactive mediators, predominantly histamine. Distinguishing characteristics of urticarial rashes are: lesions are typically transient, last less than 24 h, and often recur on different areas of the body. Between 12% and 22% of the general population will develop urticaria in their lifetime, with a female predominance [1–3]. An important factor in categorizing urticaria is by its chronicity. Acute urticaria (AU) is the presence of hives for less than 6 weeks, while chronic urticaria (CU) is defined as the occurrence of continuous or intermittent lesions for at least 6 weeks [4].

Angioedema (AE) often occurs in association with urticaria, but in approximately 40% of AE cases, it can occur in isolation [5]. It differs from urticaria in that AE are typically pale, poorly demarcated and nonpruritic lesions which are caused

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by increased capillary and venule permeability leading to interstitial edema. The most common causes of AE without urticaria include idiopathic, angiotensin-converting enzyme (ACE) inhibitor-related, complement C1 esterase inhibitor deficiency, and drug-related [6].

Although the incidence or prevalence of urticaria and AE in pregnancy is not known, it is believed to be similar to or even higher than that of the general population. This chapter will review the unique challenges in evaluating and managing urticaria and angioedema during pregnancy.

### *Hormonal Changes and Effects on Urticaria and Angioedema*

Both estriol, the primary estrogen secreted in pregnancy, and progesterone play essential roles in pregnancy including during implantation, placental growth and maintenance, and parturition [7]. These hormones gradually rise throughout pregnancy and peak just prior to delivery. While estrogen has been shown to enhance histamine release by mast cells and basophils, progesterone is capable of inhibiting this process [8–11]. However, a direct correlation between chronic urticaria and levels of estrogen or progesterone has yet to be elucidated.

These, along with other sex hormones, have long been known to modulate immune cells including T cells, B cells, eosinophils, mast cells, and basophils [12–15]. Dehydroepiandrosterone sulfate (DHEA-S) is decreased in nonpregnant, premenopausal women with chronic idiopathic urticaria, and dehydroepiandrosterone (DHEA) is decreased in type I and II hereditary angioedema [16, 17]. Fluctuations in both DHEA-S and DHEA levels during pregnancy could in theory contribute to improvements or exacerbations of these conditions [18].

## Urticarial and Urticarial-Like Conditions

### *Acute Urticaria*

Urticaria with or without angioedema lasting less than 6 weeks is termed acute urticaria [4]. This should be differentiated from anaphylaxis based on the lack of other organ system involvement including respiratory (wheezing and cough), cardiac (hypotension and changes in heart rate), nervous (syncope and dizziness), and gastrointestinal (nausea, vomiting, and diarrhea) systems. Although 30–50% of episodes of acute urticaria are idiopathic, an etiology can be found in the remainder of cases through a detailed history and appropriate allergy testing [19, 20]. Common causes include infections, drugs, foods, and insect bites or stings [21]. Most occurrences will resolve spontaneously within weeks and workup should be selective based on pertinent history [4]. No data has been published on acute urticaria during pregnancy, but the epidemiology and etiologies are likely similar to that of the nonpregnant population.

## *Chronic Urticaria*

Urticaria lasting longer than 6 weeks is defined as chronic urticaria. CU is an overarching term which can be further subdivided into chronic idiopathic urticaria (CIU), also referred to as chronic spontaneous urticaria (CSU), and physical (inducible) urticarias. Foods, insect stings, and drugs are exceedingly rare causes of such prolonged symptoms. The prevalence of CU in the general population ranges from 0.5% to 5%, with females accounting for up to 70% of all cases [4, 22].

Currently, the immunopathogenesis of CIU remains unknown, but several theories exist related to mast cell activation, basophil dysfunction, and autoimmunity [23–25]. Thirty to 50% of CIU patients have been found to have IgG autoantibodies against IgE and/or the α subunit of FcεRI, although their presence has not been found to clinically correlate to a distinctive phenotype [26, 27]. CIU is traditionally considered a benign cutaneous disease, nonetheless it is associated with a decreased quality of life as well as with systemic symptoms including joint pain, headaches, fatigue, subjective wheezing, palpitations, and gastrointestinal complaints [28]. These accompanying symptoms should not be confused with anaphylaxis as they are typically less severe, do not require epinephrine, and improve with better control of CIU. Physical urticarias represent a subgroup of CU patients that develop reproducible wheals as a result of environmental stimuli on inflammatory cells. This includes conditions such as cholinergic urticaria (exercise, heat, stress, and emotion), symptomatic dermatographism (friction), cold urticaria, delayed-pressure urticaria, solar urticaria, aquagenic urticaria, and vibratory angioedema [4].

Limited data are available on women with pre-existing CU during pregnancy. The majority of these women reported no influence, but a few exceptions were reported with either an improvement or exacerbation of their condition. One of the largest observational studies to date by Amsler et al. involved only 16 women with CU that experienced a pregnancy during the investigational period [29]. Four patients showed an aggravation of symptoms, three manifested clinical improvement, and nine reported no change. As no clear pattern exists based on available limited data, patients should be educated regarding the unpredictable clinical course of CU throughout their pregnancy. While maternal urticaria does not appear to have detrimental effects on the fetus, therapy should be discussed with patients due to a significant decrease in quality of life and associated systemic symptoms.

## *Progesterone Hypersensitivity*

Progesterone (or progestogen) hypersensitivity (PH), previously called autoimmune progesterone dermatitis, is a rare condition that presents with cyclic urticarial or other cutaneous lesions that closely correlate with progesterone levels. Symptoms can range in severity from rash to anaphylaxis which peak 3–10 days prior to menses, coinciding with the luteal phase of the menstrual cycle, and resolve soon after

menstruation [30]. Although the pathogenesis of PH is not well understood, it is likely due to a hypersensitivity to high levels of endogenous progesterone. Many, but not all, patients have a history of synthetic progesterone use which suggests possible cross-reactivity [12]. Clinical history along with confirmatory intradermal skin test, in vitro antibody detection against progesterone, or intramuscular challenge to progesterone are used to make the diagnosis [31].

Pre-existing PH can worsen during pregnancy, or PH can initially present intrapartum likely from the surge in progesterone [32, 33]. While the majority of the manifestations that occur during pregnancy are limited to the skin, more severe events including recurrent spontaneous abortions and anaphylaxis have been reported [32, 33]. Symptoms typically improve with initiation of lactation postpartum but can recur soon after cessation of breastfeeding [34]. Treatment of urticaria from PH can be similar to CU. However in nonpregnant women, suppression of ovulation with oral contraceptives or gonadotropin-releasing hormone (GnRH) agonists has been used. Rapid desensitizations to progesterone can also be performed, especially for women with infertility in need of high-dose progesterone [34].

## *Polymorphic Eruption of Pregnancy (PEP)*

PEP, previously referred to as pruritic urticarial papules and plaques of pregnancy (PUPPP), is the most common dermatosis of pregnancy which presents as variable erythematous, pruritic papules which can resemble urticaria [35]. There is a predominant abdominal involvement around striae, but the lesions can also be found on the proximal extremities. It is traditionally seen in the third trimester and occurs in every 1:200 to 1:120 pregnancies [36]. It is more often seen in patients who are primigravidas or have a multiple gestation pregnancy. Although the pathogenesis is not well understood, several proposed theories exist. First, abdominal stretching and breakage of skin connective tissue in a nulliparous mother may increase maternal exposure to fetal antigen, and second, elevated progesterone receptor reactivity in lesional keratinocytes has been shown [37].

Perinatal outcomes are not altered in PEP [38]. Several studies have shown an association with an increased rate of cesarean section and induction of labor in mothers with PEP which is likely due to a higher incidence of complicated pregnancies in this population [38, 39]. Symptoms classically resolve postpartum and infrequently recur in subsequent pregnancies [39].

## *Pemphigoid Gestationis (PG)*

PG, previously termed herpes gestationis, is a rare dermatosis of pregnancy which affects 1 in 50,000 pregnancies and is considered another urticarial-like condition [40]. An acute eruption of urticarial papules and plaques usually occurs in the

second or third trimester which characteristically involves the umbilicus. Less frequently, it can also initially present soon after delivery. The rash typically spreads peripherally to the extremities and evolves to predominantly vesicles and bullae after 1–2 weeks [40]. Routine histopathology and direct immunofluorescence can be diagnostic with the presence of linear complement three (C3) deposition with or without immunoglobulin G1 (IgG1) along the basement membrane [41].

Early-onset PG and bullae formation has been associated with preterm birth and small-for-gestational-age infants, while maternal outcomes are unchanged during pregnancy [42]. After pregnancy, women are at increased risk of secondary autoimmune diseases [41]. Most cases spontaneously resolve within months postpartum, but reports of persistent PG lasting for years are noted [43].

## Management of Urticaria

Differentiation among acute or chronic urticaria and anaphylaxis is critical as management varies significantly. Epinephrine is first-line therapy in both pregnant and nonpregnant patients for anaphylaxis [4]. Additional measures include supplemental high-flow oxygen, positioning of the mother on her left side to enhance venous return to the heart, and intravenous fluids.

As medications are often avoided during pregnancy due to concerns of their effects on the fetus, a nonpharmacologic approach is a reasonable first step for urticarial conditions. Avoidance of any triggers of acute urticaria or physical urticaria would be of clear benefit. Nonsteroidal anti-inflammatory drugs (NSAIDs) and opiates can exacerbate CU and should be avoided if possible. Antihistamines remain the cornerstone of therapy for all types of urticaria in both pregnant and nonpregnant patients.

Acute urticaria can often be managed by nonsedating antihistamines alone. If symptoms are not responsive to antihistamines, a short course of oral corticosteroids may be used while eliminating potential triggers and developing an effective steroid-sparing plan [4]. Chronic urticaria management initially is similar to that of acute urticaria in that antihistamines are typically considered first-line. Figure 8.1 depicts a stepwise approach to CU in pregnancy. In refractory cases, assessment of the risk and benefits of therapy needs to be considered due to the majority of treatment options having limited data evaluating their safety in pregnancy or being contraindicated in pregnancy.

### *Antihistamines*

Isolated urticaria with or without angioedema can often be managed with H1 antihistamines alone. As urticaria is not life-threatening, women are likely undertreated due to a lingering belief of teratogenic effects on the fetus.

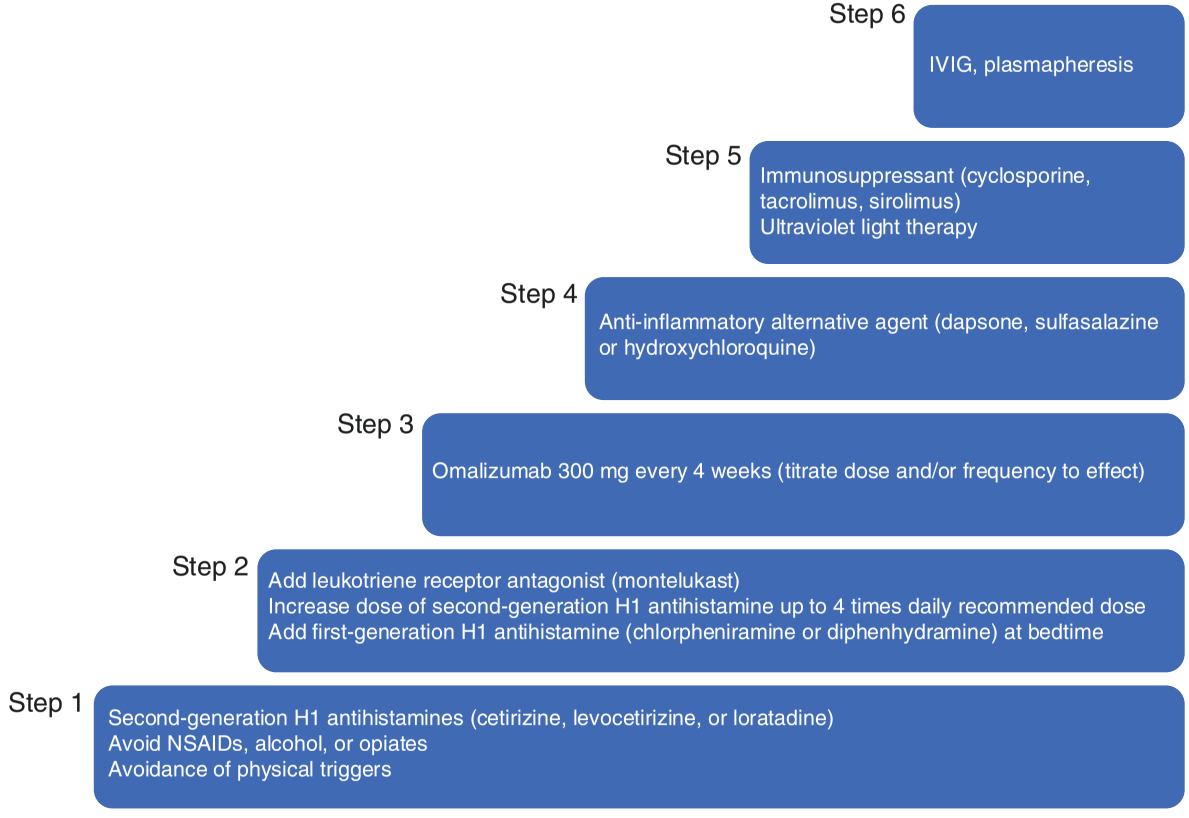


**Fig. 8.1** Stepwise treatment diagram for CU during pregnancy

Numerous retrospective cohort and case-controlled studies as well as several prospective studies have examined the safety of both first- and second-generation H1 antihistamines during pregnancy [44, 45]. No significant differences were found in the outcomes of the offspring in regard to fetal malformations, spontaneous abortions, prematurity, stillbirth, or low birth weight [46]. In addition, the timing of antihistamine use, including during the first trimester, when the fetus is thought to be most susceptible, does not appear to be significant [44, 45].

Cetirizine and loratadine are the best studied of the second-generation antihistamines and are preferentially used by most expert clinicians. While early studies linked loratadine use to hypospadias in the offspring, subsequent large prospective studies did not show this association and is now thought of as a safe, effective option [44, 47]. Less data are available for other second-generation antihistamines, including fexofenadine, levocetirizine, and desloratadine, but they are generally accepted as safe and effective during pregnancy. First-generation H1 antihistamines are considered second-line options during pregnancy due to their sedating effects. Chlorpheniramine, cyproheptadine, dexchlorpheniramine, tripelennamine, and diphenhydramine have been evaluated in prospective cohort trials without evidence of adverse fetal outcomes and can carefully be used as add-on therapy if indicated [44]. The addition of an H2 antihistamine is unlikely to add significant benefit over H1 antihistamines alone in the management of acute or chronic urticaria [48].

For chronic urticaria, higher doses of antihistamines are often used at up to four times the FDA-approved dose [4]. No studies have looked at the safety of these higher doses during pregnancy. Each case should be evaluated on an individual basis with a thorough discussion of the potential risks and benefits between the managing physician and patient before pursuing this course of therapy.

### *Systemic Glucocorticosteroids*

Long-term use of systemic glucocorticosteroids for management of acute or chronic urticaria is not recommended, even in nonpregnant patients [4]. In pregnant individuals, short courses of 1–5 days may be needed for adequate control during severe exacerbations, but the minimum effective dose and shortest duration to achieve satisfactory improvement should always be used. Short courses are unlikely to cause pregnancy complications which are more likely to occur with chronic use. Chronic use in pregnant women can cause complications such as gestational diabetes, atrial hypertension, and premature rupture of membranes. In both pregnant and nonpregnant individuals, chronic use is associated with morbidities such as hyperglycemia, hypertension, cataracts, weight gain, osteopenia or osteoporosis, and avascular necrosis of bone [49].

Prednisone and prednisolone are the steroids of choice due to their short half-life and as they are effectively metabolized by 11-β-hydroxysteroid which is pres-

ent in the placenta. Fetal exposure is approximately 10% of the maternal plasma level [50]. Oral clefts have been reported as a risk due to first trimester exposure to systemic corticosteroids, but larger studies have not substantiated this concern [51].

### *Leukotriene Antagonists*

Montelukast is often used as adjunct therapy with antihistamines for the management of urticaria. It has been evaluated in several large, prospective and retrospective studies in pregnant women. No increase in major malformations were noted with montelukast exposure during pregnancy, and it can be used as add-on therapy during pregnancy [52].

### *Omalizumab*

vOmalizumab is the only biotherapeutic that is approved by the FDA for management of CIU. It is a recombinant humanized $IgG_1$ monoclonal anti-IgE antibody which was initially introduced for the management of severe allergic asthma. The optimal starting dose for its use in CU is 300 mg every 4 weeks [53]. Omalizumab has been studied in pregnant women with severe asthma in the EXPECT trial [54]. Of the 191 women included in the study, 169 had known pregnancy outcomes for which there was no significant difference in spontaneous abortions, major congenital anomalies, prematurity, or low birth weight compared to a similar asthmatic population. Due to the small sample size, it is difficult to draw any definitive conclusions for the safety of omalizumab in pregnant females with CIU, and additional studies are needed with larger study populations. However, considering the alternatives, omalizumab may be a reasonable choice for antihistamine-refractory urticaria during pregnancy. The benefit-risk deliberations in an individual patient would also need to take into consideration the small but finite risk of anaphylaxis with omalizumab.

## *Alternative Therapies for Chronic Urticaria*

Management of refractory chronic urticaria in pregnancy follows a similar treatment algorithm as that in nonpregnant patients (Fig. 8.1). If initial treatment with antihistamines and leukotriene receptor antagonists are not adequate to control symptoms, additional therapy should be considered on a case-by-case basis. Quality of life can be drastically affected in patients with CU, and the benefits of step-up treatments to achieve satisfactory control should be weighed against the potential

risk to both mother and fetus from medications that have not been well studied during pregnancy.

Many clinicians will use omalizumab as third-line therapy after antihistamines and leukotriene receptor antagonists in pregnant females for CU due to reassuring experience with its use for asthma during pregnancy [54]. The only other medications that is used for refractory CU with reassuring yet limited human data is sulfasalazine [55]. While no cases on its use in pregnancy for CU have been published, it has been evaluated in nonpregnant patients with reasonable efficacy, and it is thought of as generally safe during pregnancy from its use in rheumatologic conditions [50]. Finally, other drugs, including dapsone, hydroxychloroquine, and cyclosporine, have very limited data in their use during pregnancy and should be used very cautiously. Methotrexate and mycophenolate should not be used during pregnancy due to their known teratogenic effects.

### *Special Considerations During Lactation*

Second-generation antihistamines are considered safe as the transfer rate to breast milk is nominal. Loratadine, cetirizine, and fexofenadine are the best studied of these [56, 57]. On the other hand, data on first-generation antihistamines are very limited with only a handful of observational studies showing no major adverse events, but a slight increase in infant irritability and drowsiness has been noted that did not require medical intervention [58]. For this reason, second-generation antihistamines are preferred.

Higher doses of loratadine and terfenadine have also been evaluated in breast milk with very minimal transmission which suggests that higher doses of second-generation antihistamines can be safely used during lactation in cases of refractory chronic urticaria [57].

The theoretical risk of decreased milk production remains with centrally acting antihistamines through its interaction with dopamine regulation of prolactin. Very limited data exist with H1-antagonists which has only evaluated serum prolactin levels in these patients [59]. In a study by Messinis et al., a significant decrease was noted in baseline prolactin after doses of promethazine or d-chlorpheniramine. However, concomitant administration of thyroid-releasing hormone or addition of suckling did not cause an alteration of stimulated prolactin release compared to antihistamine-naïve patients subjected to similar stimuli. This suggests that antihistamines do not participate in the mechanisms underlying suckling-induced prolactin release [59]. While additional studies are needed to further elucidate this connection, antihistamines do not appear to cause milk production reductions in lactating women, and their use should not be limited due to this primarily theoretical concern.

Systemic steroids are also considered generally safe during lactation without significant adverse events. Regardless, infant exposure should be limited to the lowest possible dose for the shortest duration. Studies have shown trivial amounts of prednisolone can be transferred to breast milk, but it is still recommended to wait to

**Table 8.1** Alternative agents for management of CU with their safety information during pregnancy and lactation

| | Medication | Pregnancy data | Safety during lactation |
|---|---|---|---|
| Leukotriene antagonist | Montelukast | Limited but reassuring human data[a] | Considered safe at FDA-approved dosing[a] |
| Tricyclic antidepressant | Doxepin | Inadequate human data | Avoid use if possible but can use after weighing risks and benefits |
| Anti-IgE mAb | Omalizumab | Limited but reassuring human data[a] | Probably safe but not sufficiently studied[a] |
| Anti-inflammatory agents | Dapsone | Limited but reassuring human data | Probably safe but not sufficiently studied |
| | Hydroxychloroquine | Inadequate human data | Probably safe but not sufficiently studied |
| | Sulfasalazine | Limited but reassuring human data | Avoid use if possible but can use after weighing risks and benefits |
| | Methotrexate | Contraindication based on human and animal data | Contraindication |
| Immunosuppressant agents | Cyclosporine | Inadequate human data, animal data is not reassuring | Avoid use if possible but can use after weighing risks and benefits |
| | Mycophenolate | Relative contraindication based on human and animal data | Contraindication |
| | Tacrolimus | Inadequate human data | Avoid use if possible but can use after weighing risks and benefits |
| | Sirolimus | Inadequate human data | Avoid use if possible but can use after weighing risks and benefits |
| Immunomodulatory | IVIG | Limited but reassuring human data | Probably safe but not sufficiently studied |

[a]Indicates first choice treatment

breastfeed 4 h after maternal ingestion to avoid peak plasma levels. Other agents used for management of urticaria and their safety during lactation are shown in Table 8.1.

## Angioedema

### *Hereditary Angioedema*

HAE is a rare autosomal dominant condition due to an abnormality in complement 1 esterase inhibitor (C1-INH) due to a genetic mutation in SERPING1. It is estimated to affect 1:50,000 individuals in the USA [60]. C1-INH normally plays an

important role in regulating complement activity, and its dysfunction can lead to uncontrolled activation, resulting in bradykinin formation, increase in endothelial permeability, and angioedema. Three types of HAE have been described. Type I HAE is due to a decrease in C1-INH levels, type II HAE has normal levels but abnormal function. HAE with normal C1-INH (HAE-nmlC1-INH), previously referred to as type III HAE, is the least understood and involves both normal levels and function of C1-INH [61].

HAE presents with nonpruritic, nonpitting swelling of the skin or gastrointestinal tract which can last up to 7 days without intervention. Urticaria is classically not present. Patients can have primarily gastrointestinal symptoms including abdominal pain, nausea, and vomiting; skin manifestations such as angioedema of the extremities, genitalia, face, or oropharynx; or a combination of the two. Death can occur due to laryngeal edema; therefore, medical treatment is often required in both pregnant and nonpregnant females.

HAE episodes most commonly manifest in adolescence after puberty or early adulthood. However, patients can present not infrequently in childhood or later in adulthood, including during pregnancy [62]. The diagnosis of types I and II HAE can be made with the presence of angioedema and blood complement measurements (C4, C1-INH level, and C1-INH functional assay). C4 is typically used as a screening tool due to its low cost and availability in most laboratories. Its level is low during attacks and often between attacks, although in approximately 5% of cases, it can be normal when patients are asymptomatic [61]. C1-INH level and function should be used to confirm the diagnosis. If the diagnosis of HAE is being made during pregnancy, serum C1-INH levels can be difficult to interpret due to a transient decrease in the setting of increased plasma volume [63]. This typically normalizes after delivery, and a repeat level should be drawn at least 2–3 months postpartum to confirm the diagnosis. Genetic studies are not needed for diagnosing HAE, but it can be used for prenatal diagnosis and genetic counseling when indicated [64].

Pregnancy can alter the course of previously diagnosed HAE with C1-INH dysfunction (C1-INH-HAE). Three relatively large cohort studies have evaluated women with C1-INH-HAE throughout pregnancy which revealed that the effect of pregnancy is highly variable [65–67]. Previously thought of as the one-third rule, where approximately one-third of patients have worsening of their symptoms, one-third have an improvement, and one-third are unchanged, it appears that in actuality, a slight majority experience an increase in attack rates. The most likely explanation for this increase is due to a known association between estrogen exposure and disease severity [65]. Abdominal attacks are more common during pregnancy, likely due to the immense changes to the uterus and peritoneal cavity [68]. The timing of these attacks is highly variable without clear evidence that patients may be more susceptible during a specific trimester. Angioedema attacks are rare during delivery [66]. The majority of women have similar courses during subsequent pregnancies, but this can be inconsistent and difficult to predict in certain individuals [66]. Finally, there does not appear to be any increased risk to the fetus born to mothers with C1-INH-HAE in regard to miscarriage rate, early delivery, or stillbirths [65–67].

## *Management of HAE During Pregnancy and Lactation*

### Acute Exacerbations

Management of HAE during pregnancy can be very challenging for clinicians due to worsening of symptoms, difficulty in differentiating HAE attacks from pregnancy-related complications, and limitations with certain medications during pregnancy. Plasma-derived human C1-INH concentrate (pdhC1INH) remains the standard of care for acute exacerbations in pregnant patients [69]. While no controlled trials have been performed to evaluate its use in pregnancy, multiple case reports and series have demonstrated safe and efficacious results [70].

Icatibant has been shown to be effective in randomized controlled trials for management of acute C1-INH-HAE attacks [69]. Several case reports have been published with its use in pregnancy without any significant birth defects noted [71, 72]. Due to its limited safety data in pregnancy, icatibant should only be used in cases refractory to pdhC1INH. Other therapies for acute exacerbations can be considered if pdhC1INH and icatibant are not available. Tranexamic acid and fresh frozen plasma can be used cautiously after weighing the risks and benefits, noting their inadequate data in pregnant patients [70]. No information is available for the use of ecallantide during pregnancy, and thus ecallantide should be avoided.

### Prophylactic Therapy

Many patients can be managed with careful monitoring and treatment only during acute attacks. Conversely, a select few patients may require prophylactic therapy due to frequent and severe attacks, especially those that required prophylactic therapy prior to pregnancy. The optimal choice for prophylactic therapy is pdhC1INH due to its efficacy and good, although limited, safety profile during pregnancy. Dosing should be considered on a case-by-case basis with doses ranging from 500 units once weekly to 2000 units twice weekly based on published literature regarding pregnant patients [66, 73].

Attenuated androgens, including danazol, stanozol, and oxandrolone, have been used for prophylactic therapy in nonpregnant patients with C1-INH-HAE for decades. However, they should be discontinued at least 1 month prior to conception due to their potential risk in the first trimester for fetal virilization and female pseudohermaphroditism [74]. Tranexamic acid and fresh frozen plasma have been used as prophylactic therapy when pdhC1INH was not available with moderate benefit, but their long-term effects during pregnancy is not known, and these treatments should be avoided if possible.

### Management During Surgical Procedures

A multidisciplinary approach between the surgeon, dentist, obstetrician, and allergist/immunologist should be used in the management of HAE patients prior to medical, dental, and surgical procedures. Women with HAE are at increased risk for

laryngeal edema during procedures that involve the upper airway, and short-term prophylaxis with pdhC1INH should be considered 1–6 h prior to the intervention based on the risk of the procedure and the patient's personal history [61]. Additional pdhC1INH should be immediately available during and after the procedure in the setting of breakthrough symptoms.

#### Management During Labor and Delivery

Routine short-term prophylaxis is not indicated for uncomplicated vaginal deliveries, but pdhC1INH should be available in the delivery room. Certain situations may warrant prophylactic therapy such as a history of genital edema after trauma or a history of frequent and severe attacks throughout pregnancy. Most experts recommend administering pdhC1INH prior to or immediately after the use of vacuum or forceps during delivery. Finally, a prophylactic dose is recommended prior to cesarean section, but an emergent cesarean section should not be delayed while waiting for pdhC1INH to arrive as it can be given during or after the procedure [61].

#### Considerations During Lactation

pdhC1INH is the treatment of choice for both acute and prophylactic therapy during lactation [61]. If not available, fresh frozen plasma can be used. But it is significantly less effective.

### *Other Forms of Angioedema*

Other forms of angioedema without urticaria, including angiotensin-converting enzyme (ACE) inhibitor-related, acquired angioedema with C1-INH deficiency (C1-INH-AAE), and idiopathic angioedema, can all occur during pregnancy [69]. In the setting of ACE inhibitor-related angioedema (ACEI-AAE), the offending medication should be immediately stopped and switched to an alternate antihypertensive medication. Angiotensin receptor blockers (ARBs) can be used as they are not associated with an increased risk of angioedema in these patients [69]. As this is a bradykinin-mediated process and not histaminergic, medications such as antihistamines, leukotriene inhibitors, corticosteroids, and epinephrine are not effective. Recent studies have not supported the use of icatibant (bradykinin B2 receptor antagonist) or ecallantide (plasma kallikrein inhibitor) in nonpregnant females with ACEI-AAE, and therefore they should be avoided in pregnancy due to lack of efficacy and very limited safety data in this population of patients [75, 76].

C1-INH-AAE presents, is diagnosed, and is managed similarly to C1-INH-HAE, although a genetic cause or family history is not present. These patients typically

present after the age of 40 which makes its presence during pregnancy exceedingly rare [69].

If no etiology can be identified, idiopathic angioedema can be diagnosed. Idiopathic angioedema can be further categorized into idiopathic histaminergic angioedema (IH-AAE) and idiopathic nonhistaminergic angioedema (InH-AAE) [69]. IH-AAE is managed similarly to urticaria with angioedema while InH-AAE is much more challenging, especially in pregnancy. Initially, aggressive management with antihistamines should be attempted before establishing the diagnosis of InH-AAE. Immunosuppressive therapies including cyclosporine should be avoided if possible due to potential risks in pregnancy. Omalizumab could be considered as data supporting its use is emerging [77–79].

## Summary

Acute and chronic urticaria can cause a significant decline in one's quality of life during pregnancy. Nonpharmacologic management should always be considered first as medications are often avoided due to perceived concerns of their effects on the mother and fetus. Undertreatment should be acknowledged as a prevalent issue, and a comprehensive discussion should be undertaken between the provider and patient on the risks, benefits, and personal preferences of therapy. Hereditary angioedema can be a fatal condition and should be closely monitored throughout pregnancy. There appears to be a slight increase in disease severity during pregnancy with abdominal attacks being the most common. pdhC1INH is the first-line therapy for acute exacerbations, short-term prophylaxis, and for long-term prophylaxis during pregnancy if available. A conversation should take place, ideally prior to conception, on the approach to therapy to minimize risk to the mother and fetus.

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# Chapter 9
# Hereditary Angioedema


**Bruce L. Zuraw and Sandra C. Christiansen**

## Introduction

Hereditary angioedema (HAE) is a rare autosomal dominant disease, manifesting as recurrent episodes of angioedema without urticaria (see reviews [1, 2]). HAE typically presents in childhood or young adulthood and affects women as well as men. Due to the rarity of HAE, there is often substantial delay in arriving at a correct diagnosis compounding morbidity and risk of mortality. HAE attacks characteristically last 3–5 days with the vast majority involving cutaneous swelling of the extremities or abdominal submucosal tissue. Other common attack locations include the face, mouth, pharyngeal-laryngeal area, and genitalia. Episodes of angioedema cause significant morbidity, and laryngeal attacks can result in fatal asphyxiation. The attacks are variable and unpredictable with respect to timing, frequency, severity, and location enhancing the burden of disease for affected patients. Disease severity varies enormously, both between patients and even at different times in the same patient. HAE attacks are not mediated by histamine, and the swelling does not respond to the standard histamine-induced angioedema treatments such as antihistamines, corticosteroids, and epinephrine.

Pregnancy presents a specific set of challenges for clinicians managing patients with hereditary angioedema (HAE). Treatment decisions must take into account the underlying pathophysiology of HAE, the bidirectional interactions between pregnancy and HAE, and the safety of medication use. These issues make the care of

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HAE patients during pregnancy an important and discrete aspect of HAE management. Further the clinician needs to be sufficiently knowledgeable about HAE to incorporate genetic counseling into discussions with patients who are either pregnant or considering getting pregnant. This chapter will review each of these issues in the context of our current understanding of HAE.

## Mechanistic Classification of HAE

Recent developments have shown an unexpected heterogeneity in the underlying causes of HAE. The current classification of HAE based on the underlying mutations and proposed pathophysiology is reviewed below (Fig. 9.1).

***Type I and Type II HAE*** The classification of HAE has evolved to reflect advances in our understanding of the underlying pathophysiology. When first described by Osler in 1888, the disorder was identified as hereditary angioneurotic edema (HANE), a designation that persisted until the early 1960s. In 1963, Virginia Donaldson established that the fundamental defect in HAE was a deficiency of the plasma protein C1 inhibitor (C1INH) [3]. Two years later, a second form of HAE due to a dysfunctional C1INH protein was identified, leading to the nomenclature of type I and type II HAE [4]. In the case of type I HAE, C1INH protein levels are low, while type II HAE is associated with normal or near normal C1INH protein levels but reduced C1INH function due to a dysfunctional mutant C1INH protein [4]. Subsequent studies proved that type I and type II HAE each resulted from mutations in the gene encoding C1INH, *SERPING1* [5, 6]. Type I C1INH mutant proteins are not properly secreted, leading to low plasma levels [7]. The *SERPING1* mutations associated with type II HAE were found to

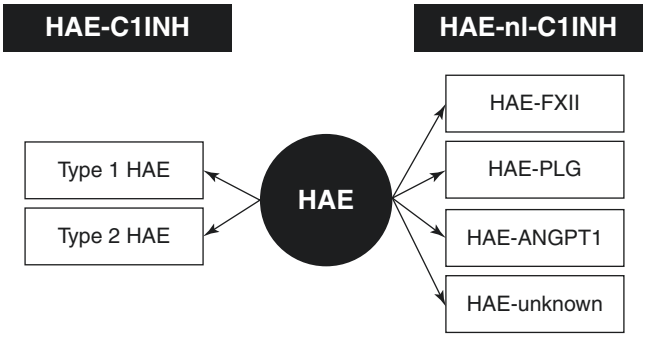


**Fig. 9.1** Types of HAE. Hereditary angioedema is broadly divided by whether the C1INH functional levels are decreased (HAE-C1INH) or normal (HAE-nl-C1INH). Each type of HAE is then subdivided further based on either the C1INH antigenic level (reduced in type I HAE and normal in type II HAE) or the underlying mutations (*F12* in HAE-FXII; *PLG* in HAE-PLG; *ANGPT1* in HAE-ANGPT1; or as yet unknown in HAE-unknown)

largely cluster around the active inhibitory site, leading to a secreted protein that was incapable of inhibiting its target proteases.

Type I and type II both result in reduced levels of functional C1INH. C1INH is a member of the serine protease inhibitor (serpin) superfamily and regulates a variety of serine proteases, including early proteases of the classical and lectin complement systems (C1r, C1s, MASP1, MASP2), contact system protease (plasma kallikrein, FXIIa, FXIIf), coagulation factor XIa, and plasmin [8]. In the absence of sufficient functional C1INH, these proteases lack adequate regulation. Multiple studies have documented that deficiency of C1INH functional activity leads to an enhanced activation of the contact system with generation of bradykinin mediating vascular leak and resultant angioedema [9–13].

***HAE with Normal C1INH*** In 2000, Bork and Binkley independently described a form of HAE characterized by normal C1INH antigenic and functional levels [14, 15]. The absence of *SERPING1* mutations in this new form of HAE meant that HAE needed to be broadly subdivided into HAE due to C1INH deficiency (HAE-C1INH) and HAE with normal C1INH (HAE-nl-C1INH). HAE-nl-C1INH has sometimes been referred to as type III HAE, but this term is now obsolete and misleading [16]. Several features suggested that HAE-nl-C1INH, like HAE-C1INH, might be bradykinin-mediated, including the lack of response to antihistamines, corticosteroids, and epinephrine and the favorable response to bradykinin pathway-targeted medications.

In 2006, families were found with a mutation in exon 9 of the F12 gene that co-sorted with disease expression [17, 18]. Four different mutations in F12 have been found to be associated with HAE-nl-C1INH, all involving exon 9. HAE-nl-C1INH patients with putative pathologic mutations in F12 are now subclassified as HAE-FXII. Interestingly, exon 9 does not code for the catalytic domain of FXII. The most common form of HAE-FXII, p.Thr309Lys, was recently shown to cause enhanced susceptibility of the contact system to become activated *ex vivo* and *in vivo* [19]. The *F12* mutations associated with HAE-FXII were also shown to enhance susceptibility of FXII to activation by plasmin [20], providing a potential explanation for the efficacy of antifibrinolytic medications in the treatment of HAE with normal C1INH, including HAE-FXII. A test for the most common HAE-FXII mutations, Thr309Lys and Thr309Arg, is widely available (Factor XII SNP Analysis, Advanced Diagnostic Laboratories, National Jewish Health, Denver CO).

More recently, some patients with HAE-nl-C1INH have been shown to have mutations in the genes for plasminogen (*PLG*) [21] or angiopoietin-1 (*ANGPT1*) [22]. A p.Ala119Ser mutation in the *ANGPT1* gene was found in an Italian family with HAE-nl-C1INH [22]. This mutation co-sorted for disease expression and may result in enhanced susceptibility to vascular permeability, placing patients at greater risk of developing angioedema from multiple mediators, including bradykinin. Based on this, a subtype of HAE-nl-C1INH called HAE-ANGPT1 has been proposed.

A number of HAE-nl-C1INH patients in a large German practice were recently found to have a p.Lys330Glu mutation in PLG [21]. This mutation also co-sorted for disease expression, and these patients have been classified as having HAE-PLG. The mechanism of angioedema in HAE-PLG is not yet known; however, the putative role of plasmin in HAE-FXII and the efficacy of antifibrinolytic treatment in HAE-nl-C1INH suggest that abnormalities in the fibrinolytic system may enhance activation of the contact system with generation of bradykinin.

A sizeable portion of HAE-nl-C1INH patients, however, do not have a known underlying mutation and are referred to as HAE-unknown. The diagnosis of HAE-unknown requires excluding histaminergic angioedema as well as other known causes of non-histamine-mediated angioedema.

## Sex Hormones and HAE

Pregnancy is associated with profound alternations in the level of a variety of hormones, including sex hormones. Early in pregnancy there is a large increase in human chorionic gonadotropins that peaks around week 10. Estrogen and progesterone levels progressively increase during the remainder of gestation. The clinical impact of sex hormones on HAE has been well recognized. This section will first review the relationships between sex hormones and HAE disease expression and severity and then dissect the mechanism of these effects.

### *Clinical Relationships*

The links between sex hormones and HAE are well recognized but complex and poorly understood. Women, on average, have more severe HAE than do men [23]. Even among healthy subjects, where high molecular weight kininogen (HMWK) levels are similar in men and women, women show higher levels of cleaved kininogen than do their male counterparts [24]. The first clue that sex hormones have a direct impact on HAE severity was the commonly observed worsening of disease severity around the time of puberty [1, 25]. Many women also notice a relationship between their menstrual cycles and angioedema attacks, with an increased number of attacks during the perimenstrual or menstrual phase [1].

A clear dichotomy between estrogens and androgens has been long appreciated. Estrogens, whether endogenous or exogenous, often lead to an escalation of HAE-C1INH severity. Many women have noted substantial worsening of their HAE-C1INH upon starting oral birth control pills or hormonal replacement therapy containing estrogen [1, 23].

The impact of estrogens on HAE severity has been particularly profound in HAE-nl-C1INH. Initially HAE-nl-C1INH was referred to as “estrogen dependent” and thought to only affect women. A number of women with HAE-nl-C1INH have

been described who only swell during states of increased estrogen exposure, including pregnancy or the use of estrogen-containing medications such as birth control pills or hormonal replacement therapy [26, 27]. While males with HAE-nl-C1INH have now been clearly identified, the overall severity of disease remains characteristically worse for affected women.

In contrast, testosterone and related male sexual hormones appear not to have a deleterious impact on HAE symptoms. Further the 17-alklylated anabolic androgens such as danazol have a striking positive effect of decreasing the number and severity of HAE attacks in both men and women. Before the development of specific effective treatments for HAE, 17-alpha-alkylated androgens were the mainstay of HAE treatment. While undeniably effective, these anabolic androgens have substantial side effects making their use relatively contraindicated in women and children and limiting their usefulness in men [28, 29]. Anabolic androgens reduce male fertility by suppressing hypothalamic secretion of gonadotrophins, decreasing endogenous testosterone synthesis and spermatogenesis [30].

The impact of progesterone, synthetic progestins, or antigonadotropic progestins on HAE-C1INH is less straightforward. Some of the progestins have androgenic effects, which might be relevant to their effects on HAE-C1INH [31]. In one study, elevated progesterone levels significantly correlated with increased number of attacks, although the progesterone levels were also correlated with estrogen levels [32]. Exogenous progestin or progesterone does not appear to worsen HAE-C1INH and may provide some prophylactic benefit. A small double-blind trial of medroxyprogesterone 60–80 mg/day had no significant effect on attack frequency compared to placebo, although the attacks were perceived as possibly milder [1]. Another retrospective patient survey reported that 9 of 14 HAE-C1INH women reported improvement in their HAE on a progestin-only pill [25].

In contrast, the use of exogenous progestins has been repeatedly shown to improve symptoms in women with HAE-nl-C1INH. In a study of 19 HAE-nl-C1INH patients, prophylactic treatment with progestins resulted in improvement in the large majority of patients [33]. Ten of 13 patients treated with progestin-only pills improved, while 2 patients noted worsening of their angioedema. Thirteen of 15 patients treated with antigonadotropic progestin agents experienced improvement with the remaining two subjects reporting no change in their angioedema. The antigonadotropic progestins are derivatives of normethyltestesterone and may therefore have androgenic effects contributing to their efficacy.

## *Mechanisms of Sex Hormone Impact on Generation of Bradykinin*

Swelling in HAE is thought to be mediated by bradykinin, generated through activation of the plasma contact system (Fig. 9.2). Sex hormones may interact with the kallikrein-kinin system at multiple levels. Oral contraceptives containing estrogen have been long known to cause a prothrombotic state balanced by increased

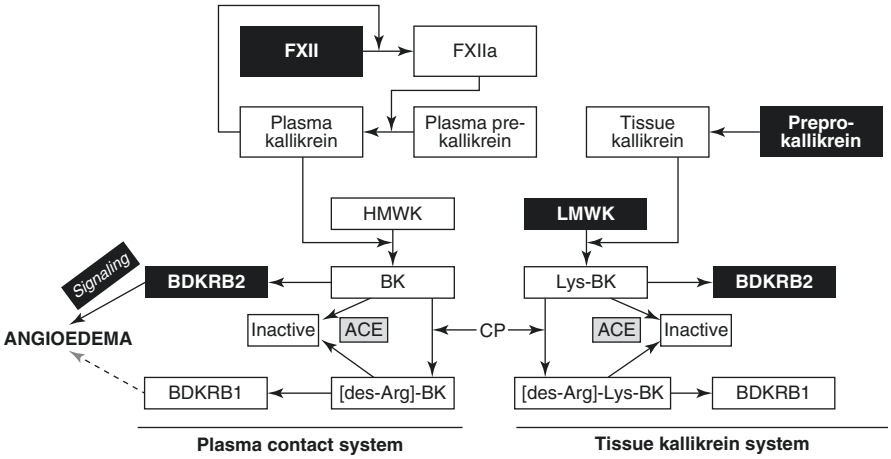


**Fig. 9.2** Molecular effects of estrogens on the kallikrein-kinin system. The components of the plasma contact system and tissue kallikrein system are schematically illustrated. Proteins and effects that are increased by estrogens are shown as black boxes or thick black lines. Proteins that are reduced by estrogen are shown as gray boxes. Abbreviations used: ACE angiotensin converting enzyme, BK bradykinin, BDKRB2 bradykinin B2 receptor, BDKRB1 bradykinin B1 receptor, CP carboxypeptidase, HMWK high molecular weight kininogen, LMWK low molecular weight kininogen

activation of the fibrinolytic system [34–37]. The best described interaction is an increase in FXII expression by 17β-estradiol based on an estrogen-responsive element in the promoter region of the F12 gene [38–40].

Estrogens may exert other effects on the kallikrein-kinin system. Signaling through the estrogen receptor has been shown to enhance responses to bradykinin *in vitro* and *in vivo*, possibly mediated by the effect of 17β-estradiol on integrins [41]. Long-term hormonal replacement therapy with conjugated estrogens (0.625 mg/day) and medroxyprogesterone (2.5 mg/day) was shown to decrease the serum level of angiotensin-converting enzyme (ACE), the primary bradykinin-degrading enzyme, with resultant increases in bradykinin levels [42]. Furthermore, estrogens have been shown to enhance the expression of bradykinin B2 receptor [43]. Estradiol also heightens the release of the prekallikrein activator, heat shock protein 90 (HSP90) [44].

Estrogen exposure increases the expression of both low molecular weight kininogen (LMWK) and tissue kallikrein [45, 46], which are components of the tissue kallikrein system. The tissue kallikrein system generates Lys-bradykinin, a kinin peptide with an additional lysine residue at the N-terminus. Lys-bradykinin has similar actions as bradykinin; however there is no evidence implicating the tissue kallikrein system in the mediation of angioedema. Estrogen does not regulate the expression of HMWK [47], which is the kininogen substrate for kinin generation in HAE.

In contrast to estrogens, androgens appear to diminish disease severity in HAE. While the mechanism remains unclear, treatment with high doses of 17α-alkylated androgens leads to increased plasma levels of C1INH [48]. Androgens also appear clinically beneficial at doses that do not increase C1INH levels.

Androgens have further been reported to increase the levels of aminopeptidase P, a kininase that is involved in the degradation of bradykinin [49].

## HAE and Pregnancy

### *The Impact of Pregnancy on HAE Severity*

Attack frequency during pregnancy is highly variable, and symptoms may worsen, improve, or not change during gestation [1, 50–53]. The clinical picture is clouded by the potential for pregnancy-associated symptoms being misinterpreted as angioedema attacks and vice versa. Some studies report that attack frequency is the highest during the first trimester of pregnancy [1, 54]. Frank et al. reported that 23 of 25 pregnancies in 10 women were associated with a marked diminution of attacks during the last two trimesters [1]. Another series of 118 pregnancies involving 41 women reported that the attack frequency increased in 48%, decreased in 33%, and did not change in 19% [51]. In this study, the greatest number of attacks occurred during third trimester of pregnancy, a trend that was most clearly seen when the fetus turned out to have HAE. They also found that pregnancy was associated with an increased ratio of abdominal to extremity attacks compared to the period before the pregnancy. Another study followed 35 pregnancies in 22 women [52]. They found an increase in the number of attacks in 29 of the 35 pregnancies, with attack rates increasing progressively with each trimester. The mean number of attacks per 9 months went from 9.4 ± 10.5 before pregnancy to 44.0 ± 38.0 during pregnancy. In this series, no relationship was identified between attack frequency during pregnancy and whether the fetus had HAE, although the level of functional C1INH trended lower in women whose babies had HAE. In women who experience multiple pregnancies, the impact may vary, but typically each has a similar influence on disease severity [51].

The disparate findings summarized above highlight that the clinical course of HAE during pregnancy for any given patient is unpredictable and that the physician needs to be prepared for any contingency (see management below). The mechanisms responsible for the pregnancy related severity variability between patients or even for the same patient are unknown. Plasma C1INH levels are known to decrease during pregnancy due to the volume expansion [55]. Pregnancy is obviously associated with marked fluctuations in hormonal levels (see above section).

While most of our information regarding pregnancy and HAE is derived from studies of HAE-C1INH patients, pregnancy has been frequently reported to precipitate angioedema attacks in women with HAE-nl-C1INH. Indeed, as alluded to in the discussion of classification, multiple women have been described who only experience HAE-nl-C1INH attacks during pregnancy or other high estrogen states [56].

### *The Impact of HAE on Pregnancy*

If severe, angioedema attacks themselves could result in obstetric complications. In addition to its effect of increasing vascular permeability to cause angioedema, bradykinin also induces uterine smooth muscle contraction. There is no clinical evidence that HAE itself has a detectable negative impact on fertility or pregnancy. Rates of spontaneous abortion, sterility, polycystic ovarian disease, and fibroids are the same among women with HAE and the general population [25, 51]. One study reported an increase in the rates of spontaneous abortions and premature labor in women with HAE compared to their healthy relatives [57]. FXII levels are often low in HAE due to consumption. Low FXII levels in non-HAE patients have been shown to be associated with premature delivery at <34 gestational weeks and recurrent pregnancy loss [58, 59].

## Management of HAE During Pregnancy

HAE treatment is conceptually divided into two distinct strategies: (1) stopping attacks as quickly as possible once a patient has begun swelling (on-demand treatment) and (2) preventing or minimizing the number and severity of attacks in the future (prophylactic treatment). The treatment of HAE has been recently reviewed [60]. All HAE patients should have easy and rapid access to an effective on-demand treatment. Determining selection of which patients should be on long-term

**Table 9.1** Licensed HAE medications and use in pregnancy

| Drug | Mechanism | Primary indication | Use in pregnancy | References |
|---|---|---|---|---|
| Antifibrinolytics | Inhibit activation of plasmin | Prophylaxis in HAE-nl-C1INH | Limited experience, crosses the placenta; avoid if possible | [86–88] |
| Berinert | pdC1INH, replaces C1INH | On-demand treatment | Not proven safe but reasonable to use | [51, 52, 61–63] |
| Cinryze | pdC1INH, replaces C1INH | Prophylaxis | Not proven safe but reasonable to use | [51, 52, 61–63] |
| Danazol | 17α-alkylated androgen; mechanism uncertain | Prophylaxis | Contraindicated | [28, 75–77] |
| Ecallantide | Plasma kallikrein inhibitor | On-demand treatment | Unknown; best to avoid | No reports |
| HAEGARDA | pdC1INH, replaces C1INH | Prophylaxis | Not proven safe but reasonable to use | [51, 52, 61–63] |
| Icatibant | Bradykinin B2 receptor antagonist | On-demand treatment | Limited experience; best to avoid | [72–74] |
| Ruconest | Recombinant human C1INH, replaces C1INH | On-demand treatment | Unknown | No reports |

prophylactic treatment is more subjective and needs to be individualized. Table 9.1 shows all of the currently licensed drugs used to treat HAE.

During pregnancy, questions about fetal safety limit the drugs used to treat HAE. Plasma-derived C1INH concentrates are frequently used and appear to be safe during pregnancy in patients with HAE-C1INH [51, 52, 61–63]. C1INH concentrates have been suggested to increase the risk of thromboembolism [64], although multiple reports have questioned this finding [65–70]. In fact, pdC1INH was used safely during pregnancy in a HAE patient who also had concomitant thrombophilia due to a methylene tetrahydrofolate reductase mutation [71]. As shown in Table 9.1, C1INH can be used for both on-demand and prophylactic indications. In general, all women with HAE should be eligible to receive on-demand C1INH during pregnancy. The need for long-term prophylaxis with C1INH during pregnancy must be individualized and should take into account HAE severity, comorbid conditions, pregnancy-related risk, and patient preference. If C1INH concentrates are not available, fresh frozen plasma (FFP) can be used to treat HAE attacks with the caveat that FFP administration has also been associated with acceleration of attack severity.

The safety of the other on-demand HAE medications (ecallantide and icatibant) during pregnancy is not known, and therefore these medications should usually be avoided. There are a small number of reports of icatibant being used to treat HAE attacks during pregnancy. Farkas et al. reported a type II HAE patient who received five treatments with icatibant during the first 6 weeks of gestation, ultimately delivering a healthy baby [72]. Kaminsky reported another woman with HAE-nl-C1INH who used icatibant repetitively during three separate pregnancies [73]. All three pregnancies resulted in normal babies, although one of them was 1-month preterm. Administration of a bradykinin B2 antagonist has, however, been shown to impair gestational outcomes in experimental animals [74].

The 17α-alkylated androgens cross the placenta and are generally considered contraindicated during pregnancy due to the risk of masculinizing the fetus and other harmful effects [75–77]. Anabolic androgens are relatively contraindicated in women and children, irrespective of pregnancy status [28]. The antifibrinolytic drugs are believed to cross the placenta, but the risks of using these drugs for prophylactic treatment of HAE during pregnancy are unknown and should be approached with caution. Because 17α-alkylated androgens and antifibrinolytics may also be present at significant concentration in breast milk, their use during breastfeeding is also discouraged.

C1INH concentrates have been tried in some HAE-nl-C1INH patients during pregnancy [78, 79]. Since these patients by definition have normal C1INH levels, the rationale for this treatment requires additional consideration. One such rationale is to boost the C1INH level to a supraphysiologic range in order to decrease the likelihood of contact system activation; however, there is no evidence that this explanation is valid. During attacks of angioedema, active kallikrein can cleave C1INH into an inactive 94 kD protein [80]. Evidence of C1INH cleavage during pregnancy in a patient with HAE-nl-C1INH has been published [81]. This implies that during attacks or in patients with frequent attacks, HAE-nl-C1INH patients may become temporarily deficient in functional C1INH. Administration of pdC1INH for attacks in two pregnant HAE-FXII women resulted in rapid improvement [78]. A prospective open-label study was recently reported in which three

HAE-nl-C1INH patients were treated with prophylactic pdC1INH during pregnancy [79]. All three subjects suffered from frequent attacks during their pregnancies. Two of the subjects were diagnosed with HAE-FXII. One subject with HAE-FXII was having weekly angioedema attacks. She was started on intravenous pdC1INH 1000 IU/week starting at 20 weeks. On this regimen, her attacks became milder and less frequent, reduced to approximately once per month. A second HAE-FXII subject was also having weekly attacks. Starting at week 32, she was treated with 1000 IU pdC1INH twice weekly with no further attacks. The third subject was diagnosed with HAE-unknown. She was experiencing two attacks per week and was started on pdC1INH 1000 IU twice weekly beginning at week 27. On this regimen she had no further attacks. All three subjects delivered normal healthy babies.

## HAE During Labor and Delivery

A striking and unexpected finding is that angioedema attacks are rare during labor and delivery in women with HAE [1]. While physical trauma is frequently recognized as a precipitating factor for HAE attacks, this doesn't appear to apply to labor and delivery. The reason for this difference remains uncertain. Starting about 48 h after delivery and continuing through the remainder of the puerperium, women frequently experience increased HAE attacks [51]. Given the risks of a severe abdominal or airway attack in the puerperium, it is generally recommended that HAE patients give birth in a medical facility with on-demand medications available if needed. Close coordination with the obstetrician is required. Short-term prophylaxis with C1INH concentrates should be considered when pregnant HAE patients require surgery, such as for a Caesarean section. Short-term prophylaxis prior to vaginal delivery may also be considered in women with a strong history of trauma-induced swelling or when a forceps delivery is anticipated. An increase in HAE attacks during breast-feeding has been observed [52, 54].

## Testing of Newborn for HAE

Each child of a parent with HAE has a 50% chance of inheriting the *SERPING1* mutation. Considering the risk of morbidity and mortality associated with HAE as well as the safe and effective treatments now available, it is crucial to establish whether the child has HAE as soon as possible. If the specific genetic mutation is known, the newborn can be tested for the presence or absence of that mutation. The diagnosis cannot be reliably established by measuring C1INH or C4 levels in newborns because the complement levels in newborns are variably reduced [82]. C4 levels reach near adult levels by 6 months to 1 year of age, at which time testing becomes practical [83].

## Prenatal Genetic Diagnosis

Prenatal diagnosis of HAE can be performed either in established pregnancy or preimplantation [84]. In both cases, the genetic mutation of the affected parent must be known prior to the testing. Since the reason to perform either of these procedures would be to avoid having a child with HAE, the recent advances in treatment of HAE (reviewed in [85]) make the need for these procedures ethically questionable.

## Conclusion

Pregnancy and use of exogenous sex hormones have potentially profound effects of both HAE-C1INH and HAE-nl-C1INH. In addition, many of the medications used to treat HAE are inadvisable for use in pregnant women. All clinicians caring for patients with HAE should be aware of the mechanisms by which sex hormones influence disease expression and the variable impact of pregnancy on the clinical course. Individualized treatment plans are essential during this vulnerable time for the mother and fetus. Fortunately, we now have effective and safe therapy to provide for women during pregnancy for the management of their HAE.

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# Chapter 10
# Drug Hypersensitivity

**Eric Macy**

## Abbreviations

| | |
|---|---|
| Cdiff | *Clostridium difficile* |
| DRESS | Drug eruption with eosinophilia and systemic symptoms |
| EHR | Electronic health record |
| GBS | Group B *Streptococcus* |
| MCM | Major congenital malformation |
| MRSA | Methicillin-resistant *Staphylococcus aureus* |
| SCARs | Serious cutaneous adverse reactions |
| SJS | Stevens-Johnson syndrome |
| Tdap | Tetanus diphtheria acellular pertussis |
| TEN | Toxic epidermal necrolysis |

## Introduction

Drug intolerance, usually labeled as drug *allergy* in the electronic medical record (EHR), is no more common in pregnant women than in other populations, corrected for age and gender. Most drug intolerance reports occur after an adverse drug reaction has occurred and are frequently mislabeled as *allergy*, because such patients will frequently acutely tolerate the drug upon re-exposure. Some drug intolerances are listed because of feared concerns, underlying medical conditions or genotypes, or after occurrence of expected drug-associated side effects. All medications are associated with adverse reactions, but only a small minority are hypersensitivity reactions that are mediated by the immune system in an antigen-specific manner

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and/or via direct or indirect mast cell activation. Immune system, B-cell, T-cell, complement, and/or mast cell-mediated, amplification of the reaction, often only requiring a sub-therapeutic drug exposure, is the hallmark of drug hypersensitivity.

The word allergy should be restricted to describe drug intolerances or adverse drug reactions that are confirmed to be both acute-onset and specifically IgE-mediated. The term hypersensitivity should be used to include all acute- or delayed-onset immunologically mediated, complement-mediated, or mast cell-mediated reactions, because with these reactions, even with a very small exposure of the implicated drug, serious systemic adverse reactions can result. This is in distinction to dose-dependent side effects or toxicities mediated through other pharmacologic mechanisms, generally only occurring with full-dose and/or prolonged exposures. Metabolic, pharmacologic, or other disease-specific-related drug intolerances, such as quinolone or sulfonamide antibiotics in glucose-6-phosphate dehydrogenase deficiency causing hemolytic anemia, high-dose nonsteroidal anti-inflammatory drugs in chronic urticaria amplifying angioedema, anticholinergic drugs in myasthenia gravis worsening muscle strength, or angiotensin-converting enzyme inhibitors causing bradykinin-mediated angioedema, should be specifically labeled as such in the drug intolerance section of the EHR.

The management of drug hypersensitivity during pregnancy is very much like the management of drug hypersensitivity in any patient. There are several specific groups of medications and medical procedure-associated antigens specifically relevant or important in the setting of pregnancy that will be discussed in detail.

## Epidemiology and Documentation

Ohel and coworkers from Israel in 2010 reported on a cohort of 186,443 deliveries and noted that 8647 (4.6%) of the mothers reported at least one drug *allergy* [1]. As expected, having any drug *allergy* was associated with advanced maternal age and age-related comorbidities including recurrent abortions, fertility treatments, hypertension, and diabetes. In their multivariate analysis, they noted that any drug *allergy*, and specifically penicillin *allergy*, was associated with increased risks of intrauterine growth restriction and preterm deliveries.

Desai and coworkers in 2017 reported on a cohort of pregnant women cared for by Kaiser Permanente in Southern California, representing about 1% of the US population over a 6-year period [2]. They noted about 70 total reported drug *allergies* for every 100 pregnant women and that about 9% carried a specific penicillin *allergy* label.

The vast majority of individuals with any reported drug *allergy* will actually tolerate the drug upon re-exposure [3]. Nash and coworkers reported in 2015 on the low accuracy of and poor documentation of drug hypersensitivity and adverse drug reactions in pregnancy handheld records in Australia [4]. Nesin and Sparer discussed in 2015 on expanding the existing vaccine monitoring systems to include all drug use in pregnant women [5]. This would greatly improve data collection and

help identify adverse drug reactions seen during pregnancy. Blumenthal and Macy discussed in 2016 the importance of improving the documentation in the EHR of adverse drug reactions, drug hypersensitivity, and drug intolerance to enable more effective management and lower the risk to the patient [6].

## General Considerations

Most reported drug *allergies* in the EHR are not drug hypersensitivity and are not reproducible upon rechallenge [3]. Multiple (more than two), non-related drug *allergies* in a single patient does not increase the probability of any of them being immunologically mediated [7]. Mild reactions do not always progress to more severe reactions [8]. Many cases of anaphylaxis have no history of any previous hypersensitivity [9]. True anaphylaxis and SCARs are extremely rare and frequently overdiagnosed [10, 11]. Reactions occur more commonly with parenteral compared to oral drug administrations [11]. Reactions occur with all drug exposures at predictable rates [12]. There is no such thing as a risk-free drug exposure. Reactions to drugs will still occur at predictable rates after all negative tests and challenges [13]. When evaluating pregnant women with drug *allergies*, it is important to determine the potential mechanism(s) of the historical reaction, is the drug really needed, is an alternative safer than re-exposure, and is avoidance more dangerous than testing and/or rechallenge.

## Mechanisms

Drug hypersensitivity can be clinically grouped in four general categories noted in Table 10.1. Management of drug hypersensitivity reactions is based on these four clinical presentations. It is essential to have enough supporting information in the drug "allergy" field of the EHR to know which of these four categories best fits the clinical history of the adverse drug reaction [6]. The management options for drug hypersensitivity are outlined in Table 10.2. Desensitization is only possible to drugs that cause IgE-mediated mast cell activation, IgG and complement-mediated mast cell activation, direct complement-mediated mast cell activation, or direct mast cell activation. It is not possible to desensitize any T-cell-mediated reactions, though, if the benefits outweigh the risks, rechallenge is sometime clinically appropriate with benign T-cell-mediated reactions. The management of non-hypersensitivity adverse drug reaction events, such as yeast or *Clostridium difficile* (Cdiff) infections after antibiotic use, nausea or vomiting, bleeding, tinnitus, headaches, acute tubular necrosis, and other somatic symptoms not potentially mediated though an immunologic mechanism or via direct or indirect mast cell activation are beyond the scope of this chapter.

**Table 10.1** Clinical categories of drug hypersensitivity

| Type (examples) | Mechanisms | Time to onset | Clinical features |
|---|---|---|---|
| Acute-onset benign (Allergy) | IgE<br>IgG and complement<br>Direct mast cell activation | Minutes to 4 h, but with a new sensitization up to several weeks | Hives<br>Other benign rashes |
| Anaphylaxis (Allergy) | IgE<br>IgG and complement<br>Direct mast cell activation<br>Direct complement activation by nanoparticles | Minutes to up to 4 h, but typically less than 30 min | Hypotension<br>2 or more organ systems involved<br>Elevated serum tryptase |
| Delayed-onset benign (Contact dermatitis) (Serum sickness) (Serum sickness-like) | T-cells | More than 4 h, but typically 2–5 days | Maculopapular rashes |
| | | | Blistering rashes |
| | IgM and complement | 7–14 days | Rashes and arthralgias |
| Serious systemic (SCARs) (DRESS) (SJS) (TEN) | T-cells<br>IgG and complement | More than 4 h, sometimes within 2–5 days, and often up to 2–3 weeks | Blistering rashes<br>Desquamation<br>Eosinophilia<br>Hepatitis<br>Nephritis<br>Hemolytic anemia or cytopenia |

*Abbreviations: SCAR* serious cutaneous adverse reaction, *DRESS* drug reaction with eosinophilia and systemic symptoms, *SJS* Stevens-Johnson syndrome, *TENL* toxic epidermal necrolysis

**Table 10.2** Drug hypersensitivity management options

| Option | Underlying mechanism |
|---|---|
| Continued absolute avoidance | Any SCAR or serious systemic reaction<br>Serum sickness or serum sickness-like reactions |
| Skin testing for IgE- mediated allergy, and, if negative, rechallenge | Acute-onset benign reactions<br>Anaphylaxis |
| Direct rechallenge | Acute-onset benign<br>Delayed-onset benign isolated rashes |
| Skin testing for IgE-mediated allergy and, if positive, desensitization | Acute-onset benign reactions<br>Anaphylaxis |
| Direct desensitization | Anaphylaxis |
| Patch testing for T-cell-mediated contact dermatitis and, if negative, rechallenge | Delayed-onset benign isolated rashes |

## Specific Medications, Materials, and Clinical Situations Associated with Hypersensitivity Reactions

### *Antibiotics*

Penicillins should be used in pregnant women, whenever indicated and possible, along with first- and second-generation cephalosporins, because of their overall safety profile, if there is no documented hypersensitivity or other contraindication [14]. Third- and higher-generation cephalosporins, though also relatively nontoxic, are unfortunately associated with an up to 3% chance of inducing *Clostridium difficile* (Cdiff) within 90 days of each use [11]. Metronidazole and nitrofurantoin are generally considered safe for use during pregnancy.

Aminoglycosides are generally not recommended in pregnancy because they are associated with increased risk of nephrotoxicity and ototoxicity. Clindamycin is associated with an increased risk of Cdiff. Tetracyclines can cause milk tooth discoloration in infants after maternal exposure in the third trimester. Quinolones are associated with direct mast cell activation as well as the tendon, muscle, joint, and central nervous system side effects, and these risks typically outweigh the benefits for treatment of acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections. Sulfonamide antibiotics are second-line agents for use in pregnancy and have the highest rash rate of all antibiotics [12]. Co-trimoxazole is however the drug of choice in most methicillin-resistant *Staphylococcus aureus* (MRSA) infections. Clindamycin, doxycycline, quinolones, and macrolides are also generally contraindicated in pregnancy because they are associated with increased risks of major congenital malformations (MCM) [15]. This same large study of 139,938 singleton infants, born in Quebec between 1998 and 2008, showed no increased risk of MCM with amoxicillin, other penicillins, cephalosporins, or nitrofurantoin.

#### Penicillins

Mylonas wrote in 2011 that penicillins and cephalosporins are the safest antibiotics for use in pregnancy and should be first line whenever possible but neglected to mention the importance of penicillin allergy testing [14].

Desai and coworkers reported in 2017 on a cohort of 170,379 unique women, who had 201,316 pregnancies, from 2009 to 2014. They noted that an unconfirmed penicillin *allergy* in pregnant women was associated with more hospital utilization and additional peripartum morbidity [2]. Women with a penicillin *allergy*, with or without group B Streptococcus (GBS), had significantly increased (~10% higher), cesarean section rates and spent significantly more days (~0.1 more), in the hospital after delivery. GBS-positive women with an unconfirmed penicillin *allergy* were exposed to significantly more cefazolin, clindamycin, vancomycin, and gentamicin and had significantly higher rates of adverse drug reactions associated with all antibiotic use.

Penicillin allergy testing can be safely performed in pregnant women. Macy reported in 2006 on a cohort of 56 penicillin *allergic* GBS-colonized pregnant women with a history of penicillin allergy, tested between August 2002 and August 2004, and only 3 (5%) were skin test positive [16]. There were only two delayed-onset rashes noted among the 47 (89%) who received an intrapartum penicillin and one immediate-onset rash associated with vancomycin use in a penicillin skin test positive woman. There were also 23 courses of cephalosporins administered to this cohort, with no rashes noted. Philipson and coworkers in 2007 reported on a cohort of 28 GBS colonized women with penicillin *allergy*, 25 (89%) of whom had negative penicillin skin testing and then received intrapartum penicillin without any adverse reactions [17].

May and coworkers at the Mayo Clinic reported in 2016 that the use of penicillin in the peripartum period for GBS treatment was not associated with an increased rate of penicillin *allergy* in children [18]. They followed a cohort of 804 children born in 2007 for at least 3 years.

Penicillin is the drug of choice for syphilis therapy. Hori and coworkers in 2015 reported on an infant presenting with a Jarisch-Herxheimer reaction at birth after his mother was given ampicillin just prior to delivery [19]. She had not had prenatal testing for syphilis. The infant had normal vital signs but had conjunctivitis, hepatosplenomegaly, and a total body blistering and maculopapular rash. The blisters were up to 1 cm. The infant was given parenteral ampicillin for 14 days. He suffered a fever, tachycardia, and tachypnea after the first injection. The maculopapular rash improved after a day and resolved in 3 days. The mother did not have any adverse reaction associated with her syphilis therapy.

Rac and coworkers in 2017 reported on the treatment of syphilis in pregnancy [20]. They noted that Jarisch-Herxheimer reactions occurred in up to 44% of pregnant women treated antepartum. They recommended penicillin therapy for all pregnant women with syphilis, specifically recommending desensitization, but interestingly also did not mentioning penicillin allergy testing to confirm a clinically significant penicillin allergy.

## Cephalosporins

Cephalosporins are widely, safely, and appropriately used in pregnant women with an unconfirmed penicillin *allergy* [11]. If a woman has an *allergy* to one cephalosporin, treatment with another, ideally with different side chains, is acceptable. Briody and coworkers reported in 2016 on the safe and appropriate use of cefazolin for GBS prophylaxis in pregnant women who reported an unconfirmed penicillin *allergy* [21]. Out of a cohort of 165 GBS-positive pregnant women, they found that 92 (55.8%) received an inappropriate antibiotic. They discussed the importance of confirming a clinically significant penicillin hypersensitivity. They concluded that in the absence of a history of anaphylaxis, cefazolin was the drug of choice, if penicillin allergy testing had not been performed.

### Metronidazole

Metronidazole is very unlikely to induce IgE-mediated or T-cell-mediated hypersensitivity and does not directly activate mast cells. Rechallenge in the setting of suspected hypersensitivity is generally successful [3].

### Nitrofurantoin

Nitrofurantoin has been associated with serious pulmonary and hepatic injury, and rechallenge in these settings is contraindicated. Benign acute- or delayed-onset rashes can be safely rechallenged [3].

## *Anti-D Immunoglobulin*

Rare cases of RhD immunoglobulin G (anti-D)-associated acute-onset hypersensitivity have been reported, but these are rarely confirmed as truly IgE-mediated by skin testing [22]. They can be managed by administering the needed anti-D in divided doses, 10%, 30%, and then the final 60% at 30-min intervals.

## *Contact Sensitizers*

Delayed-onset, T-cell mediated, contact dermatitis is very commonly seen in pregnant women. Hair dyes, sunscreens, cosmetics, and jewelry are several of the more common materials that can contact sensitize. There are several thousand chemical entities that can contact sensitize humans. With a single exposure, a rash is seen 2–5 days later and may last 4–6 weeks. The goal is avoidance of the contact sensitizer and then treatment of the T-cell-mediated rashes with several weeks of topical or systemic corticosteroids to allow new skin to grow out without the foreign antigen present. Patch testing can be safely performed in pregnant women if needed, but ideally topical exposures are avoided as much as possible. It is safe to use Dove® bar soap, any baby shampoo, and Eucerin® moisturizing cream, if needed, s these materials are very unlikely to contact sensitize. After the initial episode has completely cleared, off steroids, then if no more than one new contact exposure is made during any 1 week, the next material restarted prior to the next reoccurrence is the contact sensitizer.

### Povidone

Topical povidone can induce delayed-onset T-cell-mediated contact dermatitis. Patch testing is available to confirm. Alternative skin cleaning agents can be used.

### Oral Iodine

Excessive oral iodine ingestion associated with iodinated multi-vitamin use has been noted to result in iododerma, a pustular acneiform eruption with pathology compatible with a T-cell-mediated contact dermatitis [23].

### Topical Antibiotics

Topical antibiotics, including neomycin, polymyxin, gentamicin, and others, can induce delayed-onset T-cell-mediated contact dermatitis. Patch testing is available to confirm. Contact sensitivity to neomycin is not a contraindication to receiving a vaccine with a small amount of neomycin in it.

### Medical Adhesives

A variety of medical adhesives, specifically bandages and monitor pads, have been shown to induce delayed-onset T-cell-mediated contact dermatitis. Patch testing is available to confirm.

## *Local Anesthetics*

Local anesthetics are virtually never confirmed as a cause of IgE-mediated allergy. Rare individuals have been identified that are skin test positive to methylparaben, a common preservative in multi-dose lidocaine vials [24]. Acute tolerance in pregnant women can be safely confirmed by using prick and intradermal skin testing with lidocaine 1% with methylparaben 0.1% and then, if skin test negative, a deep subcutaneous challenge with 1 ml of lidocaine. Local anesthetics, used topically, can induce delayed-onset T-cell-mediated contact dermatitis. Lidocaine patch test positive individuals can safely tolerate subcutaneous lidocaine needed for local anesthesia with a very low risk of any clinically significant delayed-onset rashes.

## *General Anesthetics*

The incidence for intraoperative anaphylaxis varies from about 1 in 6000 in Norway to about 1 in 34,000 in the United States. The rates specifically associated with labor and cesarean section anesthesia are on the low end of the range, about 3 in 100,000 [25]. Agents most commonly associated with labor and cesarean section anaphylaxis are latex, parenteral antibiotics, uterotonics, and colloids [26]. Skin testing is available to confirm IgE-mediated acute-onset hypersensitivity to neuromuscular blocking agents and propofol [25].

## *Hormones*

### Corticosteroids

Clinically significant acute-onset hypersensitivity is extremely uncommon with any corticosteroid use. If there is concern, systemic corticosteroid acute tolerance can be safely confirmed by either an oral prednisone 5 mg challenge or a deep subcutaneous 1 mg triamcinolone and 1 h of observation. Delayed-onset topical steroid-associated rashes are rarely confirmed as T-cell mediated. Practically, just select another topical steroid preparation and treat as clinically indicated.

### Gonadotropins

Non-gonadotropin protein contaminants in urine-derived gonadotropins have been implicated as a cause of IgE-mediated acute-onset hypersensitivity, initially suspected to be from gonadotropins [27]. Recombinant follicle-stimulating hormone, luteinizing hormone, and human chorionic gonadotropin, which lack these contaminating proteins, are better tolerated [28].

### Insulin

True clinically significant IgE-mediated human insulin allergy is extremely rare but more common in individuals with early-onset autoimmune type 1 diabetes than in individuals with gestational diabetes. Human insulin allergy can be managed by continuous subcutaneous insulin infusion [29]. The presence of antihuman insulin IgE can be confirmed by commercially available in vitro testing.

### Oxytocin

Rare cases of oxytocin-associated anaphylaxis have been reported [30]. Oxytocin and vasopressin have also been implicated as cofactors in latex-associated anaphylaxis [31].

### Progesterone

Autoimmune progesterone dermatitis is a rare hypersensitivity reaction, typically associated with fluctuations in endogenous progesterone with the menstrual cycle, but can also be associated with exogenous hormone therapy [32]. Only 89 cases had been reported on through 2016 in 66 papers, with a mean age of onset of 27.3 years [33]. Only three cases have been reported to date associated with progesterone used for in vitro fertilization. The usual diagnostic test is a delayed-onset response at 24–48 h to a progesterone intradermal skin test using 0.05 mls of 0.01–1% or after intramuscular administration of 12.5–25 mg. The oil vehicle was implicated in one

case of apparent progesterone hypersensitivity [34]. The patient was intolerant of progesterone in sesame oil but tolerated progesterone in peanut oil.

#### Prostaglandins

Misoprostol (prostaglandin $E_1$) and dinoprostone (prostaglandin $E_2$) have been rarely implicated as a cause of anaphylaxis. The mechanism(s) is (are) unknown [35–37].

### *Heparins*

There is a higher incidence of heparin-induced delayed-onset hypersensitivity in pregnant women, 19.8% (95% CI 13–29%), compared to 10.3% in nonpregnant women [38]. Danaparoid was generally well tolerated in 49 women with unfractionated heparin-associated thrombocytopenia or delayed-onset rashes [39]. Low molecular weight heparins are still frequently associated with delayed-onset T-cell-mediated cutaneous reactions during pregnancy. Nadroparin had the highest rate, about 65% at 100 days, and should be avoided in pregnancy. Dalteparin was much safer. Risk factors include previous low molecular weight heparin use or inherited protein C deficiency [40]. The pragmatic approach is just to switch to another low molecular weight heparin [41]. Fondaparinux has been tolerated in pregnant patients with protein S deficiency, who also had heparin and danaparoid hypersensitivity [42]. It can also be used if low molecular weight heparins are not tolerated [43].

### *Iron Parenteral*

Parenteral iron preparations are associated with rare cases of acute-onset hypersensitivity, thought to be secondary to nanoparticles inducing direct complement activation [44]. Management is to select an alternative preparation. Even though iron sucrose is generally associated with the lowest adverse reaction rate, a rare case of fatal anaphylaxis with possible secondary acute coronary syndrome has been reported [45, 46].

### *Proteins*

#### Bovine Serum Albumin

Systemic or mucus membrane exposure to intact foreign proteins always has the risk of acute-onset IgE-mediated hypersensitivity. This can occur with pollens, dust mite, cat saliva and with peanut or other food proteins. Rare cases of IgE-mediated

anaphylaxis to bovine serum albumin in tissue culture media used for in vitro fertilization have been recurrently reported over the past 25 years [47–49]. Similar reactions are also possible with all therapeutic recombinant therapeutic human and humanized proteins.

### Human Seminal Plasma

Mucosal membrane exposure to proteins in human seminal plasm in sensitized individuals can result in acute-onset IgE-mediated hypersensitivity. The major antigen is believed to be a prostate-specific protein [50]. Interestingly, infertility has not been demonstrated to be related to human seminal plasma hypersensitivity. The reference standard test for diagnosis is tolerance of intercourse using condoms in suspected cases. Intrauterine insemination with washed sperm can still result in a significant acute-onset hypersensitivity reaction, but pregnancy still occurs [51].

### Latex

The prevalence of clinically significant IgE-mediated allergy to proteins in natural rubber latex products is currently at least an order of magnitude rarer than in the late 1980s [52]. Rare cases of latex glove-associated anaphylaxis were reported in 2002 [53]. All women with a history of an unconfirmed latex *allergy* should have a commercially available in vitro anti-latex IgE test done. If positive, avoidance of large surface area exposure to natural rubber latex protein containing materials, such as could occur with surgical gloves, rubber dams, or large balloons is essential. Potential exposure to a minute amount of natural rubber latex protein in a rubber vaccine bottle stopper would not be clinically significant. Sensitization to latex does not preclude IgE-mediated allergy to other materials such as oxytocin, and a putative cross-reaction between latex and oxytocin has been speculated [54, 55].

## *Laminaria*

Acute-onset hypersensitivity and anaphylaxis have been rarely associated with laminaria use [56]. There is no practical skin testing protocol. Synthetic, faster-acting, polyacrylate-based hydrogel rods (Dilapan-S) can be used as a safe alternative.

### Vaccines

Clinically significant immunologically mediated vaccine reactions are extremely rare, with anaphylaxis occurring in only about 1.3 in 1,000,000 exposures [57]. Delayed-onset local swelling at the site of the vaccination, potentially from

vaccine-related T-cell activation, is very common. Local swelling has been documented to occur in up to two-thirds of pregnant women after tetanus diphtheria acellular pertussis (Tdap) vaccinations and is not a contraindication to any needed future vaccinations [58]. Suspected hypersensitivity to any vaccines can usually be evaluated by skin testing with the vaccine and/or managed by administering the needed vaccine(s) in divided doses.

### Opiates

Most natural opiates, including codeine and morphine, are effective direct mast cell activators [59]. Many of the semisynthetic opiates, such as fentanyl or sufentanil, cause very little direct mast cell activation [60]. Opiates have not been shown to induce delayed-onset hypersensitivity. If a patient has noted a relative intolerance to any specific opiate, it is acceptable to select another opiate, semisynthetic if needed, and then treat any direct mast cell activation with antihistamines.

### Radiocontrast

Sikka and coworkers in 2016 noted that the management of acute radiocontrast-associated reactions is very similar for pregnant and nonpregnant women, with special attention to using left uterine displacement to improve venous return and maintaining blood pressure to ensure placental perfusion during pregnancy [61]. If a pregnant patient has a history of an acute-onset hypersensitivity to a low-osmolar nonionic radiocontrast, it is essential to select a different low-osmolar nonionic radiocontrast for any future exposures [62]. Premedication with corticosteroids has not been shown to be effective in preventing recurrent reactions to low-osmolar nonionic radiocontrast and may cause more morbidity than benefit.

## Clinical Outcomes in Pregnant Women with Serious Hypersensitivity

### *Anaphylaxis*

Mulla and coworkers in 2010 reported on all deliveries during 2004 through 2005 in Texas [63]. They identified a total of 19 maternal anaphylaxis cases, 2.7 per 100,000 deliveries (95% CI 1.7–4.2 per 100,000). Penicillin and cephalosporins were implicated in 11 (58%) along with 2 oxytocic agents, 2 other antibiotics, and one each for a radiocontrast, antihypertensive, antiemetic, and immunosuppressive agent. There were no maternal deaths, 5 patients had emergent admissions, and 14 (74%) had cesarean deliveries.

Chaudhuri and coworkers in 2009 reported on a case of penicillin-associated anaphylaxis, not confirmed by any subsequent testing, with significant neurologic damage in the infant [64]. They then reviewed the clinical outcomes of 20 cases of antepartum anaphylaxis published between 1974 and 2007. There were 11 normal fetal outcomes, 6 infants with neurologic damage, 2 unknown outcomes, and 1 fetal death.

Berenguer and coworkers reported in 2013 on a case of delayed fetal demise after maternal anaphylaxis that had not been acutely treated with adrenaline [65]. Fetal sonographic exam was normal after the maternal anaphylaxis was treated. About 24 h later, fetal distress was noted, an emergency cesarean section was performed, and the baby remained intubated and died 11 days later.

The management of anaphylaxis during pregnancy should be the same as in any other individual. The initial lifesaving treatment of choice is adrenaline 1:1000, 0.3 ml IM. Oral or parenteral antihistamines such as diphenhydramine 50 mg can also be used to help block itching and hives. Intramuscular adrenaline is effective in the treatment of anaphylaxis in pregnant patients and has little or no effect on the fetus [66]. High serum levels of tryptase and complement factor activation have been noted during amniotic fluid embolism, which can mimic anaphylaxis [67, 68]. Anaphylaxis can induce hyper fibrinolysis in pregnancy [69]. Labor can be associated with exercise-induced anaphylaxis [70, 71]. Etwel and coworkers in a systematic review in 2017 concluded that all H1 antihistamines can be safely used in pregnancy, specifically in the first trimester [72].

## *Serious Cutaneous Adverse Reactions (SCARs)*

Knight and coworkers from South Africa reported on 2015 the largest case series of SJS and TEN in pregnancy, 16 with SJS, 5 with TEN, and 1 with SJS/TEN overlap, all HIV-infected, 21 associated with nevirapine and 1 with efavirenz [73]. No cases required ICU care, and all were managed by stopping the implicated drug and providing supportive care in an isolated side ward in the dermatology unit staffed by expert nurses and medical specialists. No immune suppressive therapy was given. Pregnancy outcomes were unknown in six. There were three women with peripartum sepsis, resulting in two fetal deaths at 21 and 31 weeks. TEN was associated with poorer fetal outcomes. There was no evidence for SJS or TEN in any of the infants. There was no intrauterine HIV transmission. Currently standard anti-HIV care no longer includes nevirapine.

El Daief and coworkers from the United Kingdom reported in 2014 on a successful pregnancy after penicillin-associated SJS, though the time between the SJS and the pregnancy was not noted [74].

Struck and coworkers reviewed the literature on TEN in pregnancy in 2010, 24/28 mothers survived, 1 died, and 3 had unknown outcomes [75]. Fetal outcomes were worse, with 5/28 deaths and 1 outcome unknown.

### *Mastocytosis*

Ciach and coworkers reported in 2016 on 23 pregnancies in 17 women with mastocytosis, seen between 1999 and 2014 at a single Polish center [76]. There were 5 spontaneous miscarriages, 4 preterm deliveries, including 1 fetal death at 26 weeks. There was one neonate born with signs of cutaneous mastocytosis. There were no episodes of anaphylaxis in the peripartum period. They concluded there was no contraindication to pregnancy when mastocytosis-related pathologies are under appropriate medical control.

Lei and coworkers reviewed the management of mastocytosis in pregnant women in 2017 [77]. They noted the relative safety of most medications used to manage mastocytosis. The only medications specifically contraindicated in pregnancy were cladribine and imatinib.

## Desensitizations

Desensitizations should be done orally, whenever possible, during pregnancy, prior to parenteral drug administration if acute-onset hypersensitivity has been confirmed and the risk of avoidance outweighs the risk of desensitization. Pregnant women have been safely desensitized to penicillins using the oral route [78, 79]. There will be benign urticarial rashes noted during therapeutic penicillin use after penicillin desensitization about 30% of the time, often delayed onset. These can be treated through using antihistamines. It is critical to not allow more than three to five half-lives of the desensitized medication to elapse between doses, or the desensitization needs to be repeated.

## Conclusions

Whenever possible, medication avoidance is preferred during pregnancy. However, if a lifesaving medication is needed during pregnancy that has been associated with a hypersensitivity reaction, many pregnant patients can still be safely treated using the steps outlined above. Needless avoidance of essential medications, such as penicillin in the setting of GBS colonization or a syphilis infection, can cause increased morbidity.

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# Chapter 11
# Primary Immunodeficiencies in Pregnancy


**Ekta Kakkar and Joud Hajjar**

## Introduction

Primary immunodeficiencies (PID) are a group of rare conditions in which the immune system is compromised due to genetic or hereditary defects. Mutations in over 320 genes are thus far known to cause PID [1]. Approximately 1 in 1200 individuals has a PID [2]. PIDs typically present early in life; however, the effects can impact life at any stage, including but not limited to, women of childbearing age. With the improvements in therapy over the past few decades, more patients with PID are surviving into adulthood. This chapter will identify the major classes of PID and describe the effects of the disorders on pregnancy during and following gestation. X-linked inheritance patterns are limited to affected males; however, female carriers could be sometimes symptomatic [3], and we will touch upon a few examples in our discussion.

## Normal Immunity in Pregnancy

The maternal immune system plays a significant role in protecting both the mother and fetus in a healthy pregnancy. In general, pregnant women are considered at higher risk for infectious diseases than the general population due to the changes that occur in the immune system during pregnancy. After implantation, the maternal endometrium is infiltrated by fetal trophoblast cells [4]. The endometrium then transforms into the decidua or the maternal part of the placenta which provides nutrients for the fetus [4]. Maternal immunity must transform to prevent attack of

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fetal cells. The decidua plays a vital role in protecting the fetus from such attack and is composed of uterine NK (uNK) cells [5]. These cells predominate in the first trimester of pregnancy, and the numbers recede later during gestation [5]. They play a role in the development of the placenta and trophoblast infiltration [5]. The uNK cells recognize fetal human leukocyte antigen (HLA) expressed by the trophoblast cells, and signal cytokine release and angiogenesis factors. Early in implantation, the maternal uterine arteries are also transformed into low-resistance vessels, promoting blood flow to the fetus [4].

Systemically, the increased susceptibility to infections during pregnancy is the result of suppression of the mother's cell-mediated immunity (CMI) [6]. CMI consists of helper and suppressive T-lymphocytes. The helper cells augment immune responses to antigens and suppressor cells regulate the responses [6]. The responses of cytokines in pregnant females have been studied, and it is found that there are decreased numbers of helper T-lymphocytes in pregnancy [7]. Progesterone also limits lymphocyte proliferation in response to mitogens [8]. These shifts in immunity play a significant role in prevention of activation of the maternal immune response against fetal cells; however, they increase susceptibility to certain bacterial and fungal infections. CMI is important in the body's defense against *Cryptococcus neoformans*, *Candida albicans*, *Toxoplasma gondii*, and *Listeria monocytogenes* to name a few [8].

In this chapter, we will be reviewing the outcomes of pregnancy in patients with PID. Here we have classified PIDs based on their immunophenotypic classification [1] and summarize the experiences reported in the literature about pregnancy outcomes in each of the conditions discussed below. It is important here to note that there is a lack of clinical trials to evaluate pregnancy outcomes in PID, and most of the literature is based on case reports, case series, and retrospective reviews. Nonetheless, the prevalence of PIDs is increasing because of a decrease in mortality due to improved awareness leading to early diagnosis, treatment with immunoglobulin replacement therapy, and improved supportive care. As the life expectancy in PID population has significantly improved, some of the children who were expected to die at a young age are now reaching childbearing age and becoming pregnant; it is essential to enrich the medical literature with evidence-based data on caring for pregnant PID patients.

## Humoral Deficiencies

### *CVID*

Common variable immune deficiency (CVID) is the most common treatable PID in adults and affects approximately 1 in 10,000 to 1 in 100,000 people worldwide [9, 10]. Patients often present with recurrent upper respiratory infections, but some have noninfectious complications such as autoimmunity and malignancy [11]. Immunologically, these patients have significantly decreased immunoglobulins

(IgG, IgA, and/or IgM) and poor responses to protein and polysaccharide vaccines [10]. IgG replacement therapy either intravenously or subcutaneously is considered the standard of care for those patients and has led to significant reductions in the number of infections affecting patients [12] and possibly mortality [13, 14].

Providers frequently encounter questions from patients with CVID regarding effects on fertility and pregnancy. Although data is limited, the Immune Deficiency Foundation (IDF) and Gundlapalli et al. conducted a detailed survey in March of 2012 to determine the outcomes of pregnancies in CVID and other primary antibody deficiency disorders. Women with CVID ($n$ = 490) and hypogammaglobulinemia ($n$ = 100) completed this survey [2]. The total number of respondents with CVID or hypogammaglobulinemias who gave birth was lower than the average female population (70% vs. 85%, $p < 0.0001$); however, there was no significant difference in the number of spontaneous pregnancy losses (reported 16% in first pregnancy). There was a total of 966 pregnancies reported by respondents, 72% of those pregnancies resulted in live births, and 75% of the women reported they did not have any increased difficulty with conception. The patients did not report an increase in the number of recurrent infections during pregnancy. Although 20% of the deliveries were by C-section, only three women reported that C-section was indicated due to their PID diagnosis. All the women who had been diagnosed with CVID and were on therapy before their pregnancy reported continuation of IgG replacement therapy throughout gestation without any significant side effects [2].

**Immunoglobulin Replacement Therapy During Pregnancy**

Plasma dilution in the third trimester leads to modest reduction in serum IgG trough levels in all pregnant women, including those with primary antibody deficiency disorder [15]. Importantly, the fetus receives maternal IgG via the placenta, and the newborn child is usually dependent on maternal IgG for the first 4–6 months as of life [15]. Thus, immunoglobulin replacement therapy is crucial during pregnancy. There is some existing controversy on the dose increase in immunoglobulin replacement therapy during pregnancy, with recommendations in dose increase ranging from 10% to 50% of the baseline dose [16, 17]. Immunoglobulins could be delivered either intravenously or subcutaneously to the pregnant women.

Subcutaneous immunoglobulin therapy requires administration of the immunoglobulin under the skin; it could be self-administered, weekly, biweekly, or monthly. There have been multiple publications assuring the safety of delivery of immunoglobulin replacement therapy through the subcutaneous tissue in pregnant woman [18]. Gardulf et al. evaluated self-administered rapid, subcutaneous immunoglobulin (SCIG) therapy in 11 pregnancies of 9 women, 6 of whom had CVID and the others with IgG subclass deficiencies. Each woman would inject 100 mg/kg per week of the SCIG throughout the pregnancy [19]. After over 400 total infusions, no adverse systemic reactions or severe local reactions were reported. All of the infants were healthy and born at term, and there were no complications during gestation [19].

There is not a reported consensus on how often to monitor the immunoglobulin levels and adjust doses of the therapy for follow-up patients. Typically this is done anywhere from annually to more frequently for patients with complications and

infections [20]. In pregnancy, however, the patients should be monitored more frequently to adjust doses as necessary [18]. In our experience, we monitor pregnant patients receiving immunoglobulin replacement therapy monthly, and we target an IgG trough level of 1000 mg/dL with both intravenous and subcutaneous replacement therapy.

## *IgG Subclass Deficiency*

IgG, the main immunoglobulin in the bloodstream, is composed of four different subclasses. Patients with low levels of an IgG subclass and a normal total IgG level have IgG subclass deficiency. The various IgG subclasses are essential in protecting against specific types of pathogens, and the prevalence of each in the serum varies with age [21]. IgG2 and IgG3 subclass deficiencies are the most common [22]. For a deficiency to be clinically significant, the patients must also have a poor antibody response to a vaccine challenge [22]. Patients develop recurrent ear or sinus infections but may also present with bronchitis or pneumonia, especially those caused by encapsulated bacteria such as *Streptococcus pneumoniae* [22].

There has been no demonstrated inheritance pattern of IgG subclass deficiency [21]. Antibiotic therapy for acute infections and vaccination to prevent others is the mainstay of treatment for affected patients [21]. Immunoglobulin therapy is used in symptomatic patients with poor vaccine response and those who fail antibiotic prophylaxis [21]. The prognosis of the disease is generally good, and many children outgrow the deficiency as they get older [21].

Manfredi et al. studied 160 women with frequent abortions, and 16 of these women had IgG subclass deficiency with all having IgG3 deficiency, 12 with IgG1, 8 with IgG4, and 6 with IgG1 deficiency. All the women were treated with immunoglobulin replacement therapy at 200 mg/kg/month throughout pregnancy [23]. The successful pregnancy rate in this study was >90% (all the women with IgG1 deficiency, 14/16 with IgG3, 6/8 with IgG4, and 4/6 with IgG2). The others had recurrence of spontaneous abortion. Before the use of immunoglobulin therapy during pregnancy, these patients had a higher spontaneous abortion rate [23].

## *IgA Deficiency*

Selective IgA deficiency is defined as an IgA level less than 7 mg/dL; this concentration is the lowest detectable limit established by most of the laboratories [24]. The incidence varies by ethnic background with the least prevalence among the Asian population (from 1:2600 to 1:5300 in China) and the highest in Caucasians (between 1:223 and 1:1000 in the USA) [24]. Most of the body's IgA is found in mucosal secretions and protects from sinopulmonary and gastrointestinal infections [25]. Some patients with selective IgA deficiency can progress through life

asymptomatic, while others suffer from recurrent infections, autoimmunity, or allergies [25]. IgA deficiency is predominantly treated with antibiotic prophylaxis for frequent infections, as there is no direct replacement therapy for this condition [25].

IgA deficiency might pose some risks for both mothers and infants. A prospective cohort study in Sweden published by Ludvigsson et al. with 613 mothers with IgA deficiency showed that, when compared to normal deliveries ($n = 5913$), babies of women with IgA deficiency had a 79 g lower birth weight ($p < 0.001$) and 1.4 days shorter gestation time ($p = 0.001$). There was no difference in preterm births, but the babies were often smaller than gestational age at birth (4.3% vs. normally 2.8%) [26]. There was also an increased number of cesarean sections (16.9% vs. normally 11.9%) [26]. In selective IgA deficiency, it is important to note that maternal transplacental anti-IgA may influence fetal immunity. In a study of pregnant women with IgA deficiency, 21 of 27 offspring had serum IgA levels below the normal mean. Of the seven offspring with serum IgA levels two standard deviations below the mean, five had mothers with circulating anti-IgA antibodies [27]. At this time, there is no evidence to treat these patients differently during pregnancy.

## *Specific Antibody Deficiency*

Specific antibody deficiency (SAD) occurs when patients have normal levels of immunoglobulins but do not produce sufficient specific IgG antibodies that protect against infections [28]. These patients often present with frequent bacterial infections; however, some may present in childhood, while others present as adults because they still have functioning T cells, complement, and other antibodies that protect against viruses and bacteria [28]. Diagnosis is made by testing responses to vaccines, and the treatment is with prophylactic antibiotics or Ig replacement therapy in patients with more severe and frequent infections [28]. We could not identify any reports in the literature addressing SAD and pregnancy, but it would be reasonable for pregnant women with severe SAD requiring Ig replacement therapy, to continue it during pregnancy.

## *Hyper-IgE Syndrome*

Hyper-IgE syndrome is a rare immunodeficiency characterized by high serum IgE levels, eczema, and recurrent infections [29]. Hyper-IgE is better defined by its molecular diagnosis when known. The autosomal dominant hyper-IgE, also known as Job's syndrome, is caused by loss of function in the transcription factor STAT3 [30]. Patients with STAT3 deficiency often have atypical facial features including a prominent forehead, deep-set eyes, high-arched palate, thickened skin pneumatoceles, cavitary lung lesions, candidiasis, hyperextensibility, retained primary teeth, scoliosis, and osteopenia [30]. DOCK8 deficiency causes the autosomal recessive

form of the hyper-IgE syndrome [30]. DOCK8 deficiency is a combined immunodeficiency disorder, with defects in both the humoral compartment and T cell leading to susceptibility to viral infections like *Herpes simplex*, *Herpes zoster*, and *Molluscum contagiosum*, in addition to other complications such as encephalitis and vasculitis [30]. Both types are associated with an increased risk of malignancy [30].

STAT3 deficient patients are treated with supportive therapy such as prophylactic antibiotics and immunoglobulin replacement therapy [30]. In DOCK8 deficiency, hematopoietic stem cell transplant is considered, especially for patients at risk for lymphoproliferative disorders [31].

With close monitoring and treatment of infections with antibiotics and antifungals, patients with hyper-IgE syndrome are surviving into their 50s or even older [32]. There is scarce literature regarding the outcomes or complications with pregnancies in patients with hyper-IgE syndrome. One case report describes a 21-year-old woman with hyper-IgE syndrome (molecular diagnosis was not reported, but clinical history suggests autosomal dominant hyper-IgE) in whom the pregnancy course was complicated by bronchitis; dehydration due to *Giardia* infection at week 27; cough and weight loss, with sputum culture growing *Pseudomonas* and *Proteus*; and gingival abscess requiring surgical drainage. The women delivered a healthy baby at week 40. However, the child was subsequently diagnosed with hyper-IgE syndrome [33]. Another case report described (possibly the same patient) a second pregnancy that was complicated by septic arthritis of the right hip caused by *Staphylococcus aureus* that was treated by surgical drainage; she delivered a healthy-appearing child but developed several abscesses postpartum [34]. Those reports indicate that infections could lead to complications during pregnancy in hyper-IgE patients and that measures should be taken to prevent infections using immunoglobulin replacement therapy and possibly prophylactic antibiotics during pregnancy.

## *Hyper-IgM Syndrome*

Hyper-IgM syndrome is characterized by decreased levels of IgG or IgA in the blood with normal or elevated IgM levels [35, 36]. It is most commonly inherited as an X-linked disease which affects T-cell function in addition to antibody deficiency. Hyper-IgM can also be inherited in an autosomal recessive pattern [35]. The defect in hyper-IgM is caused by genetic defects leading to impaired class-switch recombination (which allows antibody isotype production to change from IgM to IgG, IgA, or IgE) leading to elevated IgM levels but absent or very low IgG, IgA, and IgE [36]. Most patients develop both bacterial and viral upper and lower respiratory tract infections within the first few years of life [35]. There is an increased susceptibility to opportunistic infections and cancer as well [35]. Because patients have IgG hypogammaglobulinemia, immunoglobulin replacement therapy is considered standard of care [35].

Case studies have demonstrated two successful pregnancies in a woman with hyper-IgM syndrome with subcutaneous immunoglobulin therapy beginning at the end of the third trimester with weekly dose adjustment to maintain an IgG level of about 700 mg/dL [37]. The patient's dose had to be increased during the second trimester of both pregnancies due to weight gain. The patient had a urinary tract infection during the first trimester of the first pregnancy, and she successfully delivered two-term babies and continued the higher dose of immunoglobulin therapy for 4 weeks postpartum before resuming her prepregnancy maintenance dose [37].

## Combined Immune Deficiencies

### *SCID*

Severe combined immunodeficiency (SCID) is the most serious immune deficiency disorder and is often fatal in the 1st year of life without proper diagnosis and therapeutic intervention. Immunologically, SCID patients have a genetic defect that results in complete absence of T-cell development, leading to absent T-cell-mediated immunity, and, due to the lack of T-cell co-stimulation, those patients have an impaired B-cell function as well. Those defects lead to increased susceptibility to bacterial, viral, and fungal infections [38]. SCID is usually diagnosed within the 1st year of life due to recurrent infections and failure to thrive [38]. Currently, in the USA, newborn screening for SCID has been implemented in all 50 states [39]. Immunologically those patients have profound T-cell lymphopenia and decreased lymphocyte proliferation to mitogens. At least 13 genetic defects have been identified in the pathophysiology of SCID [40]. Leaky SCID is a term that describes patients with hypomorphic mutations (usually in recombination activating genes (RAG1 and RAG2 mutation), usually leading to partial function of the protein that can give rise to an atypical form of SCID in which patients usually have autoreactive T cells and immune dysregulation. However, some of those patients live to adulthood without hematopoietic stem cell transplant (HSCT) [41]. Geirer et al. reported a case of a woman who was initially diagnosed with CVID based on hypogammaglobulinemia and subsequently had leaky SCID due to RAG1 mutation. In this report, the woman, who was 41 years old, had two healthy children aged 9 and 6 years, with no report of any pregnancy complications [41].

HSCT is curative for CVID, and, if performed by 3 months of age, has a 96% survival rate [38]. Gene therapy has also been studied in these patients. In gene therapy, a portion of the patient's white blood cells are removed from the bone marrow, and the normal gene is inserted into these cells. The cells are then returned to the infant [38].

Depending on the conditioning regimen used for HSCT, fertility could be preserved in those SCID patients of child bearing age. There are limited data regarding pregnancy outcomes in patients with SCID following successful bone marrow

transplantation. There is one published case report describing a woman with SCID (molecular diagnosis was not available), who received HSCT (haploidentical from father) at birth and successfully delivered a healthy baby [42]. Interestingly, this patient had Rh alloimmunization resulting from bone marrow transplantation, Rh (D) positive, she received bone marrow from her Rh (D)-negative father, and she underwent close monitoring and was followed by serial ultrasounds to assess the growth of the fetus [42]. She was continued on IG replacement therapy throughout her pregnancy [42]. Women with a history of bone marrow transplant are high-risk pregnant patients and should be followed closely, but successful term deliveries are possible in these patients.

In patients with SCID due to ADA deficiency, enzyme replacement therapy with pegademase bovine (PEG-) ADA injections have been used worldwide in over 150 patients, which allows stabilization of patients awaiting transplant and some to reach adulthood with no HSCT [43]. Shams et al. reported a patient with ADA deficiency who was maintained on PEG-ADA injections since diagnosis and became pregnant at the age of 27 [44]. PEG-ADA treatment was continued throughout her pregnancy, and her immunoglobulin and lymphocyte responses were monitored periodically. The patient's lymphocyte levels began to decline, and she was started on antibiotic prophylaxis at the 16th week of gestation. She progressed and developed gestational hypertension that was treated. At week 33, she was admitted for preeclampsia and an abnormal liver panel. The baby was delivered shortly after and was in the NICU for jaundice and temperature dysregulation [44].

Another case report of a 21-year-old woman with purine nucleoside phosphorylase (PNP) deficiency and developmental delay described her successful delivery of a viable child [45]. The patient was maintained on monthly immunoglobulin replacement therapy throughout her pregnancy. Although she did have preeclampsia at 37 weeks of gestation that was treated with magnesium sulfate, she was inducted and delivered a healthy baby boy [45].

Genetic counseling is important in families of patients affected with SCID. However, much of the genetic analysis has been complicated by the fact that over 80% of the mutations are unknown [46]. Successful prenatal diagnosis has been reported at 20 weeks gestation with fetal blood sampling for lymphocyte and functional analysis [46]. All pregnant patients with a history of SCID should undergo fetal blood sampling and further genetic counseling and evaluation because of the potential fatality of the disease [46].

## *Ataxia Telangiectasia*

Ataxia telangiectasia (AT) is a rare autosomal recessive disorder caused by mutations in the ATM gene, which is involved in cell division and DNA repair [47]. The incidence is 1 in 40,000 to 100,000 people, and life expectancy is usually into early adulthood, although some patients have lived into their 50s [48]. Patients present with difficulty with coordination, or ataxia, in childhood and dilated blood vessels

on mucous membranes (telangiectasias). Affected patients are typically wheelchair-bound by adolescence due to difficulty with balance and coordination [47]. AT is considered a PID as these patients have T- and B-lymphopenia and antibody deficiency leading to lung and sinus infections. Given the defect in DNA repair, affected individuals also have a higher risk of leukemias and lymphomas and often develop chronic lung infections due to aspiration and the weakened ability to clear mucus from the lungs [48]. Unfortunately, there is no cure for any of the symptoms associated with ataxia telangiectasia, and the treatment is all supportive [48].

There is not much literature regarding ataxia telangiectasia during pregnancy, which might be due to the natural history of the disease. Due to telangiectasias, females with AT might be potentially are at risk for uterine bleeding. Tattersall et al. reported heavy menstrual cycles in a female patient with AT, who eventually underwent hysterectomy at age 29 due to fibroids [49]. Interestingly, there is one case report of a 27-year-old wheelchair-bound woman with otherwise mild ataxia telangiectasia symptoms (normal speech and swallowing) who gave birth to a healthy term baby at 39 weeks [50]. The patient was placed on thromboprophylaxis during pregnancy due to decreased mobility. She underwent a planned induction at 39 weeks gestation and, due to failure to progress (thought to be unrelated to her disease), required an emergent C-section. She delivered a healthy baby boy who did not have ataxia telangiectasia. Additionally, the mother's symptoms remained unchanged both during the pregnancy and after delivery [50]. In patients with more severe disease complicated by aspiration, nutrition during pregnancy is a bigger issue. The best way to manage these patients is frequent office visits and a multidisciplinary approach with immunologists, neurologists, and nutritionists.

## T-Lymphocyte Deficiencies

### *DiGeorge Syndrome*

DiGeorge Syndrome (DGS) is caused by abnormal migration and development of thymus cells, leading to thymus hypoplasia that results in T-cell immunodeficiency, cardiac anomalies, and hypoparathyroidism. Patients usually have characteristic facial features of hypertelorism, saddle nose, shortened philtrum, and low-set and abnormally shaped ears [51]. Deletion on chromosome 22 at 22q11.2 is detected in about 90% of patients with DGS [51]. The syndrome can either be complete with no T-cell function or partial (some T-cell function exists) [52]. In addition to T-cell defects, patients with DGS have defects in humoral immunity leading to antibody deficiency [53]. People with DGS are more likely to develop autoimmune diseases such as those of the thyroid and parathyroid glands, hemolytic anemia, and idiopathic thrombocytopenic purpura [54]. The incidence is approximately 1 in 4000 births, and the genetic defect usually occurs spontaneously and is not passed on by the parents [55]. Of note, mothers with diabetes mellitus have been shown to have a higher risk of having children with DGS [56].

Therapy for DGS is directed at correcting the affected systems. Patients with complete absence of the thymus have a severe T-cell defect that needs to be restored either by thymus transplant or HSCT [55]. Patients with some residual thymus tissue have variant levels of immunodeficiency and are usually treated with supportive therapy depending on their level of immunodeficiency, in addition to specific treatment to the other organs involved.

The associated defects of the syndrome, such as cardiac or neuropsychiatric conditions, can increase adverse outcomes in pregnancy. Chan et al. reviewed the outcomes of 25 pregnant women with DGS. Pregnant patients with DGS has a higher rate of small for gestational age children ($p < 0.001$), especially in the infants who also had DGS. There was also an increased prevalence of stillbirths ($p < 0.05$) [57]. Chan et al. highlighted important morbidities that are associated with poor outcomes in pregnancies in DGS including the multiple comorbidities of the pregnant mother, possible lack of social support, sexual education, genetic counseling, and sometimes the delayed diagnosis [57]. Preconception management and prenatal planning along with genetic counseling are very important in autosomal dominant conditions [57].

Costain et al. assessed the reproductive fitness (reproductive success and the average contribution to the gene pool of the next generation) in 141 adults (both males and females) with DGS. Not surprisingly, patients with DGS had fewer children compared to their unaffected siblings, and 85.5% of DGS patients were childless [58]. Younger age, mental retardation, and schizophrenia were predictors of lower reproductive fitness. Interestingly, women who did not have those comorbidities had similar reproductive fitness compared to unaffected female siblings [58]. Mothers with congenital cardiac defects from 22q11.2DS also have a higher risk of maternal and fetal complications and thus should be counseled on contraception [59].

The Canadian health research recommends that DGS patients should discuss pregnancy options before conception and, in case of pregnancy, to carefully monitor endocrinological disorders (such as diabetes and thyroid disorder), monitor psychiatric disorders and their treatment, offer prenatal genetic testing, and consider delivery in a tertiary care center where newborns could be rapidly assessed for possible DGS and screened for cardiac abnormalities [59].

## Neutrophil Deficiencies

### *CGD*

Chronic granulomatous disease (CGD) is a genetic disorder that leads to neutrophil dysfunction. Neutrophils are essential in fighting bacterial and fungal infections. In CGD, the neutrophils lack NADPH oxidase which is essential in producing chemicals like hydrogen peroxide that kills invading pathogens [60]. Affected patients will often have abscesses, chronic inflammation and lymphadenopathy, bone

infections, and unusual pneumonias [61]. It is a rare but life-threatening condition that affects about 1 in 200,000 people worldwide [61]. It can be X-linked or autosomal recessive in inheritance depending on the genetic mutation involved [61]. Children are often healthy at birth but present with a severe infection in infancy or early childhood. Treatment usually consists of prophylactic antibiotics and antifungals and aggressive care during acute infections [60]. Bone marrow transplantation has been shown to cure some forms of CGD, but the potential for cure depends on the genetic mutation involved and the severity of symptoms [62]. Most patients with treatment live into adulthood with the survival rate at about 90% at 10 years [60].

Women with CGD who become pregnant can have healthy babies and deliveries but will need genetic counseling to determine the possibility the child may have CGD [63]. Some antibiotics or antifungals can have teratogenic effects and will need to be changed to alternative suppressive therapy at similar therapeutic doses [63]. Some pregnant patients can develop severe, life-threatening infections despite antibiotic prophylaxis that can lead to miscarriages [63]. The reported incidence of bacteremia in obstetric patients with CGD is 7.5 in 1000 with the most common infections being endoparametritis, pyelonephritis, and chorioamnionitis [64]. Prompt diagnosis and treatment can help prevent complications, but patients with CGD are at higher risk for infections.

Hisano et al. described a CGD patient with a mutation in the *CYBA* gene encoding p22phox who had been managed on trimethoprim-sulfamethoxazole 160–800 mg prophylaxis into adulthood. This patient first became pregnant at age 29, but she developed a severe uterine infection resulting in hemophagocytic syndrome and septic pulmonary emboli [65]. She was treated with steroids and cyclosporine but had a spontaneous miscarriage at week 7. This patient became pregnant again at age 31. She continued prophylactic antibiotics, and, to ensure early detection of severe bacterial or fungal infections, a CBC, serum CRP, and blood 1,3-beta-D glucan were checked at each obstetric follow-up visit. Her second pregnancy was uneventful, and no significant fluctuations in her labs were noted. She reached 40 weeks of gestation at which time C-section was performed to avoid the risk of infection with prolonged labor. She delivered a healthy female baby and was treated with 72 h of cefazolin prophylaxis without further complications [65].

X-linked female carriers of CGD can range from asymptomatic disease to having autoimmune symptoms like painful oral ulcers and skin rashes, abscesses, lupus symptoms, or fatigue [66]. The amount of chromosomal skewing (lionization) and the resulting percent inactivation strongly predict the outcomes in those patients; when there is more skewing toward the affected X chromosome, those patients have lower oxidative burst and higher infection risk [3].

X-linked carrier's neutrophil function can decline, making them more susceptible to infections with age [67]. Rosen et al. reported a case of an X-linked CGD carrier who had declined in her neutrophil function from 40% at age 21 to only 6–8% at age 45 [67]. As a result, X-linked CGD carriers might be susceptible to infections during pregnancy. Haidar et al. described a 22-year-old pregnant woman who was an X-linked carrier for CGD who had chorioamnionitis during two prior pregnancies and during her third pregnancy presented with the same infection

requiring delivery at 25 weeks gestation [68]. This report suggested that even asymptomatic X-linked carriers should be started on antibiotic prophylaxis during pregnancy to prevent poor maternal and fetal outcomes due to infections [68].

## Innate Immune Deficiencies

### *Complement Deficiency*

The complement system consists of several proteins present on cells, in tissues, and in the blood, which are essential for immune activation, protection from infection, and removal of damaged cells. Affected patients will often have recurrent bacterial infections, autoimmune disease, or episodes of angioedema [69]. Family history is important as the inheritance pattern is autosomal codominant like the AB blood type [69].

The various components of the complement system are essential in mounting an immune response, and patients should be tested following vaccination for an antibody response [69]. Of note, complement deficiencies of the classical pathway predispose patients to development of systemic lupus erythematosus (SLE) [70]. However, the implications of SLE and associated outcomes in pregnancy are beyond the scope of this chapter and will not be discussed here. In general, treatment for complement deficiencies consists of vaccination, antibiotic therapy to treat infection, and chronic suppression for patients with recurrent infections [69].

Severe complement deficiency predisposes to infections with encapsulated bacteria including *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* [71]. In a study of women with recurrent pregnancy loss (≥3 losses before 10 weeks gestation or ≥2 losses after 10 weeks gestation), mutations in C4b-binding protein and CD46 were identified [72]. A higher incidence of preeclampsia and HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome has been reported in patients with deficient alternative pathway activation [72].

Complement regulation is essential in protecting the fetus from the mother's innate immune system. Pregnant mice models with deficient C1q have demonstrated abnormal placentation and fetal loss, and those with C3 deficiency showed fetal growth restriction [73]. Other adverse outcomes linked to complement dysregulation have been preterm birth, early pregnancy loss, and preeclampsia [72]. More specifically, increased Factor Bb early in pregnancy and increased C5a have both been associated with preterm birth [74, 75]. Complement regulator CD55 has also been shown to be increased in preterm labor [76]. Increased C5a as well as terminal complement pathway (C5b-C9) have been associated with preeclampsia [77]. Increased C5b-C9 has also been linked with fetal growth restriction.

Because complements are essential in inflammation and protecting against infections, gene therapy targeting specific factors in the complement pathway is being studied as a way of altering poor outcomes. In humans, one case report showed how

eculizumab (a humanized monoclonal antibody functioning as a terminal complement inhibitor) 1200 mg IV (a therapy used in atypical hemolytic-uremic syndrome) has been effective in treating preeclampsia and HELLP syndrome by reducing the level of maternal C5b-C9 in blood and urine. The pregnancy was prolonged 17 days with resolution of HELLP syndrome, and the baby was born at 29 weeks gestation without complications [78]. Due to the risk of infection with encapsulated bacteria, all pregnant women with complement deficiency should receive the meningococcal vaccine [79].

### *Mannose Binding Lectin Deficiency*

Mannose binding lectin (MBL) is a central component of the lectin pathway of complement, which contributes to the defense against microbial organisms. Genetic variations in the MBL2 gene, which encode the MBL protein, lead to MBL deficiency, which is defined as MBL2 protein level <100 ng/ml [80, 81]. MBL deficiency is present in about 5% of people of European descent and in about 10% of sub-Saharan Africans [80]. Most MBL2-deficient adults appear healthy, but there is an association between low levels of MBL2 and recurrent infections in infants and immunocompromised adults, such as patients receiving chemotherapy or those post solid organ transplant [82]. MBL2 deficiency has been associated with autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and inflammatory bowel disease [81, 83].

In pregnancy, MBL deficiency has been associated with poor pregnancy outcomes including recurrent late pregnancy loss, shorter gestational age, chorioamnionitis, and preeclampsia [84, 85]. Decreased MBL levels were observed in pregnant women with autoimmune thyroiditis and diabetes [86]. The effects on the newborn included premature birth and low birth weight [87]. The etiology of those complications remains unclear; however, some studies suggested an association between MBL deficiency and increase production of antiphospholipid antibodies leading to hypercoagulable state and recurrent pregnancy loss [86]. Management of patients with MBL deficiency includes proper immunization and possible prophylactic antibiotics for patients with severe recurrent infections [82]. There are no specific recommendations for treatment of MBL deficient pregnant women. Some studies suggested screening MBL deficiency in women with history of recurrent late pregnancy loss, pregnancy autoimmune thyroiditis, and diabetes [86].

## Conclusions

As patients with PID are living longer due to early identification, increased awareness, newborn screening, and improved supportive care, it is expected that the number of patients with PID who will become pregnant will increase. Pregnancy in PID

patients carries high risk and can be associated with multiple complications related to infections, immune dysregulation, as well as the specific treatments of the underlying PID. Also, PID patients could have nonimmune complications of their genetic disorders (CNS, cardiovascular and other organ systems) that could interfere with the outcomes. Supportive care including prophylactic antibiotics and immunoglobulin replacement therapy are the most commonly used treatment modalities in pregnant PID patients, and collaboration between the immunologist and the obstetrician are important during pregnancy. Finally, as PIDs are often genetic disorders, genetic counseling is essential in PID women of childbearing age.

## *Fetal Monitoring in Pregnant PID Patients*

Fetal monitoring in PID pregnant women depends on the specific PID diagnosis. Several PID diagnoses have been associated with recurrent miscarriages, late pregnancy loss, and increase in the rate of perinatal infections [2, 65]. In addition, pregnant women with germline variants in PID genes may pass on those variants to the offspring in a Mendelian inheritance fashion [88]. In such cases, screening the offspring for those specific genetic variants in utero or shortly after birth could be considered. For SCID, newborn screening is now incorporated in across the USA [39]. Finally, early screening for known specific complications associated with specific PIDs is recommended such as screening for cardiac anomalies in offspring of DGS mothers [59] (Table 11.1).

**Table 11.1** Comparing IVIG vs. SCIG therapy [89]

| IVIG | SCIG |
|---|---|
| Generally given once every 3–4 weeks | Given biweekly, weekly, or more frequently |
| Achieves an initial high concentration of IgG, which decreases gradually until the next infusion | No peak in serum IgG level once steady state is achieved, the IgG level varies little |
| Requires IV access and a healthcare professional to establish access and monitor the infusion | Does not require IV access and can be self-administered but still does require one or more needlesticks |
| Requires a healthcare professional to establish access and monitor the infusion | Requires a committed, compliant patient and/or caregiver for administration |
| Generally well tolerated by most people but adverse effects are possible with infusion such as chills, rigors, nausea, and backache | Systemic side effects are rare, but local reactions including redness, swelling, and itching are frequent but tend to decrease with each infusion |
| Post-infusion adverse effects can include headache, malaise, and fatigue | |
| Premedication with acetaminophen, NSAIDs, diphenhydramine, and/or short-acting steroids may be required to prevent adverse effects | As reactions are local, there is seldom a need for systemic premedication |
| Cost for drug and infusion center/nursing | Cost for drug and supplies |

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# Chapter 12
# Obstetric Management of High-Risk Asthmatic, Allergic Patients and Anaphylaxis

**Mitchell Dombrowski**

## Obstetric Management of High-Risk Asthmatic Patients

Asthma may be the most common potentially serious medical condition to complicate pregnancy; approximately 4–8% of pregnancies are complicated by asthma [1, 2]. This chapter will be limited to obstetric considerations of gravida with high-risk asthma.

### *Preconceptual Counseling*

Ideally, a woman considering pregnancy should consult with a pulmonologist, allergist, and/or a maternal-fetal medicine specialist with expertise in asthma. Baseline pulmonary function testing should be obtained. Optimization of asthma control should be achieved prior to conception. Strategies for optimization include stopping smoking, avoiding secondhand smoke, avoiding triggers, and continuing asthma medications after conception. Avoiding or controlling such triggers can reduce asthma symptoms, airway hyper-responsiveness, and the need for medical therapy [3].

The woman considering pregnancy should be informed that asthma severity may change during pregnancy. If her asthma is well-controlled, her chances for a successful pregnancy are excellent. Other than systemic corticosteroids, there is no consistent evidence that other recommended asthma medications are associated with adverse pregnancy outcomes. During pregnancy, the benefits of systemic corticosteroids are considered to outweigh their risks [4].

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The use of allergen immunotherapy or "allergy shots," has been shown to be effective in improving asthma in allergic patients [3]. However, anaphylaxis is a risk of allergy injections, and they should only be initiated prior to pregnancy. Patients with persistent asthma who have not previously been tested for allergies may undergo blood testing for specific IgE antibodies to allergens such as dust mites, cockroaches, mold spores, and pets. Advice on environmental control measures for reducing exposure to allergens can be provided on the basis of the results of this testing.

All asthmatic women should be educated about the relationship between asthma and pregnancy, and they should be taught about self-treatment, including inhaler techniques, adherence to medication, and control of potential environmental triggers. They should know that discontinuation of medications during pregnancy is associated with more severe asthma for all categories of asthma severity [5]. Physicians should discuss self-reported adherence to treatment with controller medication and, if needed, address barriers to optimal adherence (e.g., cost, convenience, concern about side effects).

A detailed medical history should be obtained, with attention to medical conditions that can complicate the management of asthma, including rhinitis, sinusitis, reflux, or depression. The patient should be questioned about her smoking history and the presence and severity of symptoms, episodes of nocturnal asthma, the number of days of work missed, and emergency care visits related to asthma. Asthma severity should be determined and control efforts planned. The type and amount of asthma medications, including the number of puffs of albuterol used each day, should be noted.

Pregnant asthmatic women should be aware that controlling asthma during pregnancy is especially important for the well-being of the fetus. They should have a basic understanding of the medical management of asthma during pregnancy, including self-monitoring of PEFRs and the correct use of inhalers. They should be instructed on proper PEFR technique—for example, to make the measurement while standing, take a maximal inspiration, have a forceful expiration, and note the reading on the peak flow meter. Proper technique is especially important as the gravid uterus grows.

A written patient asthma action plan can be helpful; google "nhlbi asthma action plan" or visit url www.nhlbi.nih.gov/files/docs/public/lung/asthma_actplan.pdf.

Except for systemic corticosteroids, the preponderance of evidence does not find adverse fetal effects for asthma medications. It is safer for pregnant women with asthma to be treated with asthma medications than it is for them to have asthma symptoms and exacerbations [1]. Asthma medication use has been reported to significantly decline in the first trimester according to the number of prescriptions filled; there was a 23% decrease in inhaled corticosteroids, a 13% decrease in beta agonist, and a 54% decrease in rescue corticosteroids [6]. Moreover, a substantial proportion of asthma exacerbations during pregnancy have been associated with nonadherence to inhaled corticosteroids. In a 2013 publication of a retrospective cohort study of 17,044 gravida with asthma, Mendola et al. [7] reported a significant increase (adjusted OR, 1.48; 95%CI, 1.04–2.09) in congenital

malformations that were associated with exacerbations during the first trimester. Therefore, a woman contemplating pregnancy should be warned that stopping or decreasing asthma medications in the first trimester may actually increase the risk of anomalies.

Oral corticosteroid use during the first trimester of pregnancy, including treatment for conditions other than asthma, has been associated with a threefold increased risk for isolated cleft lip (background incidence is about 0.1%) with or without cleft palate [1, 8]. Oral corticosteroid use has also been associated with an increased incidence of preeclampsia, preterm delivery, and low birthweight [9–12]. However, it is difficult to separate the effects of the oral corticosteroids on these outcomes from the effects of severe or uncontrolled asthma. Because of the uncertainties in these data and the definite risks of severe uncontrolled asthma to the mother and fetus, the NAEPP recommends the continuation of oral corticosteroids for those women with severe persistent asthma [1].

## *Obstetric Monitoring and Management During Acute Asthma Episodes*

Aggressive management of an asthma exacerbation will almost always result in a good fetal outcome; it is not common that an emergency cesarean is required to salvage a fetus that has attained viability. There is no universal definition of when a fetus is considered viable. A fetus may be considered viable following counseling by the obstetrician and pediatrician and/or neonatologist; the patient and her obstetrician will then agree to perform a cesarean section at an agreed-upon gestational age solely for fetal indications. For example, we will not perform a cesarean section at less than 23 completed weeks of gestation because of the very poor chance of intact fetal survival, the risk of maternal morbidity, and the frequent need for a vertical uterine incision. Therefore, an intubated patient at 21 weeks gestation admitted to the ICU for an asthma exacerbation will not have any fetal monitoring; only daily fetal heart tones will be documented.

Because of the risk of fetal compromise or death, continuous electronic fetal monitoring until resolution of the exacerbation should be initiated if the pregnancy has progressed to the point of fetal viability. A fetal monitor displays a continuous recording of fetal heart rate. This is evaluated for heart rate baseline, heart rate variability, and the presence of heart rate accelerations and/or decelerations. If fetal monitoring is not reassuring, a biophysical profile (BPP) can be performed. A BPP is an ultrasound that also includes evaluation of fetal tone, amniotic fluid volume, fetal movement, and fetal breathing.

Obstetric management would also include IV access, oxygen to maintain pulse oximetry at 95%, and possible maternal repositioning to the left side. For those with moderate or severe persistent asthma who may need early delivery, betamethasone should be administered from 24 to 37 weeks gestation in order to reduce the chances

of neonatal respiratory distress syndrome and necrotizing enterocolitis. Magnesium sulfate is recommended from 24 to 32 weeks gestation to reduce the risks of neonatal cerebral palsy and mental impairment.

## *Antenatal Surveillance*

In general, data are lacking to guide the optimal obstetric management of the woman with asthma, and recommendations are based on extrapolation of data from other clinical settings and expert opinion [13]. Women with asthma should be offered influenza vaccination as appropriate. All gravida should be instructed to be attentive to fetal activity including kick counts. Those with asthma that is not well controlled should be considered to be at risk for pregnancy complications and may benefit from fetal surveillance generally by nonstress testing (NST) beginning at 32 weeks gestation. If the NST is nonreactive, then a BPP would be performed in most cases. The intensity and gestational age of initiation of antenatal surveillance of fetal well-being should be considered on the basis of the severity of the asthma and any other high-risk features of the pregnancy. Monitoring may be needed at an earlier gestational age due to exacerbations or more severe asthma or a severe asthma exacerbation.

Because asthma has been associated with intrauterine growth restriction and preterm birth, it is important to establish pregnancy dating accurately by a first trimester ultrasound. In the opinion of NAEPP [1], the evaluation of fetal activity and growth by serial ultrasound examinations may be considered for women who have sub-optimally controlled asthma, for those with moderate to severe asthma, and after recovery from a severe asthma exacerbation. The frequency of an ultrasound for fetal growth would be determined by the degree of asthma control. If the fetus has intrauterine growth restriction, then Doppler studies of the umbilical artery would be indicated. Adverse outcomes may be more common if asthma severity is underestimated and the asthma undertreated.

Scheduling of prenatal visits for gravidas with moderate or severe asthma should be based on clinical judgment. In addition to routine care, monthly or more frequent evaluations of asthma history (i.e., emergency visits, hospital admissions, symptom frequency, severity, nocturnal symptoms, and medication dosages and compliance) and pulmonary function (i.e., FEV1 or PEFR) are recommended. Patients should be instructed on proper dosages and administration of their asthma medications.

Daily PEFR monitoring should be considered for patients with moderate or severe persistent asthma and especially for patients who have difficulty perceiving signs of worsening asthma [1]. It may be helpful to maintain an asthma diary containing a daily record of symptoms, PEFR measurements, activity limitations, medical contacts initiated, and regular and as needed medications taken. Identifying and avoiding asthma triggers can lead to improved maternal well-being and reduced need for medications.

For a pregnant woman who is experiencing asthma symptoms at home, the response is considered to be good if symptoms are resolved or become subjectively mild, normal activities can be resumed, and the PEFR is at least 80% of the personal best value [1]. The patient should seek further medical attention if the response is incomplete or if fetal activity is decreased.

## *Case Presentation*

We received a stat maternal-fetal medicine consultation for a 24-year-old G1P0 at 34 weeks gestation. We were told that respiratory therapy gave her an albuterol treatment and posttreatment her PEFR was 150 L/min. When we reached OB triage, she was sitting up in a stretcher with her legs outstretched. I asked her if respiratory therapy got her PEFR on the stretcher, and she confirmed that was the case. We had her stand up and instructed her to take a maximal inhalation and to "blast out" an exhalation; this time her PEFR was 350 L/min, and she was discharged home. This case illustrates that proper PEFR technique is especially important during pregnancy.

## *Management During Labor*

Asthma medications should not be discontinued during labor and delivery. Although asthma is usually quiescent during labor, consideration should be given to assessing PEFRs on admission and at 12-h intervals for those with persistent asthma. The patient should be kept hydrated and should receive adequate analgesia to decrease the risk of bronchospasm.

Continuous electronic fetal monitoring should be initiated if gestation has advanced to the point of potential fetal viability.

It is commonly recommended that women who are currently taking systemic corticosteroids or who have received several short courses of systemic corticosteroids during pregnancy receive intravenous corticosteroids (e.g., hydrocortisone at a dosage of 100 mg every 8 h) during labor and for 24 h after delivery to prevent an adrenal crisis [13].

It is rarely necessary to perform a cesarean section for an acute asthma exacerbation during labor. Maternal compromise and fetal compromise usually respond to aggressive medical management. An elective delivery should be postponed if the patient is having an exacerbation. Prostaglandin (PG) E1 or E2 [14] can be used for cervical ripening, the management of spontaneous or induced abortions, or postpartum hemorrhage, although the patient's respiratory status should be monitored. The Cook catheter balloon for cervical ripening would also seem an appropriate choice. Especially carboprost (15-methyl PGF2α) but also ergonovine and methylergonovine (Methergine) can cause bronchospasm [2] and should be avoided if possible.

Magnesium sulfate is a bronchodilator, but indomethacin can induce bronchospasm in the aspirin-sensitive patient.

A recent national database study evaluated the use and risk of the beta blocker labetalol among 12,486 deliveries in women with asthma and complications of postpartum hemorrhage or preeclampsia. Labetalol was used in 18.5% of those with asthma. Of these, 0.65% had status asthmaticus, a significant increase compared to 0.17% who received nifedipine and/or hydralazine [15].

Meperidine and morphine should be avoided if possible because they can induce histamine release. Lumbar anesthesia has the benefit of reducing oxygen consumption and minute ventilation during labor [2]. A 2% incidence of bronchospasm has been reported with regional anesthesia [2]. Communication between the obstetric, anesthetic, and pediatric caregivers is important for optimal care.

### *Postpartum Management*

Prenatal asthma management should be continued in the postpartum period. Asthma symptoms may abate if they worsened during pregnancy, may stay the same, or may become worse. Only small amounts of asthma medications enter breast milk. None of the commonly used asthma medications are considered to be contraindications for breastfeeding [1]. However, among sensitive individuals, theophylline may cause toxic effects in the neonate, including vomiting, feeding difficulties, jitteriness, and cardiac arrhythmias.

## Obstetric Management of High-Risk Allergic Patients

Unlike the published literature on asthma, there is a paucity of literature regarding high-risk or severe allergy during pregnancy. A MEDLINE search during January 2018 of “severe allergy” and “pregnancy” only yielded two results, neither of which was relevant to this chapter. As with any allergy, a primary element of management is avoidance of the triggering allergen when possible. Allergen avoidance is particularly important during pregnancy because the use of systemic medications may be minimized.

Women with significant allergic disease should ideally be evaluated before they become pregnant, so that any skin testing, challenge procedures, or other exposures that might be necessary for definitive diagnosis can be safely performed. Allergen immunotherapy for insect venom and environmental allergens may be continued during pregnancy, but should not be initiated during pregnancy because of the risk of anaphylaxis [16]. Pregnant patients who have had severe allergic reactions and/or a history of anaphylaxis [16] should carry an epinephrine autoinjector.

Many women are extremely sensitive to latex products, and it is becoming common for hospitals to become “latex-free.” However, patients with histories of reac-

tion to latex should be evaluated for IgE-mediated sensitivity, the presence of which would dictate absolute latex avoidance.

It is especially important to test for penicillin and cephalosporin allergies because they are commonly given during labor and delivery to prevent neonatal group B streptococcal infection and cephalosporins are routinely given to prevent infections during cesarean sections. Avoidance of these two antibiotics may result in the patient receiving clindamycin or even vancomycin depending upon group B streptococcal sensitivity testing.

## Obstetric Management of Anaphylaxis During Pregnancy

Fortunately, anaphylaxis during pregnancy is extremely uncommon. In a study of approximately 700,000 postpartum women from Texas hospitals in 2004 to 2005, there were only 2.7 cases of anaphylaxis per 100,000 deliveries [17]. Anaphylaxis can cause significant maternal morbidity and intrauterine fetal demise. Therefore, gravida at risk for anaphylaxis should carry epinephrine autoinjectors and should have an action plan (see Table 12.1).

Except for obstetric considerations, the medical management of anaphylaxis is the same as for nonpregnant patients (see Chap. 8). This includes immediate administration of epinephrine, large-bore IV access, oxygen, IV fluid resuscitation, and possible maternal repositioning to the left side (see Table 12.2).

### *Anaphylaxis During Term Labor*

No maternal morbidity or mortality was reported when anaphylaxis occurred during labor [18]. In contrast, among those who had a delayed cesarean section, or did not receive epinephrine despite undetectable arterial blood pressure, 46% of neonates had neurological abnormalities. These included neonatal death, rigidity of the extremities, seizure-like movements, brain damage, and/or hypoxic encephalopathy [18].

It is preferable to manage non-reassuring fetal heart rate patterns by correcting maternal hypotension and/or hypoxemia with aggressive maternal medical management, but stable hemodynamic status during anaphylaxis does not guarantee

**Table 12.1** Pregnant women at risk for anaphylaxis [16]

| |
|---|
| Carry one or more epinephrine autoinjectors. Patients should be trained in how and when to correctly use it |
| Carry an anaphylaxis emergency action plan that lists the importance of prompt intramuscular injection of epinephrine, laying on her left side, and calling 911 or emergency medical services |
| Provide their healthcare providers with known allergies and any relevant comorbidities and wear a medical identification bracelet or necklace listing this information |
| Referral to an allergy specialist |

**Table 12.2** Hospital obstetrical and medical management of anaphylaxis [18, 19]

| |
|---|
| Epinephrine 0.3–0.5 mg IM in the mid-outer thigh, repeat every 5–15 min (or more frequently), as needed. Most patients respond to 1–3 doses if epinephrine is promptly administered. If not responding admit to the ICU |
| Immediate intubation by the most experienced clinician if evidence of impending airway obstruction from angioedema. Delay may lead to complete obstruction |
| Start continuous monitoring of BP, heart rate, respiratory status, and pulse oximetry. Continuous electronic fetal monitoring may be indicated depending upon gestational age |
| Call for multispecialty resuscitation team including an anesthesiologist, obstetrician and/or maternal-fetal medicine specialist, and neonatologist |
| Oxygen 6–8 L/min via facemask up to 100% as needed. Ideally, pulse oximetry should be at least 95% |
| Position to the left side and elevate the lower extremities. Manual displacement of the gravid uterus to the left may be helpful. Avoid the supine position due to vena cava compression by the gravid uterus |
| Maintain systolic blood pressure of 90 mmHg. Manage hypotension with rapid infusion of 1–2 L of normal saline IV. Massive fluid shifts with severe loss of intravascular volume can occur necessitating the need for additional IV fluids |

appropriate placental perfusion and fetal oxygenation [16, 18]. However, normal fetal heart rate variability is reassuring [18]. Even with aggressive maternal resuscitation, emergent cesarean section should be considered early in cases of persistent maternal hemodynamic instability [18]. Emergency cesarean section should also be performed for a persistently non-reassuring tracing including, but not limited to, absent baseline variability plus recurrent late decelerations, recurrent variable decelerations, or bradycardia [16, 18].

## *Anaphylaxis During Cesarean Section*

Probably because of the rapid delivery, no neonatal neurological abnormalities or deaths were reported when maternal anaphylaxis occurred during cesarean section [18]. However, maternal morbidity was reported in 20% of cases. This included abnormal renal function or renal failure, increased liver enzymes, disseminated intravascular coagulation, severe hypertension associated with pulmonary edema, and acute respiratory distress syndrome [18]. Cesarean section can have beneficial maternal effects; emptying the uterus reduces aortocaval compression by the uterus, resulting in an increase in cardiac output.

## *Anaphylaxis Before Term*

Successful medical management with reassuring fetal status is the optimum outcome when pregnancy is remote from term. It has been recommended that continuous fetal monitoring be continued for 48–72 h following anaphylaxis [19].

Betamethasone and magnesium should be given as appropriate (see discussions in asthma section of this chapter).

In some cases, persistently non-reassuring tracing will occur despite aggressive maternal medical management. The potential benefits of emergency cesarean delivery in patients with anaphylaxis refractory to medical treatment need to be balanced against the potential maternal risks of surgery in an unstable patient with hypoxemia and/or hypotension [20]. In addition, the potential benefits should be balanced against neonatal morbidity and mortality secondary to prematurity, especially if the gestation is less than 32 weeks [16, 20].

This becomes a serious ethical dilemma when the fetus is near the limits of viability, for example, 23–24 weeks. In such cases the neonatal prognosis is extremely poor both due to prematurity and due to complications of anaphylaxis. And, as noted above, there is about a 20% incidence of maternal morbidity when anaphylaxis complicates cesarean delivery. In addition, a very preterm uterus may have minimal vena cava compression, and emptying it may not significantly increase maternal cardiac output. Therefore, each case will have to balance fetal and maternal benefits and risks depending upon the gestational age.

### *Anaphylaxis and Emergency Cesarean Delivery*

If medical resuscitation has not been successful, cesarean delivery should be initiated with the goal of delivering the fetus within 5 min; this results in about 90% of neonates being neurologically intact [18, 20]. Unfortunately, very few cases of perimortem cesarean delivery occur this rapidly, and fewer than 60% of neonates delivered within 15 min are likely to be neurologically intact [18, 20]. Emptying the uterus reduces aortocaval compression by the uterus, resulting in 60–80% increase in cardiac output, which increases the chance of maternal survival [18, 20].

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# Chapter 13
# Prevention of Asthma and Allergic Diseases During Childhood


**Stephanie A. Leonard**

## Introduction

Allergic diseases, including atopic dermatitis, food allergy, allergic rhinitis and asthma, often begin in childhood. Up to a third of newborns have a first degree relative with an allergic disease and therefore may be considered at risk. Over the past 40 years, there has been an increased incidence of allergic disease leading to significant morbidity and mortality in children and adults.

Atopy refers to an amplified immune response, usually in the form of immunoglobulin E (IgE) sensitization, to environmental and/or food allergens. The atopic march refers to the development of allergic disease in a typical progressive order starting with atopic dermatitis, followed by food allergy, then allergic rhinoconjunctivitis, and finally, asthma. While allergic diseases are related, in that patients with one type are more likely to have another, they are not mutually inclusive.

Atopic dermatitis is a chronic skin disease characterized by dry skin, pruritus, and inflammatory lesions affecting up to 20% of children [1]. The onset of atopic dermatitis typically begins within the first few years of life. Current management focuses on emollients, topical corticosteroids, antihistamines, and avoidance of exacerbating triggers in order to restore the barrier function of the epidermis. The prevalence of food allergy has been estimated at 6–8% of children under the age of 18 years [2]. Food allergy is commonly diagnosed in infancy and toddlerhood as foods are introduced into the diet, although food allergies can develop later in childhood and even adulthood. The most common food allergens in childhood include milk, egg, peanut, tree nuts, soy, wheat, fish, and shellfish. About 80% of children may outgrow egg, milk, soy, and wheat allergies, while peanut, tree nut, fish, and

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shellfish allergies often persist into adulthood. Currently there is no cure for food allergy; management involves strict avoidance of the allergen and treatment of accidental ingestions and reactions. Recent research has focused on prevention of food allergy development and treatments to protect food-allergic children by decreasing the incidence or severity of reactions to unintentional exposures.

Symptoms of environmental allergies may develop in infancy, usually to indoor allergens such as dust mites or pets. It is more typical for allergic rhinoconjunctivitis and pollen allergy to develop during preschool years and older. A cross-sectional study performed in 2005–2006 reported hay fever in 10% and respiratory allergies in 12% of children under age 18 years [3]. Management of allergic rhinoconjunctivitis symptoms includes strategies for allergen avoidance, medications including antihistamines and intranasal corticosteroids, and immunotherapy for long-term control. Asthma is one of the most common chronic diseases worldwide with a high prevalence in industrialized countries. About 8.3% of children under the age of 18 years have asthma in the United States [4]. Asthma is a heterogeneous disease with prevalence that has increased over last several decades along with other atopic disorders. Therapies for managing asthma symptoms include trigger management, bronchodilators, inhaled corticosteroids, anti-leukotrienes, and newer immunomodulatory biologics.

Strong family histories of allergic diseases support a role for genetic predisposition; however there are no known gene mutations that result in a specific phenotype. Numerous environmental exposures, including maternal and infant diet, microbial colonization, and toxin exposures, have been investigated for possible association with the development of allergic disease. In this chapter we will review the existing data on environmental factors that may influence the development of asthma and allergic diseases in predisposed children. These studies provide insight into the mechanism of atopy as well as highlight potential preventive measures during pregnancy and early childhood.

## Hygiene Hypothesis

The hygiene hypothesis associates decreased exposure to microbial diversity with the rise of asthma and allergic diseases in the recent decades. Immunologically, a shift from T helper (Th)1 to Th2 immune pathways is thought to underlie increased allergic responses. Interferon gamma (INFγ) production is the hallmark of the Th1 response to combat infectious agents, while cytokines interleukin (IL)-4, IL-5, and IL-13 leading to IgE production drive the Th2 response. There is evidence that proper immune development requires initial colonization and stimulation with the appropriate microbes, while low microbial diversity or dysbiosis leads to disease states. Low gut microbiota diversity in infancy has been associated with increased risk of atopy ($p = 0.003$), peripheral blood eosinophils ($p = 0.034$), and allergic rhinitis ($p = 0.007$) by age 6 years [5]. In addition, exposure to antibiotics early in life has been associated with increased atopic disease [6, 7]. In an allergic asthma

murine model, the use of an antibiotic, vancomycin, in the neonatal period decreased diversity, changed the composition of the microbiota, and was associated with increased asthma disease severity [8]. A meta-analysis of antibiotic exposure in the first 2 years showed increased risk of hay fever (odds ratio [OR] = 1.23, 95% CI 1.13–1.34; 22 studies), eczema (OR = 1.26, 95% CI 1.15–1.37; 22 studies), and food allergy (OR = 1.42, 95% CI: 1.08–1.87; 3 studies), but not with allergen sensitization later in childhood [9].

Exposure to specific microbes may be protective against atopic conditions. Studies have associated foodborne and orofecal infections, such as *Helicobacter pylori*, *Toxoplasma gondii*, hepatitis A, and herpes simplex virus 1 with reduced prevalence of atopy, asthma, and hay fever [10, 11]. In particular, parasitic infections induce Th2 responses similar to those affecting allergic diseases. Helminth infections have been inversely associated with atopy, perhaps via induction of regulatory responses [12]. For example, *Schistosoma mansoni* antigens share cross-reactive carbohydrate determinants (CCDs) with plant products, such as birch pollen, timothy grass pollen, and peanut allergens, and may protect against atopy by blocking IgE responses via the production of IgG4 antibodies [13, 14].

Infections in early childhood shape immune maturation and may affect the overall Th1/Th2 balance. In a cross-sectional study, daycare attendance starting at a later age was associated with increased risk of atopy at 5–14 years in children from small families (up to three people; presumably without siblings): an OR = 1.99 (95% CI 1.08–3.66) when starting daycare between age 1 and 2 years and an OR = 2.72 (95% CI 1.37–5.40) when starting after age 2 years [15]. This increased risk was not seen in children from larger families (more than three people; presumably with siblings) who would more likely be exposed to increased infections with each additional household member. Correspondingly, a study associated ≥1 siblings and daycare attendance in the first 6 months of age with decreased risk of asthma at age 6–13 years (OR = 0.8; 95% CI 0.7–1.0 and OR = 0.4, 95% CI 0.2–1.0, respectively) [16]. Children with these exposures may have more infectious symptoms earlier but appear to be protected against respiratory symptoms later in childhood.

The observation that living on a farm is associated with decreased atopic disease has been noted for decades. Two large cross-sectional studies showed that living on a farm was associated with greater microbial diversity (as measured in house dust) and decreased risk of asthma (PARSIFAL study OR = 0.49, 95% CI 0.35–0.69; GABRIELA study OR = 0.76, 95% CI 0.65–0.89) and atopy (PARSIFAL study OR = 0.24, 95% CI 0.18–0.34; GABRIELA study OR = 0.51, 95% CI 0.46–0.57) as compared to a control group living in the same area but not on a farm [17]. Increased exposure to the fungal taxon *Eurotium* and bacterial species *Listeria monocytogenes*, *Bacillus*, and *Corynebacterium* appeared relevant; however diversity in general was more important. A meta-analysis of eight studies examining the effect of farm exposure in the first year of life showed there was a protective effect against allergen sensitization (OR = 0.60, 95% CI 0.52–0.70) [18].

The GABRIELA and PARSIFAL studies also investigated the effect of farm (raw) milk consumption and found that consumption was protective against

asthma, atopy, and hay fever [19, 20]. A recent study has implicated active microRNA in raw milk, which is homologous to human microRNA in breast milk and plays a role in regulating proinflammatory mediators, as a possible reason of farm milk benefit [21]. Pasteurizing milk may inactivate these microRNAs and lose their protective effect. A cohort study reported increased Tregs in children exposed to farm milk, and a decreased risk of asthma (OR = 0.26, 95% CI 0.08–0.88) and atopy (OR = 0.21, 95% CI 0.08–0.59), indicating another possible mechanism [22]. While ingesting raw, unpasteurized milk is not recommended for health reasons, a sterilization process that does not diminish immunomodulatory protection could be explored.

Besides raw, unpasteurized milk, animals are another common exposure on farms. In one cohort study, farm exposure to stables and consumption of farm milk during infancy (versus between age 1 and 5 years) decreased the risk of asthma, hay fever, and atopy, with the lowest incidences associated with prolonged exposure up to 5 years of age [23]. In a large cohort study, exposure to dogs (OR = 0.87, 95% CI 0.81–0.93) or farm animals (OR = 0.48, 95% CI 0.31–0.76) during infancy decreased the risk of asthma at 6 years of age, but only when analyzing firstborn children [24]. And lastly, in another cohort study, exposure to two or more dogs or cats during infancy decreased the risk of positive skin testing (OR = 0.23, 95% CI 0.09–0.60) and detectable allergen-specific IgE levels (OR = 0.33, 95% CI 0.13–0.83) at 6–7 years of age [25]. In an urban population, exposure during infancy to cockroach, mouse, and cat allergens decreased the risk of recurrent wheeze ($P \leq 0.01$), while decreased exposure to *Firmicutes* and *Bacteroidetes* bacteria in house dust increased the risk of atopy and atopic wheeze [26]. Cumulative allergen exposure in the first 3 years in this study, however, increased the risk of atopy. One meta-analysis on exposure to pets showed that there was no association with an increased risk for asthma in younger children and a small increased risk of wheezing in children >6 years of age [27]. Heterogeneity of the studies and selection bias likely influenced the results. In an example of how genetics and environment may interact in atopic disease, a recent cohort study reported that exposure to cat in childhood decreased the risk of asthma at age 12 years only in the specific 17q21 genotype variant, which is known to be a risk factor in asthma [28]. Most of the beneficial effects of animals were noted with exposure in the first year of life when the immune system is being established. Infancy appears to be a critical window for allergen sensitization versus tolerance.

One of the theories on why animals may affect the immune response is due to increased exposure to endotoxin. Endotoxin is a lipopolysaccharide (LPS) molecule that exists on gram-negative bacteria membranes and is recognized by the innate immune system, leading to Th1-type responses. Common environmental exposures to endotoxin include livestock and pets. Endotoxin was found in higher levels from mattresses of children living on a farm ($p < 0.001$) in one study, and was associated with a decreased risk of hay fever ($p < 0.001$), atopic asthma, and atopy [29]. Another study compared household endotoxin in Amish and Hutterite homes, populations that are similar in ancestry and lifestyles even though the Amish have a much lower prevalence of asthma and atopy. Endotoxin levels were

found to be 6.8 times higher in Amish homes compared to Hutterite homes ($p < 0.001$), and innate immune responses differed between the two populations with increased peripheral neutrophils and decreased peripheral eosinophils in the Amish [30]. In a prospective cohort study of children at risk for allergic disease living in a metropolitan area, exposure to endotoxin was associated with a decreased risk of eczema in the first year of life (OR = 0.76 for each quartile increment, 95% CI, 0.61–0.96) [31]. Overall, higher endotoxin levels may represent a more abundant and diverse microbial environment.

## Microbiome and Probiotics

The microbiome is believed to be an important part of the gastrointestinal and immune system and has been linked to allergic disease, inflammatory bowel disease, obesity, and cardiovascular disease. Infancy is a vital time for colonization, and composition of the microbiome may be influenced by many factors, including maternal microbiota, type of delivery, type of feeding, use of antibiotics, and exposures to pre- or probiotics. It has been demonstrated that by 4–6 months, infants born by cesarean section (C-section) have lower rates of intestinal *Bacteroides* spp. compared to infants born vaginally [32, 33]. In the gut microbiota of breastfed infants, *Bifidobacterium* spp. represented predominant strains and *Lactobacillus* spp. minor strains, while *Clostridium* spp. and *Bacteroides* spp. were overrepresented in formula-fed infants [34, 35]. In two studies, the gut microbiota profiles in the first month of life were already significantly different between children found to be atopic versus nonatopic at age 1–2 years, with atopic children showing increased *Clostridium* spp. and decreased *Bifidobacterium* spp. [36, 37].

The differences in microbiota profiles in infancy suggest that C-section delivery and formula feeding may be a risk for allergic disease. Indeed, in a cross-sectional study, C-section was associated with increased risk of asthma (OR = 1.41, 95% CI 1.09–1.83) and atopy (OR 1.67, 95% CI 1.08–2.60) at age 8 years [38]. A recent Swedish nation-wide birth cohort followed children for 13 years and found that C-section birth was associated with food allergy (hazard ratio [HR] = 1.21, 95% CI 1.18–1.25) [39]. These observations support the concept that a healthy and diverse gut microbiota is important for the normal nonatopic development of the immune system.

Supplementing with beneficial bacteria or optimizing the intestinal environment to encourage the growth of beneficial bacteria may be an option in infants delivered by C-section or who are formula-fed. In a germfree murine model, sensitization to ovalbumin was prevented by reconstituting the gut with *Bifidobacterium infantis* that suppressed Th2-mediated responses in newborns [40]. Using probiotic supplementation, *Bifidobacterium longum* (BL999), one study showed that formula-fed infants could develop profiles similar to breastfed infants [41]. In a randomized controlled trial in formula-fed infants, adding prebiotics decreased the risk of dermatitis by 44% ($P < 0.04$) with a number needed to treat (NNT) of 24 infants [42]. Inoculation of

newborns born by C-section with maternal vaginal microbiota has been suggested; however it is not recommended at this time until necessity, efficacy, and safety can be determined [43]. Moreover, the effect of C-section delivery on the microbiota of the newborn may not be related to the absence of maternal vaginal microbiota but rather to the indication for the C-section, use of intrapartum antibiotics, absence of labor, differences in breastfeeding behaviors, maternal obesity, and/or gestational age [43].

In an observational cohort study, maternal probiotic milk product consumption during pregnancy was associated with a decreased risk of atopic eczema in infants at age 6 months (RR = 0.94, 95% CI 0.89–0.99) and allergic rhinitis between the ages of 18 and 36 months (RR = 0.87, 95% CI 0.78–0.98), but not with asthma at age 36 months [44]. Studies investigating the effect of probiotics on the development of atopic disease have utilized different combinations of administration to pregnant women, breastfeeding mothers, and/or infants (Table 13.1). One study that systematically investigated maternal probiotic supplementation during pregnancy only did not show an effect on eczema or atopic eczema [45]. However, a meta-analysis of the effect of maternal probiotics during both pregnancy and breastfeeding using direct and indirect evidence showed protection for eczema during infancy (RR = 0.72, 95% IC 0.61–0.85 and RR = 0.61, 95% CI 0.50–0.74, respectively) [65]. Several studies have investigated probiotics given to the infant only, others to both pregnant women and their infants. A meta-analysis of the effect of probiotics during infancy using indirect evidence from 15 trials showed protection for eczema (RR = 0.81, 95% CI, 0.70–0.94), while direct evidence from 5 trials did not show an effect on eczema [65]. There were no effects on other allergic diseases reported when using probiotics in infancy. Due to heterogeneity of the studies and indirectness of the data, evidence was considered overall weak. Additional caution is warranted when pooling data from studies using different strains of probiotics as they are not all equal in their immunomodulatory effects [66]. Further studies are needed to provide proper guidance; however probiotics during pregnancy, lactation, and infancy appear mostly safe. One exception was reported in a study where *Lactobacillus acidophilus* was given to infants and an increase of allergic sensitization was noted at 12 months ($p = 0.03$) [46].

The lung microbiome is another area of interest, although the amount of microbiota is significantly less than in the gut, and the gut microbiota may influence the airways. It is likely that the gut and lung microbiota interact to regulate inflammation and immune responses [67]. In a study comparing the airway microbiota in children, phyla *Proteobacteria* and genera *Haemophilus* spp. and *Staphylococcus* spp. were more prevalent in the airways of asthmatics, while phyla *Bacteroidetes* genera *Prevotella* spp. were more prevalent in controls [68]. These differences support a role for microbiota in airway disease but do not necessarily indicate causality. However, in a germfree murine model, increased numbers of airway lymphocytes and eosinophils in response to ovalbumin sensitization could be reversed by colonizing the mice with complex commensal flora from controls [69]. Allergic inflammation of the airways correlated with increased Th2 cytokine and IgE production. Supplementing with probiotics that could also beneficially colonize the lung may be a strategy in atopic asthma.

**Table 13.1** Studies investigating effect of probiotics during pregnancy, lactation and infancy on childhood atopic disease

| Authors | Year | Country | Type of study | Population | Subjects | Intervention | Results [if OR = odds ratio (95% CI)] |
|---|---|---|---|---|---|---|---|
| *Probiotic use in pregnant women only* | | | | | | | |
| Boyle et al. [45] | 2011 | Australia | RCT | High-risk infants | $N = 250$ women | LGG from 35 weeks to delivery | No decrease in eczema or atopic eczema in first year of life. |
| *Probiotic use in infants only* | | | | | | | |
| Taylor et al. and Prescott et al. [46, 47] | 2007 2008 | Australia | RCT | High-risk infants | $N = 231$ | *L. acidophilus* daily for first 6 months of life | No decrease of eczema at 6 months, 12 months, or 2.5 years. Increased allergic sensitization at 12 months ($p = 0.03$). |
| Soh et al. [48] | 2009 | Singapore | RCT | High-risk infants | $N = 253$ | *B. longum* and *L. rhamnosus* daily for first 6 months | No decrease of eczema or allergen sensitization in the first year of life. |
| West et al. [49] | 2009 | Sweden | RCT | Infants | $N = 179$ | *L. F19* from 4 to 13 months of age | Decreased eczema at age 13 months ($p < 0.05$). NNT = 9. |
| *Probiotic use in pregnant women and infants* | | | | | | | |
| Abrahamsson et al. [50] | 2007 | Sweden | RCT | High-risk infants | $N = 232$ mother-infant pairs | *L. reuteri* ATCC 55730 from 36 weeks until delivery and in infants 0–12 months | Decreased atopic eczema during age 2 years ($p = 0.02$). Decreased atopy in infants with mothers with allergies ($p = 0.02$). No prevention of wheeze or other allergic disease. |
| Allen et al. [51] | 2014 | UK | RCT | Infants, most at high risk | $N = 454$ mother-infants pairs | *L. salivarius* and *L. paracasei* plus *B. animalis* and *B.bifidum* to mothers in the last month of pregnancy and to infants 0–6 months | At age 2 years, decreased atopic eczema, OR = 0.40 (0.18–0.91), and atopy, OR = 0.52 (0.28–0.98). Associated with reduced cord blood eosinophil count ($p = 0.024$). |

(continued)

**Table 13.1** (continued)

| Authors | Year | Country | Type of study | Population | Subjects | Intervention | Results [if OR = odds ratio (95% CI)] |
|---|---|---|---|---|---|---|---|
| Kuitunen et al. [52] | 2009 | Finland | RCT | High-risk infants | $N = 1223$ mother-infants pairs | Probiotic mixture (lactobacilli, bifidobacteria, and propionibacteria) in the last month of pregnancy and to infants 0–6 months. Some infants also received prebiotics | At age 5 years, decreased allergic disease in C-section infants receiving probiotics, OR = 0.47, 0.23–0.96). No decrease in eczema, atopic eczema, allergic rhinitis, or asthma. |
| Kukkonen et al. [53, 54] | 2007 2011 | Finland | RCT | High-risk infants | $N = 1223$ mother-infant pairs | Mixture of *LGG*, *L. rhamnosus LC705*, *B. breve*, and *Propionibacterium freudenreichii* ssp. To mother 2–4 weeks prior to delivery and to infants 0–6 months. Some infants also received prebiotics | At age 2 years, decreased eczema, OR = 0.74 (0.55–0.98) and atopic eczema, OR = 0.66 (0.46–0.95). No decrease in cumulative incidence of all allergic disease. At 5 years, no effect on airway inflammation. |
| Niers et al. [55] | 2009 | Netherlands | RCT | High-risk infants | $N = 102$ mother-infant pairs | *B. bifidum*, *B. lactis*, and *L. lactis* prenatally and to infants 0–12 months | At 3 months of age, decreased eczema ($p = 0.035$). NNT at 3 months and 1 year: 5.9; NNT at 2 years: 6.7. |
| *Probiotic use in pregnant women and breastfeeding mothers* | | | | | | | |
| Dotterud et al. [56] | 2010 | Norway | RCT | Infants | $N = 415$ mothers | LGG, *L. acidophilus*, and *B. animalis* subsp. from 36 weeks to 3 months postnatally during breastfeeding | At age 2 years, decreased atopic dermatitis, OR = 0.52 (0.3–0.87). No effect on asthma or atopy. |
| Rautava et al. [57] | 2002 | Finland | RCT | Infants | $N = 62$ mothers | LGG from 4 weeks prior to delivery and during breastfeeding until infant was 3 months | At age 2 years, decrease atopic eczema, RR = 0.32 (0.12–0.85). |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Rautava et al. [58] | 2012 | Finland | RCT | High-risk infants | $N = 241$ | *L. rhamnosus* + *B. longum* or *L paracasei* ST11 + *B. longum* for 2 months before delivery and during the first 2 months of breastfeeding | At age 2 years, decreased eczema with *L. rhamnosus* + *B. longum*, OR = 0.17 (0.08–0.35), and ST11+BL999, OR = 0.16 (0.08–0.35). |
| *Probiotic use in pregnant women, breastfeeding mothers and infants* | | | | | | | |
| Kalliomaki et al. [59, 60] | 2001 2003 | Finland | RCT | High-risk infants | $N = 132$ mother-infants pairs | LGG prenatally and 6 months postnatally to mothers or infants | Decreased eczema at age 2 years, RR = 0.51 (0.32–0.84), and 4 years, RR = 0.57 (0.33–0.97). No effect on asthma or allergic rhinitis. |
| Kim et al. [61] | 2010 | Korea | RCT | High-risk infants | $N = 112$ mothers | *B. bifidum*, *B. lactis*, *L. acidophilus* from 4 to 8 weeks before delivery to 6 months after delivery, exclusively breastfed for first 3 months | At age 1 year, decreased cumulative incidence of eczema ($p = 0.029$). No effect on total IgE level or atopy. |
| Koop et al. [62] | 2008 | Germany | RCT | High-risk infants | $N = 105$ mothers | *LGG* from 4–6 weeks prior to delivery to 6 months postnatally | At age 2 years, no decrease in atopic dermatitis or severity of atopic dermatitis. |
| Wickens et al. [63, 64] | 2008 2012 | New Zealand | RCT | High-risk infants | $N = 474$ | *L. rhamnosus* HN001 or *B. animalis* subsp. *lactis* HN019 to mothers from 35 weeks until 6 months postnatally if breastfeeding and to infants from birth to 2 years | *L. rhamnosus* but not *B. animalis* decreased eczema at 2 years, HR = 0.51 (0.30–0.85), and at 4 years, HR = 0.57 (0.39–0.83), and decreased rhinoconjunctivitis at 4 years, RR = 0.38 (0.18–0.83). No effect on atopy. |

*Abbreviations: RCT* randomized controlled trial, *NNT* number needed to treat, *OR* odds ratio, *RR* relative risk, *HR* hazard ratio, *C-section* cesarean section, *LGG Lactobacillus rhamnosus* GG

## Breastfeeding

Besides initial colonization of microbiota in infants during delivery, breast milk provides the next earliest means of colonizing the newborn gut with varied microbiota. Common breast milk strains such as *Bifidobacterium*, *Lactobacillus*, and *Bacteroides* stimulate Treg cells and support the balance of Th1/Th2 responses [70]. Fermentation of breast milk oligosaccharides by bacteria in the gut creates an acidic environment that in turn promotes bacterial growth, while breast milk short-chain fatty acids enhance the barrier function of the gut and activate anti-inflammatory responses. Additionally, defensins and lactoferrin in breast milk inhibit pathogenic bacteria and help shape the composition of the microbiome. The composition of infant formulas along with the addition of prebiotics and probiotics is an attempt to mimic these beneficial aspects of breast milk. A randomized controlled trial investigated the use of prebiotics in low-risk infants recruited before age 2 months and found a decreased risk of atopic dermatitis in the prebiotic formula group versus regular formula (5.7% vs. 9.7%, $P = 0.04$) with a NNT of 25 infants [42].

There are studies that suggest a protective effect of breastfeeding on atopic diseases. Meta-analyses found that exclusive breastfeeding in the first 3 months was associated with a decreased risk of asthma (OR = 0.70, 95% CI 0.60–0.81) and atopic dermatitis (OR = 0.68, CI 0.52–0.88), but was not significant for allergic rhinitis (OR = 0.74, 95% CI 0.54–1.01) [71–73]. The effect of breastfeeding on asthma was more pronounced in populations from medium- to low-income countries. Another meta-analysis showed that exclusive breastfeeding in the first 3 months was associated with a decreased risk of atopic dermatitis as compared to conventional formula feeding (OR = 0.70, 95% CI 0.50–0.99) [74]. A systematic review of breastfeeding for at least 4 months in high-risk infants showed a decreased risk of cow's milk allergy but not food allergy in general at 18 months compared to conventional formula feeding [75]. It is unclear if breastfeeding is protective for food allergy in the general population [76].

It also has not been established whether the duration of exclusive breastfeeding, particularly beyond the first 3 months of life, has any effect on atopic dermatitis [76]. In a more recent meta-analysis of studies on breastfeeding and allergic disease, a longer duration of breastfeeding was associated with decreased risk of asthma in children aged 5–18 years, allergic rhinitis in children ≤5 years, and eczema in children ≤2 years, without an association with food allergy [77]. Several studies investigating introduction of solid food prior to age 4 months, in other words exclusive breastfeeding less than 3 months, was associated with increased risk of eczema at age 10 years [78] and wheeze at age 7 years [79].

Other studies on breastfeeding and allergic disease are conflicting. One study showed that exclusive breastfeeding in high-risk infants in the first 3 months of life was associated with decreased risk of asthma and food allergy < age 7 years but an increased risk of asthma after age 7 years and increased

risk of food allergy and allergic rhinitis at age 44 years [80]. Results from studies showing increased risk of atopic disease with breastfeeding could be confounded by the fact that families with infants at high risk may make an effort to breastfeed longer [81].

## Environmental Exposures to Antigens

Exposure to house dust mites has long been implicated in the development of allergic disease. House dust mites have been shown to induce both innate and humoral immune responses, and a nonlinear dose response may determine the type of immunological response with low and high levels inducing protection and moderate levels inducing allergy [82, 83]. In a cohort of high-risk children, house dust mite exposure at age 1 year was associated with an increased risk of asthma at 11 years (RR = 4.8, $p = 0.05$) [84]. In two cohort studies, sensitization to house dust mite prior to age 5 years was associated with increased risk of asthma or persistence of asthma in later childhood [85, 86]. It has also been demonstrated that breast milk contains dust mite allergen that is immunologically active [87]. A subsequent birth cohort investigated early exposure to dust mite allergen via breast milk and found that high levels of dust mite in breast milk were associated with an increased risk of atopy at age 5 years and, in children with maternal history of asthma or allergy, an increased risk of asthma or allergy [88]. However, in another birth cohort study, while sensitization in general to indoor allergens was associated with asthma, sensitization did not correlate with the level of indoor allergen exposure at 6, 18, and 36 months [89]. This suggests that exposure to house dust mites may not be sufficient for the development of asthma and other factors may play a role in the development of sensitization.

Effect of pest exposure, such as cockroach and mouse, has also been investigated in the development of allergic disease. In a metropolitan birth cohort, increased risk for wheeze in the first year of life was associated with exposure to high levels of cockroach (OR = 1.83, 95% CI 1.09–3.08), mouse (OR = 1.83, 95% CI 1.14–2.95), and endotoxin (OR, 2.32; 95% CI, 1.19–4.54) in the first 3 months of life [90]. Another birth cohort reported a significantly increased risk of wheeze within the first 3 years in children with specific IgE to cockroach (OR = 3.3, 95% CI 1.8–6.2), mouse (OR = 4.6, 95% CI 2.3–9.0), or both (OR = 9.7, 95% CI 3.4–27.3), and this association was also seen for atopic dermatitis and allergic rhinitis [91]. These data appears to conflict with studies showing protection from living on a farm and proposed protection from animals and endotoxin. This may indicate that different factors in conjunction with exposure to allergens on a farm versus in the city may influence the development of atopy, such as, for example, air pollution.

Supporting the hygiene hypothesis, fungal diversity in one birth cohort was related to decreased risk of aeroallergen sensitization at age 6 years (OR = 0.26, 95% CI 0.10–0.70) and wheezing at 10 years (OR = 0.42, 95% CI 0.18–0.96) [92]. However, in a murine model, it was demonstrated that fungi induce Th2 responses in a non-IgE-dependent manner and Th17 responses via the innate immune system,

leading to a severe asthma phenotype [93]. Thus, exposure to fungi after establishment of atopic disease may be a risk factor for disease severity, while exposure prior to development of atopic disease may modulate the immune response in a protective manner.

While early exposure to common viruses has been associated with a decrease in allergic diseases, certain pathogenic viruses, such as respiratory syncytial virus (RSV) and human rhinovirus, may increase the risk of wheeze and asthma development. In a prospective cohort of children who developed severe RSV bronchiolitis infection in infancy, 48% developed asthma by age 7 years [94]. In a case-control study investigating the effect of severe RSV infection in infancy, RSV infection was significantly associated with asthma/recurrent wheezing, allergic rhinitis, and atopy to aeroallergens at age 13 years [95]. Differences in airway obstruction and reactivity of airways in children with history of RSV may indicate some remodeling of the airways as a contributing factor. Administration of anti-RSV monoclonal antibody, palivizumab, in a cohort of preterm infants was associated with decreased risk of recurrent wheezing up to age 2 years compared to untreated patients [96].

## Allergen Sensitization and Immunotherapy

While allergen sensitization does not always reflect clinical disease, it precedes and increases the risk of the development of atopic disease. A meta-analysis of food sensitization in the first 2 years reported increased risk of eczema (OR 2.7, 95% CI 1.7–4.4), asthma (OR = 2.9, 95% CI 2.0–4.0), and allergic rhinitis (OR = 3.1, 95% CI 1.9–4.9) between age 4 and 8 years [97]. In another study, the presence of allergic sensitization in hospitalized children with first-time wheezing was associated with increased risk of persistent asthma [98]. Thus, preventing sensitization could potentially decrease the risk of atopic disease. In a randomized open control study, 205 children aged 6–14 years with seasonal allergic rhinitis were treated with pollen immunotherapy, and of those without a history of asthma, the active group had significantly fewer new asthma symptoms after 3 years of treatment ($p < 0.05$) [99]. Two studies in dust mite-monosensitized children receiving immunotherapy indicated that treatment prevented new sensitizations when compared to controls [100, 101]. And in a murine model, milk epicutaneous immunotherapy (EPIT) was shown to prevent subsequent sensitization to peanut or house dust mite, as did transfer of milk Treg cells [102]. In a randomized, double-blind, placebo-controlled study, non-sensitized infants at high risk for atopy (≥2 first-degree relatives with atopic disease) were treated with oral house dust mite immunotherapy or placebo for 1 year [103]. There was a significant reduction in sensitization to any allergen ($p = 0.03$), but not specifically to house dust mite and not in the incidence of eczema, wheeze, or food allergy. More studies are needed to elucidate the protective benefit of immunotherapy against subsequent sensitization or development of new atopic disease.

## Role of Epicutaneous Allergen Exposure

Several studies have supported the theory that cutaneous exposure to allergens is more likely to lead to sensitization, while oral exposure is more likely to lead to tolerance [104]. This is most apparent in patients with eczema, where a compromised dermis increases the chance that the immune system will interact with allergens through the skin and may lead to the high rates of allergen sensitization seen in these patients. Food and aeroallergen sensitization has been reported to be as high as ~80% in children with atopic dermatitis [105]. However, not all sensitization manifests in clinical symptoms. In referral populations, IgE-mediated food allergy diagnosed by oral food challenges was reported in 33–37% of children with eczema [105, 106].

In several murine models, it has been demonstrated that primary exposure to egg proteins and peanut through eczema-like skin lesions leads to a Th2 response with production of antigen-specific IgE and systemic allergic reactions upon oral exposure [107–109]. In one of these studies, the mechanism was shown to be dependent on thymic stromal lymphopoietin (TSLP) and basophils [107]. In another study, not only did epicutaneous exposure of peanut and ovalbumin lead to an allergic response upon oral challenge, but it was shown that it prevented oral tolerance from developing [108].

In clinical studies, high household consumption of peanut was shown to be related to an increased risk of peanut allergy in infants with eczema, and peanut in dust from infants' bedrooms and play areas was shown to correlate with reported peanut consumption as well as activate basophils from peanut-allergic patients [110, 111]. Importantly, while high levels of environmental peanut exposure was associated with peanut sensitization, maternal consumption during pregnancy and lactation was not. A randomized control study showed that, conversely, early oral introduction of peanut in infants with severe eczema is protective and may prevent the development of peanut allergy, presumably prior to significant environmental exposure [112].

Genetics studies support the relationship between a disrupted skin barrier and atopic diseases. Filaggrin is a protein in the skin that binds epidermal cells together. Loss-of-function mutations in the profilaggrin gene (FLG) are present in 10% of the population and cause loss of moisture from the epidermis that leads to dry, scaly skin [113]. A meta-analysis of studies investigating filaggrin and atopic disease reported that FLG mutations were associated with increased risk of allergen sensitization, atopic dermatitis, allergic rhinitis, and asthma [114]. The incidence of food allergy was not evaluated in these studies. It was subsequently shown that FLG mutations were significantly associated to clinical peanut allergy even after controlling for coexisting atopic dermatitis [115]. Lastly, a murine model with FLG mutations reported development of food allergy upon epicutaneous exposure when the food allergen, peanut or ovalbumin, was co-exposed with dust mite or *Alternaria alternata* [116]. Oral exposure to peanut prior to skin exposure prevented development of anaphylaxis, unless *Alternaria alternata* exposure happened at the same time, suggesting dual allergens or other adjuvants may play a vital role in sensitization.

One of the keys to preventing allergen sensitization in childhood may therefore be prevention of epicutaneous allergen exposure prior to oral exposure by using barrier creams, repairing disruption to the skin barrier in eczema, and decreasing allergen burden. One randomized controlled trial examined the effect of daily emollient application beginning in the newborn period and reported a 50% relative risk (RR) reduction of atopic dermatitis at age 6 months [117]. This is a practical and feasible prevention therapy for infants at risk for eczema. In the presence of established eczema, early oral exposure to food allergens prior to significant epicutaneous exposure would be an important goal in the prevention of food allergy. Primary eczema prevention may decrease food and aeroallergen sensitization and the risk of clinical food allergy, allergic rhinitis, and asthma.

## Age of Food Introduction

In 2008 the American Academy of Pediatrics rescinded the recommendation to delay introduction of common food allergens due to a lack of evidence that it prevented the development of food allergy [75]. It was subsequently observed that in Israel, where infants ingest peanut early, the prevalence of peanut allergy was low at 0.17%, whereas in the United Kingdom (UK) where infants ingest almost no peanut, the prevalence of peanut allergy was ten times higher at 1.85% [118]. The concept that early introduction of food allergen might prevent instead of cause food allergy took hold.

In the pivotal Learning Early About Peanut (LEAP) study, 640 infants age 4–11 months at high risk for peanut allergy (defined as a history of severe eczema or egg allergy) were randomized to consume or avoid peanut until age 5 years [112]. Subjects were separated into two groups: those with negative peanut skin testing (unsensitized) versus those with a small positive peanut skin test (wheal of 1–4 mm diameter) at baseline. Those subjects who were randomized to introduce peanut and tolerated a peanut oral food challenge consumed 6 g of peanut protein over three meals each week. In those with baseline negative skin testing, 13.7% of subjects avoiding peanut and 1.9% of subjects assigned to consume peanuts developed peanut allergy ($p < 0.001$) for an 86% relative reduction. In those with baseline small positive testing, 35.3% of subjects avoiding peanut and 10.6% of subjects assigned to consume peanuts developed peanut allergy ($p = 0.004$) for a 70% relative reduction.

Guidelines for preventing primary and secondary (i.e. those showing some signs of sensitization on testing) peanut allergy based on the LEAP study findings have been established [119]. It is recommended that infants who are at risk for peanut allergy, specifically those with severe eczema, egg allergy, or both, be tested for sensitization to peanut first. If only one test is performed and peanut-specific IgE is undetectable <0.35 kU/L, or peanut skin prick test wheal is negative 0–2 mm, the risk of reaction is considered low (<10%) and introduction of peanut is encouraged. A peanut-specific IgE level can be sent by a general practitioner with the caveat that if the level is detect-

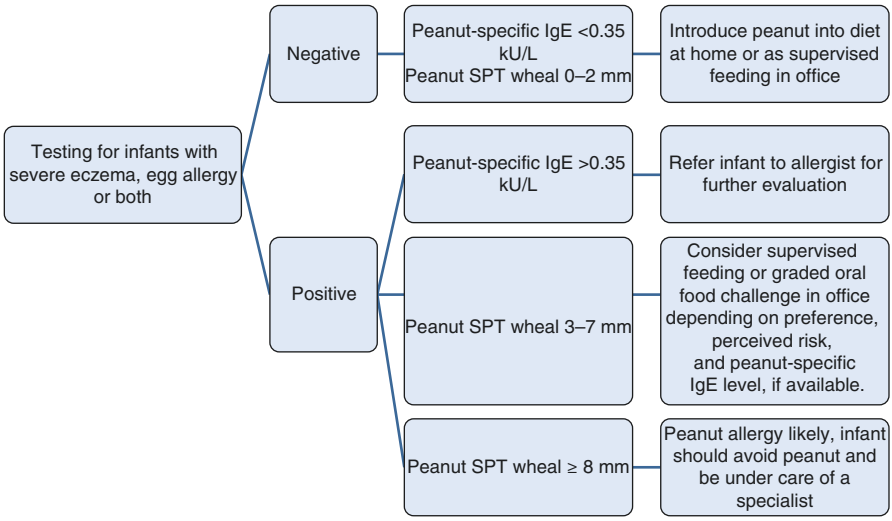


**Fig. 13.1** Peanut testing and introduction guidelines for infants 4 months and older at risk for peanut allergy [119]. SPT skin prick test

**Box 13.1 Recommendations on Introducing Peanut Into the Diet of an At-Risk Infant in an Effort to Prevent Peanut Allergy** [119]

Goal: 6–7 g of peanut protein over three servings weekly, with a maximum of 2 g per serving

- Option 1: 2 tsp of smooth peanut butter (~2 g peanut protein) thinned out with hot water (then cooled) or mixed into previously tolerated fruit or vegetable baby food puree
- Option 2: 2 tsp of peanut flour or peanut powder (~2 g peanut protein) mixed into previously tolerated fruit or vegetable baby food puree
- Option 3: 21 pieces of peanut puffs (~2 g peanut protein); for age <7 months, soften with 4–6 tsp of water

Note: Whole/parts of peanuts (including chunky peanut butter) or clumps of peanut butter directly from a spoon should not be given to infants due to choking hazards.

able or there are other concerns for a peanut allergy, a referral to an allergist is recommended. If testing is positive, further evaluation is warranted as outlined in Fig. 13.1. When peanut is introduced in infants, 6–7 g of peanut protein over three servings weekly is recommended, with a maximum of 2 g per serving. Box 13.1 contains recommendations on how to introduce peanut into an infant's diet. Additional details about introducing peanut in infancy are included in the guidelines by Togias et al. [119]. It is important to note that these guidelines are for high-risk infants and cannot

be extrapolated to the general population. Infants with siblings or a parent with a peanut allergy may also be considered at high risk as they are seven times more likely than the general population to develop a peanut allergy; thus tesing may considered for this population as well [120]. Otherwise there are no current recommendations to avoid or proactively introduce peanut for the general population.

Studies investigating the effect of introducing other food allergens early have reported mixed results. From the same team as the LEAP study, the Enquiring About Tolerance (EAT) study randomized breastfed infants from the general populations to early introduction of peanut, egg, cow's milk, sesame, fish, and wheat at age 3 months versus standard introduction of solids by 6 months [121]. Per-protocol but not intention-to-treat analysis showed significant decrease in food allergy prevalence by age 3 years (2.4 early vs. 7.3% standard introduction, $p = 0.01$) with a 67% relative risk reduction. Among individual foods, only peanut (0% early vs. 2.5% standard introduction, $p = 0.003$) and egg (1.4% early vs. 5.5% standard introduction, $p = 0.009$) was associated with a significant decrease in allergy prevalence. A dose response was noted, with consumption of 2 g of peanut and egg protein per week being the most effective. Introducing several food allergens to very young infants was challenging for practical reasons and perhaps bias (families with atopic histories may have been more hesitant to give foods that could be allergens to their infants), and this likely affected compliance and results in the intention-to-treat analysis. Adherence was 32% in the early introduction and 80.5% in the standard introduction groups, with adherence lower in cases where parents associated reported symptoms with early introduction of the foods. Importantly, early introduction of common food allergens appeared safe without reported anaphylaxis or adverse effects on growth or breastfeeding.

Studies investigating prevention of egg allergy by early introduction are conflicting. Similar to results of the EAT study, a cross-sectional population-based study found that introducing egg between age 4 and 6 months was associated with decreased risk of egg allergy by age 1 year [122]. Compared to introduction of egg between age 4 and 6 months, the adjusted OR when introducing egg between age 7 and 9 months was 1.3 (95% CI, 0.8–2.1), between 10 and 12 months was 1.6 (95% CI, 1.0–2.6), and after 12 months was 3.4 (95% CI, 1.8–6.5), ($p < 0.001$). Introduction of cooked egg was slightly more effective than baked egg with an OR of 0.2 (95% CI, 0.06–0.71). However, three double-blind randomized controlled trials reported no significant difference in egg allergy when introducing egg between 4 and 6 months versus placebo in infants from the general population, infants with eczema, and infants with a maternal history of atopy but no eczema [123–125]. It was noted that many infants were already sensitized and clinically reactive between 4 and 6 months. For this reason a stepwise approach in a subsequent double-blind randomized controlled trial was attempted by introducing 25 mg of egg protein/day from ages 6 to 9 months and then 125 mg of egg protein/day from ages 9 to 12 months to infants with eczema [126]. Preliminary analysis showed decreased egg allergy in the active group as compared to placebo (9% vs. 38%, respectively) for a RR of 0.22 (95% CI 0.08–0.61), $p = 0.0012$. Recruitment into the study was stopped due to these significant results. This last study's protocol may have acted as a form of immunotherapy in already sensitized infants with its stepwise protocol.

As recent as 2014, delayed cow's milk protein introduction in high-risk infants was being recommended to possibly decrease the incidence of atopic dermatitis, wheezing, and cow's milk allergy [76, 127, 128]. The EAT study did not report decreased prevalance of cow's milk allergy in children with early introduction in the general population [121]. Lowe et al. randomized infants with family history of allergic disease to conventional cow's milk versus hydrolyzed whey or soy formula when no longer breastfeeding and did not find a decrease in eczema or food reactions in infants on nonconventional formulas in the first 2 years of life [129]. In a retrospective case-control study, delayed (>1 month of age) or no (less than once a day) cow's milk formula introduction was associated with increased IgE-mediated cow's milk allergy, with an OR of 23.74 (95% CI, 5.39–104.52) compared to controls [130]. In a prospective population-based cohort study, authors report that 0.05% of infants who were introduced to cow's milk protein within the first 14 days of life versus 1.75% of infants who were introduced between age 105 and 195 days of life developed IgE-mediated cow's milk allergy, suggesting very early supplementation may prevent allergy [131]. Early introduction of cow's milk protein in infants needs further study, and future recommendations should be sensitive to the myriad of health benefits from breastfeeding. Overall, it may be that there are different windows of tolerance for different allergenic foods.

## Maternal Avoidance Diets

Due to the lack of evidence, maternal avoidance of common food allergens during pregnancy or lactation is not recommended for the primary prevention of allergic disease [76]. Studies examining the effect of maternal ingestion of peanut on childhood peanut allergy are conflicting. In one cohort study of infants and toddlers with egg or milk allergy, frequent maternal ingestion of peanut during pregnancy (two or more times a week) was associated with peanut IgE ≥ 5 kU/L, a level considered predictive of clinical allergy in young children (OR = 2.9, 95% CI, 1.7–4.9; P < .001), particularly in exclusively formula-fed infants (OR = 4.99, 95% CI 1.69–14.74; P < .004) [132]. Three studies found no association of maternal peanut avoidance during pregnancy and lactation and the development of peanut allergy in children [133–135]. And by contrast, one study reported frequent maternal consumption of peanut and tree nuts during pregnancy (≥5 times per month compared to <1 time a month) decreased the risk of peanut or tree nut allergy in their children at age 16–20 years (OR = 0.31, 95% CI 0.13–0.75) [136]. Overall, a systematic review of clinical studies concluded that results do not support an association between maternal consumption of peanut and sensitization or clinical allergy in children and that murine models suggest that the dose of peanut exposure may influence the development of allergy versus tolerance in offspring [137]. Several studies have reported that maternal avoidance of cow's milk and egg during pregnancy was not associated with allergic disease in childhood [76]. And lastly, a systematic review reported no protective effect of maternal dietary antigen avoidance during pregnancy or lactation on atopic eczema in the first 18 months or on atopy in the first 7 years [138]. The

ootential benefits of allergen avoidance during pregnancy and lactation do not appear to outweigh the risks of nutritional deficiencies in mother and/or infant, or the risk of cessation of breastfeeding due to an unnecessarily restricted maternal diet.

## Vitamin D

Vitamin D is considered immunomodulatory with anti-inflammatory and antimicrobial functions. It has been shown that vitamin D downregulates IFN-γ production and increases IL-10 production by peripheral mononuclear cells (PBMCs) from healthy controls [139]. There is some evidence that vitamin D promotes T regulatory (Treg) development [140]. Conversely, in a murine model, vitamin D was shown to promote production of Th2 cytokines (IL-4 and IL-13) along with IgE [141]. Other studies suggest that vitamin D plays a role in airway and intestinal microbiome and in response to respiratory infections [142].

Deficiency of vitamin D has been associated with autoimmunity, malignancy, and lung disease. A modern, more sedentary lifestyle, use of sunblock, and lack of vitamin D-containing foods in the Western diet (e.g., fish) may contribute to vitamin D deficiency. An observational study showed that epinephrine auto-injectors prescriptions were highest in more northern states in the United States, with Massachusetts having the highest rate and Hawaii the lowest [143]. Subsequently it was shown that the incidence of food allergy anaphylaxis was higher in northern versus southern US (RR = 1.81, 95% CI 1.66–1.98; $P < 0.001$) states, while there was no difference for medication allergy anaphylaxis [144]. On the other hand, vitamin D fortification and supplementation are more common in industrialized countries where atopic diseases are also on the rise. This dichotomy may reflect a complicated relationship between vitamin D status and atopic disease.

In a high-risk birth cohort, 25-hydroxy vitamin D levels were inversely related to atopy and eczema at age 6 months, 2 years, and 3 years, and deficiencies were associated with increased risk for asthma, eczema, and atopy at age 10 years [145]. Two recent high-risk large birth cohort studies investigating the effect of maternal vitamin D supplementation 2400–4000 IU/day during pregnancy on asthma symptoms in children reported decreased persistent wheeze, recurrent wheeze, or asthma, but results were not statistically significant [146, 147]. In a meta-analysis of four cohort studies, maternal vitamin D intake was associated with a decreased risk of wheeze (OR = 0.56, 95% CI 0.42–0.73), while a meta-analysis of two other studies showed that maternal vitamin D intake was not related to risk of asthma at age 5 years [148]. One study implicated cod liver oil supplementation in early childhood with increased atopy in children aged 6–16 years (OR = 1.78, 95% CI 1.03–3.07); however it is possible not all confounding factors were considered [149]. Interestingly, in one recent general population birth cohort, dietary sources of vitamin D but not vitamin D supplements during first and second trimester were associated with decreased risk of allergic rhinitis in children at school age (OR = 0.79, 95% CI 0.67–0.92 and OR = 0.80, 95% CI 0.68–0.93) [150]. It has been suggested that synthesized vitamin D may be related to increased allergy [151]. Overall, studies on the protection of vitamin D against the development of atopic diseases are inconclusive, and additional research is needed.

## Dietary Influences

Dietary influences may be an environmental factor that impacts the immune system and allergic responses through its effect on inflammation. Studies have investigated the relationship between atopic disease and specific nutrients, such as vitamin D, as well as dietary patterns, such as Mediterranean versus Western diet. Common in southern European countries such as Italy and Greece, the Mediterranean diet was associated with lower coronary artery disease mortality in the 1990s [152]. The Mediterranean diet is high in antioxidants, fiber, monounsaturated fatty acids (MUFA), and omega-3 polyunsaturated fatty acids (PUFA), and low in saturated fatty acids, omega-6 PUFA, sugar, and sodium. This means a diet high on fruits, vegetables, whole grains, and olive oil; moderate on legumes, nuts, low-fat dairy, eggs, fish, seafood, and poultry; and low on red meat, sweets, and processed foods. The Western diet on the other hand is predominated by processed foods, red meat, refined grains, high-fat dairy, and sweets [153].

In general, the Western diet is considered pro-inflammatory. High dietary fat has been shown to increase inflammatory markers such as serum IL-6, tumor necrosis factor (TNF)α, and c-reactive protein (CRP) [154]. Increased CRP and IL-6 levels have been associated with neutrophilic asthma and worse asthma outcomes [155]. Specific dietary fat profiles, such as an overbalance of omega-6 to omega-3 fatty acids, may affect atopic disease by increasing prostaglandin E2 (PGE2) production [156]. This skews the immune response to a Th2 phenotype by reducing IFNγ and increasing the production of IgE. Low antioxidants in the diet may decrease the ability to offset damage by reactive oxygen species, activating the nuclear factor kappa B (NFκB) pathway leading to increased inflammation of the airway mucosal surfaces [157]. Saturated fats may directly activate toll-like receptor 4 (TLR4), which also leads to activation of NFκB pathway. Airway inflammation may increase sensitization due to greater exposure of submucosal T cells to antigens and increase the risk of asthma development [158]. Conversely, omega-3 PUFA, unsaturated fatty acids, antioxidants, fiber, vitamin E, vitamin C, β-carotene, and magnesium present in the Mediterranean diet have been associated with low levels of inflammation [158].

## Mediterranean Diet

Several studies have investigated the effects of the Mediterranean diet during childhood on the development of atopic disease. Primarily cross-sectional and cohort studies have been performed in mostly general populations of different ages using a variety of data collection, analysis methods, confounder controls, and outcomes. With such heterogeneity, it is not surprising that results are inconsistent (Table 13.2). A meta-analysis reviewing the effect of the Mediterranean diet in children found that the highest adherence scores were protective in subjects from Mediterranean populations (<100 km from the Mediterranean coast) against current wheeze (OR 0.85, 95% CI 0.75–0.98) and current severe wheeze (OR 0.66, 95% CI 0.48–0.90),

**Table 13.2** Studies investigating effect of Mediterranean diet during pregnancy and childhood on childhood atopic disease

| Authors | Year | Country | Type of study | Population | Subjects | Measure | Results [if OR = odds ratio (95% CI)] |
|---|---|---|---|---|---|---|---|
| *During pregnancy* | | | | | | | |
| Chatzi et al. [159] | 2008 | Spain | Cohort | Children of mothers presenting for prenatal care | $N = 507$ mothers, 460 children | Maternal diet during pregnancy and adherence score | At age 6.5 years, protective for:<br>Persistent wheeze, OR = 0.23 (0.09–0.6)<br>Atopy, OR = 0.34 (0.12–0.97)<br>Atopic wheeze, OR = 0.30 (0.32–0.97) |
| De Batlle et al. [160] | 2008 | Mexico | Cross-sectional | Random sample of children from Mexicali age 6–7 years | $N = 1476$ | Maternal diet during pregnancy and adherence score | No association with asthma, wheezing, rhinitis, sneezing ever, itchy watery eyes. Protective for current sneezing, OR 0.71 (95% CI 0.53–0.97). |
| Castro-Rodriquez et al. [161] | 2010 | Spain | Cohort | Infants/toddlers mean age 16 months | $N = 1409$ | Maternal diet during pregnancy and adherence score | No association of diet with wheezing in the first year. Olive oil consumption was associated with less wheezing during first year, OR = 0.57 (0.4–0.9). |
| Lange et al. [162] | 2010 | US | Cohort | Mother-infant pairs | $N = 1376$ | Maternal diet during 1st and 2nd trimester and adherence score | At age 3 years, no association with recurrent wheeze. |
| Chatzi et al. [163] | 2013 | Spain and Greece | Cohort | Mother-infant pairs | $N = 2516$ | Maternal diet during pregnancy and adherence score | No association with wheeze or eczema in the 1st year of life. |
| *During childhood* | | | | | | | |
| Chatzi et al. [164] | 2007 | Greece | Cross-sectional | Rural children aged 7–18 years | $N = 690$ | Dietary intake last 12 months and adherence score | Protective for allergic rhinitis, OR = 0.34 (0.18–0.64). Decreased risk but not significant for wheezing and atopy. |
| Garcia-Marcos et al. [165] | 2007 | Spain | Cross-sectional | Children aged 6–7 years | $N = 20,106$ | Dietary intake and adherence score | Protective in girls for current severe asthma, OR = 0.9 (0.82–0.98). No association with current rhinitis in either gender. |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Castro-Rodriquez et al. [166] | 2008 | Spain | Cross-sectional | Random sample of preschools from 3 cities, mean age = 4.08 ± 0.8 years | $N = 1784$ | Dietary intake last 12 months and adherence score | Protective for current wheezing, OR = 0.54 (0.3–0.9). |
| De Batlle et al. [160] | 2008 | Mexico | Cross-sectional | Random sample of children age 6–7 years | $N = 1476$ | Dietary intake last 12 months and adherence score | Protective for: asthma, OR = 0.60 (0.40–0.91); wheezing, OR = 0.64 (0.47–0.87); rhinitis, OR = 0.41 (0.22–0.77; current sneezing, OR = 0.71 (0.52–0.96); current itchy-watery eyes, OR = 0.63 (0.42–0.95). |
| Chatzi et al. [159] | 2008 | Spain | Cohort | Children of mothers presenting for prenatal care | $N = 468$ | Yearly dietary intake and adherence score | At age 6.5 years: negatively associated with persistent wheeze and atopy but not significant. |
| Romieu et al. [167] | 2009 | Mexico | Cohort | Children aged 6–14 years | $N = 158$ asthmatic, 50 non-asthmatic | Dietary intake last 12 months and adherence score | Positively related to lung function ($p < 0.05$) in asthmatic children. No effect in non-asthmatics. |
| Nagel et al. [168] | 2010 | 20 countries | Cross-sectional | Children aged 8–12 years | $N = 50{,}004$ | Dietary intake last 12 months and adherence score | Protective for wheezing, OR = 0.97 (0.94–0.0.99) per unit increase of score ($P_{trend} = 0.03$), and asthma OR = 0.95 (0.92–0.99) per unit ($P_{trend} = 0.03$). Not significant for positive SPT. |
| Suárez-Varela et al. [169] | 2010 | Spain | Cross-sectional | Children aged 6–7 years | $N = 13{,}153$ | Dietary intake and adherence score | No association with atopic dermatitis. |
| Arvaniti et al. [170] | 2011 | Greece | Cross-sectional | Children aged 10–12 years | $N = 700$ | Dietary intake and adherence score | Score inversely associated with wheeze ($p = 0.001$), exercise wheeze ($p = 0.004$), asthma diagnosis (p-0.002), asthma symptoms ($p < 0.001$). Each unit score increase associated with 14% lower likelihood of asthma symptoms, OR = 0.86 (0.75–0.98). |

(continued)

**Table 13.2** (continued)

| Authors | Year | Country | Type of study | Population | Subjects | Measure | Results [if OR = odds ratio (95% CI)] |
|---|---|---|---|---|---|---|---|
| Grigoropoulou et al. [171] | 2011 | Greece | Cross-sectional | Children age 10–12 years | $N = 1125$ | Dietary intake and adherence score | Protective for asthma in urban areas, OR = 0.81 (0.77–0.91) and rural areas, OR = 0.87 (0.75–1.00). |
| Akcay et al. and Tamay et al. [172, 173] | 2013 2014 | Turkey | Cross-sectional | Children aged 13–14 years | $N = 9991$ | Dietary intake and adherence score | No association with asthma or physician-diagnosed allergic rhinitis. |
| Tamay et al. [174] | 2014 | Turkey | Cross-sectional | Children aged 6–7 years | $N = 9875$ | Dietary intake and adherence score | No association with allergic rhinitis. |
| Silveira et al. [175] | 2015 | Brazil | Case-control | Children aged 3–12 years | $N = 268$ cases, 126 controls | Dietary intake last 12 months and adherence score | No association with severity of asthma. |
| Rice et al. [176] | 2015 | Peru | Case-control | Children aged 9–19 years | $N = 287$ cases, 96 controls | Dietary intake and adherence score | Protective for asthma, OR = 0.55 (0.33–0.92). No association with asthma control, FEV1, allergic rhinitis, or atopic status (detectable specific IgE). |
| *During pregnancy and childhood* | | | | | | | |
| Castro-Rodriquez et al. [177] | 2016 | Spain | Cohort | Mother-infant pairs and preschoolers | $N = 1000$ | Maternal diet during pregnancy and adherence score. Dietary intake at age 1.5 and 4 years and adherence score | At age 4 years: no association with current wheezing, rhinitis, or dermatitis. |

*Abbreviations: OR* odds ratio, *RR* relative risk

and in all subjects against asthma ever (OR 0.86, 95% CI 0.78–0.95) [178]. Only one of four studies investigating allergic rhinitis found a protective effect of the Mediterranean diet [164]. And the two studies investigating atopic dermatitis did not find an association between the Mediterranean diet and dermatitis [169, 177].

Studies investigating the effects of a maternal Mediterranean diet during pregnancy on the development of atopic disease in children are also inconsistent; however one study showed a protective effect for persistent wheeze, atopy, and atopic wheeze by age 6.5 years in children (Table 13.2) [159]. Another reported that olive oil consumption during pregnancy but not overall diet decreased the risk of wheezing in infancy [161]. Heterogeneity of the studies here as well highlights the need for randomized controlled trials. One such pilot study is currently ongoing investigating the effect of a Mediterranean diet during pregnancy on allergic disease in offspring [179]. Pregnant women who are at high risk for having a child with asthma or allergic disease due to atopic disease in self, partner, or another child have been recruited. Standard dietary advice is given to both intervention and placebo groups; however the intervention group receives additional dietary guidance at baseline, after 12 weeks, and on demand throughout the study.

## Western Diet

Some studies have investigated the effects of the Western diet on the development of atopic disease. In one birth cohort, daily maternal fast food intake during pregnancy was associated with increased risk of childhood severe and current asthma at age 3.5 years (RR = 4.46, 95% CI 1.36–14.6) [180]. In another birth cohort, high maternal meat intake and "processed" meat intake during pregnancy were associated with an increased risk of wheeze in infancy (RR = 1.22, 95% CI 1.00–1.49 and RR = 1.18, 95% CI 1.02–1.37, respectively) [163]. In a large cohort, intake of artificially sweetened soft drinks during pregnancy was associated with increased risk of asthma at age 18 months (OR = 1.23, 95% CI 1.13–1.33), without an association for sugar-sweetened soft drinks [181]. Surprisingly, one Japanese cohort study reported that a maternal Western diet during pregnancy was protective against childhood wheeze (OR = 0.59, 95% CI: 0.35–0.98) [182].

In children, a cross-sectional study also reported an association of high adherence to the Western diet with current asthma at age 8 years (OR = 2.59, 95% CI 1.15–5.81; $p = 0.02$) and age 11 years (OR = 2.20, 95% CI 1.07–4.51; $p = 0.03$), but not with allergic sensitization [183]. Even in younger children, the Western diet was associated with asthma symptoms and frequent wheeze at 3 years of age (RR = 1.39, 95% CI 1.02–1.89) [184]. Two cohort studies associated juice and sugary drinks with increased risk of asthma, one in children 2–9 years of age who consumed these drinks five times/week and the other in 11-year-olds who consumed ≥10 glasses per week of juice or >21.5 glasses per week of sugar-containing beverages [185, 186].

There are limited studies on the effect of obesity and development of atopic disease, but results have suggested that in older adolescents and adults, increased body

mass index (BMI) is associated with increased prevalence of asthma, but not hay fever or atopy [187]. In a cross-sectional study, obesity was associated with an increased risk for atopy (OR = 1.26, 95% CI 1.03–1.55), particularly with sensitization to food (OR = 1.59, 95% CI 1.28–1.98) [188]. Conversely, a birth cohort reported that higher weight gain in the first 15 months of life reduced the risk of atopy, although without an effect on allergic symptoms [189].

## Individual Nutrients

Other studies investigating risk of allergic diseases have focused on specific nutrients or groups of foods. Nuramtov et al. provides a good systematic review and meta-analysis of many of these studies, and details of the studies can be found in this publication [148]. In summary, meta-analysis of two case-control studies revealed higher vitamin A levels in children were protective against the development of asthma (OR = 0.25, 95% CI 0.1–0.4), while there was no association between maternal intake of β-carotene and risk of wheezing in children at age 2 years from two birth cohort studies. A meta-analysis of vitamin C intake from these same two birth cohort studies reported no association between maternal intake during pregnancy and wheezing at age 2 years, and other studies did not support a protective effect [148]. Meta-analysis from three cohorts demonstrated an association between maternal vitamin E intake during pregnancy and significantly decreased risk of wheezing in children at age 2 years (OR = 0.68, 95% CI 0.52–0.88), while other studies did not report an association [148]. A review of ten studies investigating selenium intake in pregnancy or early childhood did not show an association with wheezing, asthma, or atopic dermatitis [148]. Several studies suggest that zinc intake during pregnancy and early childhood is protective against childhood asthma, wheeze, and atopic dermatitis, and three case-control studies reported that serum or hair zinc levels were significantly lower in children with asthma or wheeze. However, a meta-analysis of two cohort studies showed no association of umbilical cord zinc levels and early childhood wheezing [148]. Overall, studies investigating dietary influences of allergic diseases have been judged as methodologically weak, and additional studies are needed.

## Fruits and Vegetables

A recent meta-analysis reviewed 41 studies investigating the effect of fruit and vegetable intake in children on asthma and wheezing and reported 22 studies that showed protection, 7 that did not show an association, and 12 that had mixed results [190]. In children aged 10–14 years, a meta-analysis of three to four

cross-sectional studies showed a protective effect of fruit intake against wheezing (OR = 0.75, 95% CI 0.60–0.94), but not of vegetable intake [148]. In pregnancy, results of studies investigating maternal fruit and vegetable intake on development of allergic disease in children are inconsistent. One cohort study reported decreased incidence of asthma in children with maternal ingestion of fruits and vegetables during pregnancy [191]. Another study reported maternal that intake of green and yellow vegetables and citrus fruit was protective against eczema, but not wheeze, OR = 0.41 (95% CI 0.24–0.71) and 0.53 (95% CI 0.30–0.93), respectively [192]. Maternal apple intake was shown to be protective against wheeze (OR = 0.63, 95% CI 0.42–0.95) and asthma (OR = 0.54, 95% CI 0.32–0.92) in children at age 5 years in another cohort study without an association with vegetable intake [193]. Conversely, maternal ingestion of vegetables more than eight times per week was protective against persistent wheeze, without an association with fruit intake [159]. An additional study reported no association of maternal fruit and vegetable intake and risk of childhood wheeze [194]. And lastly, one study associated vegetable intake during pregnancy with increased risk of allergic disease (atopic dermatitis, food allergy, and asthma) in infancy [195]. It appears that while fruit and vegetable intake during pregnancy may not have an effect on atopic disease in childhood, fruit and vegetable intake during childhood may be beneficial in decreasing asthma and associated symptoms.

## Omega-3 Polyunsaturated Fatty Acids and Fish

A meta-analysis of maternal fish intake during pregnancy did not find an association with childhood atopy, eczema, allergic rhinitis, wheeze, asthma, or food allergy [196]. Of note, two of these studies indicated that maternal shellfish intake was a risk for childhood food allergy, eczema, and wheezing [197, 198]. However, a review of maternal intake of omega-3 PUFA or fish during pregnancy reported that 9 of 13 cohort studies and 5 of 7 randomized controlled studies showed a protective effect against childhood allergic disease [199]. Meta-analysis of these studies showed a decreased risk of atopic eczema (RR = 0.53, 95% CI 0.35–0.81; $P = 0.004$), atopy (RR = 0.68, 95% CI 0.52–0.89; $P = 0.006$), sensitization to egg (RR = 0.55, 95% CI 0.39–0.76; $P = 0.0004$), and sensitization to any food (RR = 0.59, 95% CI 0.46–0.76; $P < 0.0001$) in infancy. Authors cautioned that due to heterogeneity of studies, the meta-analysis was limited, and these dietary factors should be viewed as suggestive but not conclusive. This likely holds true for studies investigating fish or fish oil intake in children. A meta-analysis of fish intake during childhood reported a protective effect against eczema (RR = 0.61, 95% CI 0.47–0.80) and allergic rhinitis (RR = 0.54, 95% CI 0.36–0.81) [196]. However, a double-blind randomized controlled trial in infants at high risk for atopy showed that daily fish oil consumption from birth to age 6 months did not prevent eczema, food allergy, asthma, or sensitization at 12 months of age [200].

## Toxins

An association between tobacco smoke and air pollutants with allergic disease has been observed in several studies. One birth cohort showed that pre- and postnatal exposure to smoke increased the risk of food allergen sensitization (OR = 2.3, 95% CI 1.1–4.6), but not inhalant allergen sensitization [201]. In a large birth cohort, regular maternal cigarette smoking increased the risk of atopy (OR = 4.8, 95% CI 1.3–18.2) and wheezing (OR = 5.7, 95% CI 1.7–19.0) in children at 10 years when both parents were allergic [202]. Results were also significant for children with one allergic parent, but not if there was no parental history of allergy, and there was no association with allergic rhinitis. Even without maternal smoking, secondhand smoking in the first year of life increased risk of food sensitization (OR 1.47, 95% CI 1.08–2.00) and atopic eczema (OR 1.62, 95 CI 1.20–2.18) in childhood [203]. A meta-analysis of 15 European birth cohorts showed that maternal exposure to secondhand smoke during pregnancy increased the risk of asthma up to age 2 years (OR 1.11, 95% CI 1.03–1.20) and this risk increased further in children with postnatal exposure of secondhand smoke, even further in children from atopic families [204]. Maternal secondhand smoke exposure alone was also associated with increased risk of asthma at age 7 years even when adjusting for postnatal secondhand smoke in the home [205]. In a meta-analysis of cohorts, secondhand smoke exposure in children and adolescents was associated with increased risk of allergic rhinitis (RR = 1.40, 95% CI 1.24–1.59), atopic dermatitis (RR = 1.36, 95% CI 1.17–1.46), and food allergy (RR = 1.43, 95% CI 1.12–1.83) [206].

Pre- and postnatal exposure to air pollutants, including benzene, nitrogen dioxide, particulate matter less than 10 μm in diameter ($PM_{10}$), and $PM_{2.5}$, has been associated with decreased lung function (FEV1 <80% of predicted value), increased risk of wheezing, increased risk of asthma, and increased atopy in early and late childhood [207–212]. In a birth cohort, exposure to traffic-related nitrogen oxide pollutants during the first year of life increased the risk of pollen sensitization at age 4 years (OR = 1.83, 95% CI 1.02–3.28) and food sensitization at age 8 years (OR = 2.30, 95% CI 1.10–4.82) [213]. One study suggests a dual antigen process in the development of asthma where children who were atopic by age 4 years and exposed to high levels of traffic-related air pollution during the first year of life had increased risk of asthma at age 7 years compared to nonatopic children (10% vs. 27%, respectively, $p = 0.038$) [214]. However, a meta-analysis of five European birth cohorts did not find a significant association between pollutant exposure at birth address and asthma or current wheeze between the ages 4–5 and 8–10 years [215]. A subsequent meta-analysis using multiple European birth cohorts with over 14,000 children studied more longitudinal data and reported that exposure at the birth address to nitric oxide and $PM_{2.5}$ was associated with increased risk of incident asthma up to 14–16 years of age (OR = 1.13 per 10 μg/m$^3$, 95% CI 1.02–1.25 and OR = 1.29 per 1 unit, 95% CI 1.0–1.66, respectively) [216]. There was no effect on allergic rhinitis. A possible mechanism is suggested by two studies showing decreased cord blood Treg cells related to maternal exposure to $PM_{10}$ 3 months

before pregnancy and during pregnancy in one study and related to maternal smoking or exposure of environmental tobacco smoke during pregnancy with increased risk of atopy in 1st year of life in another [217, 218].

## Conclusion

The increase in asthma and allergic disease in recent decades cannot be accounted for by intergenerational genetic changes. Thus, environmental factors likely play a significant role, and a summary of potential risks and interventions can be found in Table 13.3. The hygiene hypothesis has evolved into a discussion of the complex

**Table 13.3** Summary of prevention of asthma and allergic disease in childhood

| Potential risk | Potential intervention |
|---|---|
| **Suggestive evidence** | |
| *Hygiene theory*: decreased exposure to beneficial microbials resulting in microbiota imbalance and immunological shift toward more allergic (Th2) responses | |
| Birth by cesarean section (C-section) | Encourage measures that decrease rates of C-section. |
| Formula feeding | Encourage measures that increase breastfeeding rates. Supplement formula with pre/probiotics. |
| Antibiotic use in infancy | Prudent use of antibiotics during infancy. |
| Decreased exposure to older children (siblings/daycare) as proxy for microbial infection risk | Purposeful exposure to microbial infections not advised for other health reasons. Some pathogenic viruses, such as RSV, may increase atopic risk, and vaccines such as palivizumab may decrease this risk. |
| Decreased exposure to parasites, primarily in industrialized countries | Purposeful exposure to parasites not advised for other health reasons. |
| Living in suburban or urban cities as opposed to rural areas or on a farm as a proxy for decreased microbial diversity | Risks not fully understood to recommend purposeful exposure to particular fungal or bacterial strains. |
| Decreased exposure to pets or farm animals primarily as a proxy for decreased endotoxin exposure | Risks not fully understood to recommend purposeful exposure to endotoxin. Conflicting evidence shows increased atopic risk with high levels of endotoxin and mouse exposure. |
| Decreased farm fresh milk consumption | Purposeful exposure to unpasteurized milk not advised for other health reasons. |
| Gut microbiota not colonized with beneficial microbials | Probiotic supplementation in pregnancy, during lactation, and in infancy. Which probiotic is the most beneficial is still under investigation. Some strains may increase atopic risk. |

(continued)

**Table 13.3** (continued)

| Potential risk | Potential intervention |
|---|---|
| *Environmental allergen exposure* | |
| Cutaneous exposure of food allergens | Repair of skin disruption and early oral introduction (i.e., prior to cutaneous exposure) of food allergens in infants, particularly those with eczema. |
| Cockroach exposure | Cockroach avoidance for at-risk children. Exposure to high levels of cockroach in urban populations and cockroach sensitization has been associated with increased atopic risk. Casual relationship is unclear. |
| *Dietary factors* | |
| Exposure to common food allergens | Early introduction of common food allergens may be protective. Evidence is supportive of peanut introduction in infancy. Additional studies are needed for other foods. |
| Western diet (high in processed foods, red meat, refined grains, high-fat dairy, and sweets) | Encourage the Mediterranean diet (high in antioxidants, fiber, whole grains, MUFA, and omega-3 PUFA). Meta-analysis shows a protective effect of diet in childhood. Data not supportive of protective effect of diet during pregnancy but randomized controlled trial currently underway. |
| Fruit and vegetables | Intake during childhood may be beneficial for decreasing asthma symptoms, but intake during pregnancy may not have an effect on prevention of childhood allergic disease. |
| Omega-3 PUFA and fish | Meta-analysis of maternal intake of omega-3 PUFA or fish during pregnancy shows protective effect against childhood allergic disease. Double-blind randomized controlled trial of fish oil intake during infancy did not show protection. |
| *Toxins* | |
| Exposure to tobacco smoke | Pre- and postnatal secondhand exposure to tobacco smoke increases risk for childhood allergic disease. Encourage smoking cessation and avoidance of secondhand smoke. |
| Air pollutants | Pre- and postnatal air pollutant exposure increases risk for childhood asthma. Encourage measures that decrease air pollution. |
| **Weak/conflicting evidence** | |
| *Environmental allergen exposure* | |
| Dust mite exposure | Encourage dust mite avoidance for at-risk children. Exposure to moderate levels has been associated with increased risk of atopy, while low and high levels have been associated with protection. Dust mite sensitization has shown increased risk for asthma. Some studies are conflicting. |
| *Dietary factors* | |
| Exposure to food allergens during pregnancy or lactation | Due to the lack of evidence, maternal avoidance of food allergens during pregnancy or lactation is not recommended for the primary prevention of childhood allergic disease. |

**Table 13.3** (continued)

| Potential risk | Potential intervention |
|---|---|
| Vitamin D | Overall, studies on vitamin D supplementation and protection against childhood allergic disease are inconclusive. Additional research is needed. |
| Vitamin A | A small number of studies show higher vitamin A levels in children are protective against asthma but there was no association between maternal intake of β-carotene and risk of wheezing in children. |
| Vitamin C | No association between vitamin C intake and allergic disease. |
| Vitamin E | A meta-analysis showed that maternal intake of vitamin E during pregnancy was associated with decreased risk of wheezing in children; however other studies showed no association. |
| Selenium | No association of intake of selenium during pregnancy or early childhood with allergic disease. |
| Zinc | Several studies support protective effect of zinc intake during pregnancy and early childhood against allergic disease in children, but a meta-analysis of two birth cohorts showed no association between umbilical cord zinc levels and childhood wheezing. |

*Abbreviations: MUFA* monounsaturated fatty acids, *PUFA* polyunsaturated fatty acids

homeostasis of gut and lung microbiota that requires colonization and stimulation of the appropriate microbes. Determining the right probiotic supplementation at the right time will require additional study. Breastfeeding is encouraged for a myriad of health reasons; however studies are not conclusive as to its potential protection against atopic disease. There is little evidence that avoidance diets during pregnancy and lactation prevent food allergy or other allergic disorders and are not recommended at this time due to nutritional concerns and in an effort to support continued breastfeeding. A breakthrough study showing that early consumption of peanut during infancy can prevent the development of peanut allergy has led to new guidelines on food introduction. Introducing allergens during a window of opportunity in the manner that encourages tolerance and not sensitization is the primary goal. Other dietary interventions, such as adherence to a Mediterranean diet and vitamin D supplementation, are suggestive of protection, but the heterogeneity of studies provide weak evidence. Additional micronutrients and types of foods may influence allergy, but more data is needed. In terms of environmental toxins, environmental tobacco smoke has been correlated with an increased risk of asthma and allergic disease, and approaches to decrease exposure are vital for a myriad of health reasons. Studies suggest that traffic-related air pollution promotes inflammation and may directly or indirectly augment the allergic response. It is intriguing to think that preventing one allergic disease may in turn prevent the next along the atopic march, but it is likely not that straightforward. More probable is that allergic diseases are intertwined and affected by many of the similar immunologic, genetic, and environmental factors.

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