INTRODUCTION

Allergic diseases are among the most prevalent diseases in industrialized countries, affecting 18%–30% of women of childbearing age. While the risk of allergic diseases is higher in males during childhood, there is a shift during adolescence toward females. In particular, allergic rhinitis, asthma, atopic dermatitis, and food allergy represent the most important allergic phenotypes. In pregnancy, asthma has been associated with increased adverse perinatal outcomes, such as preterm birth, low birth weight, and preeclampsia. Thus, adequate disease control and education of patients and healthcare providers are essential to ensure the best care of mother and baby. This review focuses on allergic diseases during pregnancy and maternal counseling. Furthermore, this review provides the clinician with an up-to-date overview of the literature regarding management approaches and pharmacological treatment of allergic diseases during pregnancy. Finally, we discuss the impact of COVID-19 on pregnancy, particularly in patients with allergic diseases.
2 | IMMUNOLOGIC CHANGES DURING PREGNANCY AND THEIR IMPACT ON ALLERGIC DISEASES

Immunologic changes in pregnancy ensure a coordinated balance between effective immune defense against infections and subtle immune modulation specific to every pregnancy stage (Figure 1). It was previously suggested that maternal immunological tolerance must prevail throughout pregnancy to prevent rejection of the paternal antigens expressed in the fetus. However, implantation and placentation, fetal growth, and parturition are distinct processes that require a specific immune environment. Implantation and placentation require the presence of immune cells and involve creating a local pro-inflammatory process. Natural killer (NK) cells play an important role and interact with self-molecules such as HLA-C, and their response patterns vary from inflammatory to regulatory. The fine-tuning of these interactions is considered to be critical for placental perfusion. Dysregulation may be a key factor in the development of preeclampsia. Effective crosstalk between maternal decidual immune cells and fetal trophoblast cells is needed for the depth of trophoblast invasion and spiral arteries remodeling. Fetal growth and development require an anti-inflammatory milieu. The second trimester is characterized by a shift toward type 2 immunity and the promotion of regulatory mechanisms. T-regulatory cells (Tregs) have a central role in maintaining an anti-inflammatory environment by controlling immune responses against paternal antigens and protecting fetal cells from rejection by the maternal immune system. In the third trimester, a switch toward a more inflammatory and type-1 immune state happens in the context of labor and delivery. The influx of immune cells into the myometrium is crucial to promote the contraction of the uterus, delivery of the baby, and release of the placenta. The extensive exchange of factors between the mother and the child does not involve IgE. There is a general paradigm that IgE does not cross the placenta, which has been challenged recently, but there is limited knowledge on the potential role of IgE in pregnancy on IgE receptor-positive maternal effector cells. In line with the type 2 response promoting periods, an increase in IgE levels is observed. The clinical significance and impact of IgE levels on pregnancy outcomes remain unclear.

3 | MANAGEMENT OF ASTHMA

One of the most common chronic medical conditions in pregnancy is asthma. It represents the best-studied allergic disease in pregnancy. Uncontrolled asthma puts mother and baby at risk for adverse outcomes. Lack of disease control is associated with an increased risk of preeclampsia, cesarean delivery, preterm delivery, low birth weight, and small for gestational age babies. It also increases the risk of early-onset asthma in the offspring compared to non-asthmatic mothers and is more pronounced if asthma is uncontrolled early in pregnancy. Hormonal, immunological, and physiological changes are responsible for differences in the course of asthma during pregnancy.

**FIGURE 1** Immunologic changes during pregnancy. During the course of pregnancy type 2 responses are enhanced to protect the fetus as part of the process to maintain the immunological homeostasis at the feto-maternal interface. This increased type 2 responses may aggravate pre-existing allergic conditions.
Sex hormones such as estrogens, progesterone, and prostaglandin E have broncho-dilating effects, while hormones such as prostaglandin F promote broncho-constrictive effects. Immunological changes during pregnancy, which may enhance Type 2 phenomena that favor airway inflammation, are critical factors to consider. This adaptation of immune responses also increases susceptibility for viral respiratory tract infections in pregnant women, which are the most common triggers for asthma exacerbations. Influenza vaccination is recommended annually for asthma patients and can safely be done anytime during pregnancy. Since asthma at childbearing age is predominantly driven by Type 2 mechanisms, the relative Type 2 shift within a prolonged time of pregnancy may contribute to the deterioration of asthma control during pregnancy in a group of patients. Thus, asthma control and symptoms can change during pregnancy. Earlier work showed that about 30% of pregnant women suffer from asthma deterioration, 30% improve, and the remaining 30% experience no change in asthma control. This is based on data from the 1990s and early 2000. A recent Italian study indicates a lower risk for asthma deterioration in pregnancy of 18.8%. These data are based on extensive questionnaires, including the Asthma Control Test. Thus, a significant proportion of asthma patients experience worsening of their asthma during pregnancy.

Moreover, pregnancy-associated physiologic changes may contribute to poor disease control in pregnant patients. Increased blood volume, adipose tissue, rhinitis, and edema during pregnancy contribute to upper airway narrowing. GERD (gastroesophageal reflux disease) is common in pregnant women because of decreased esophageal sphincter tone and decreased gastric motility. Rhinitis occurs in about 65% of pregnant women with asthma and can be of the allergic and non-allergic type. Sleep-disordered breathing in pregnancy (SDBP)/Obstructive sleep apnea syndrome (OSAS) is often underdiagnosed during pregnancy and may be a reason for poor asthma control and increases the risk of several adverse maternal and fetal outcomes. Assessment of these comorbidities (such as obesity) and smoking history before and during pregnancy has the potential for preventive strategies to improve mothers’ and their offspring’s health.

The goals of asthma management in pregnancy are identical to the non-pregnant population: risk control and symptom reduction. A stepwise approach, for example, by the GINA guidelines, is recommended. The most frequently used medications are inhaled short-acting beta-agonists (SABA), inhaled corticosteroids (ICS), inhaled long-acting beta-agonists (LABA), leukotriene receptor antagonists (LTRA), inhaled tiotropium bromide, oral steroids (OCS), and biologicals (Table 1).

Fractional exhaled nitric oxide (FeNO)-based treatment strategies might be superior to exclusively symptom-based management and reduce asthma exacerbations during pregnancy and the risk of asthma in offspring. This was reported in 140 mother-child pairs, with children followed up to the age of six. Again, these data support the importance of close monitoring and optimal control of asthma-related inflammation.

4 | MANAGEMENT OF ASTHMA EXACERBATIONS

Asthma exacerbations during pregnancy are a significant clinical problem that is linked to poor pregnancy outcomes. Asthma exacerbations are associated with an increased risk of pregnancy-induced hypertension, cesarean delivery, low birth weight, small for gestational age (SGA), and preterm birth. Asthma exacerbation is proportional to the severity of the disease and ranges from 13% to 52% during pregnancy. Exacerbations that require oral corticosteroid treatment affect approximately 10% of pregnant asthma patients. Most exacerbations occur in the second, beginning of the third trimester, with a decrease in asthma-related symptoms during the last weeks of pregnancy. Treatment of exacerbations requiring emergency admission is similar to non-pregnant asthmatic women with special attention for adequate oxygenation. Inflammation-based asthma management via inhaled steroids reduces exacerbations and may also improve pregnancy outcomes.

In pregnancy, the course of asthma is difficult to predict therefore, regular monitoring is decisive. Risk factors for uncontrolled asthma or exacerbations during pregnancy include non-adherence to inhaled corticosteroid medication, pre-existing poor lung function, severe asthma prior to pregnancy, smoking, and obesity. Enrollment in an asthma management program with regular monitoring of disease activity and reassessment of inhaler use and techniques leads to improved medication adherence and asthma self-management.

5 | MANAGEMENT OF ATOPIC DERMATITIS IN PREGNANCY

The European task force on atopic dermatitis (ETFAD) proposed the following stepwise approach during pregnancy: the first step consists of emollient usage, which is extended in the next step by applying topical corticosteroids class II or III for 2 weeks or a maximum of 200 g total. If sufficient control is not reached, narrow-band UVB should be added. In case of control but relapse within a week, proactive interval therapy or topical calcineurin inhibitors are added. In case the topical treatment does not result in AD control, narrow-band UVB may be added. The next step would be systemic therapy. Patients and healthcare providers should discuss in an informed, shared process systemic treatment. Detailed recommendations regarding the current evidence for applying a paramount of medications used to treat AD in pregnancy are provided below.

6 | MANAGEMENT OF ALLERGIC RHINITIS AND CHRONIC RHINOSINUSITIS

The treatment of allergic rhinitis in pregnancy is similar to the general population. Pregnancy rhinitis due to hyperemia and edema of
| Drug class                      | Drug                  | Adverse fetal/neonatal outcomes                                                                                                                                                                                                                                                                                                                                 |
|--------------------------------|-----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| **Oral antihistamines**        |                       |                                                                                                     |                                                                                                     |                                                                                                     |                                                                                                     |
| **First (old) generation**     |                       |                                                                                                     |                                                                                                     |                                                                                                     |                                                                                                     |
| the second (new) generation    | Chlorpheniramine       | Based on animal studies, the use is not expected to increase the risk of malformations. Human studies have reported associations with varied birth defects                                                                                                                |                                                                                                     |                                                                                                     |                                                                                                     |
| antihistamines should be used  | Diphenhydramine       | Based on animal studies and available human data diphenhydramine is not expected to increase the risk of congenital anomalies                                                                                                                                    |                                                                                                     |                                                                                                     |                                                                                                     |
|                                | Doxepin               | Based on animal and rare human data, doxepin is not expected to increase the risk of congenital malformations                                                                                                                                      |                                                                                                     |                                                                                                     |                                                                                                     |
|                                | Hydroxyzine           | Hydroxyzine showed adverse pregnancy effects in rodents. Limited published data during human pregnancy                                                                                                                                         |                                                                                                     |                                                                                                     |                                                                                                     |
| **Second (new) generation**    | Azelastine            | Based on animal data, it is not expected to increase the risk of congenital anomalies. Fetal toxicity occurred at dose levels that produced maternal toxicity. No human data are available                                                                                   |                                                                                                     |                                                                                                     |                                                                                                     |
|                                | Bilastine             | Information is limited. Based on animal and human data, no increased risk of adverse pregnancy outcome expected                                                                                                                                                                                                                     |                                                                                                     |                                                                                                     |                                                                                                     |
|                                | Cetirizine            | Based on animal and human data, the use is not expected to increase the risk of adverse pregnancy outcomes                                                                                                                                                                                                                     |                                                                                                     |                                                                                                     |                                                                                                     |
|                                | Desloratadine         | Based on animal data, the use during pregnancy is not expected to increase the risk of congenital anomalies. No human data are available                                                                                                                          |                                                                                                     |                                                                                                     |                                                                                                     |
|                                | Fexofenadine          | Based on animal data and human reports for the parent compound, terfenadine, exposure during pregnancy is not expected to increase the risk of adverse outcomes                                                                                                                                                                                   |                                                                                                     |                                                                                                     |                                                                                                     |
|                                | Levocetirizine        | Based on animal and reported human data, the use is not expected to increase the risk of adverse pregnancy outcomes                                                                                                                                                                                                                     |                                                                                                     |                                                                                                     |                                                                                                     |
|                                | Loratadine            | Based on animal data and human reports, loratadine is not expected to increase the risk of adverse pregnancy outcomes.                                                                                                                                                                                                                          |                                                                                                     |                                                                                                     |                                                                                                     |
|                                | Rupatadine            | Based on animal data, therapy with rupatadine is not expected to increase the risk of congenital anomalies                                                                                                                                                                                                                                         |                                                                                                     |                                                                                                     |                                                                                                     |
| **Intranasal antihistamines**  | Azelastine            | Based on animal data, the use is not expected to increase the risk of congenital anomalies. No human data are available                                                                                                                                           |                                                                                                     |                                                                                                     |                                                                                                     |
|                                | Olopatadine           | Based on animal data, the use is not expected to increase the risk of congenital anomalies. No human data are available                                                                                                                                           |                                                                                                     |                                                                                                     |                                                                                                     |
| **Inhaled/intranasal corticosteroids** | Budesonide        | Budesonide, beclomethasone, and fluticasone are preferred as more safety information is available for these ICS. However, if the patient’s asthma was already well controlled on an alternative ICS (eg, ciclesonide, mometasone) prior to pregnancy, there is no need to change therapy |                                                                                                     |                                                                                                     |                                                                                                     |
|                                | Fluticasone           |                                                                                                     |                                                                                                     |                                                                                                     |                                                                                                     |
|                                | Beclomethasone        |                                                                                                     |                                                                                                     |                                                                                                     |                                                                                                     |
|                                | Mometasone            |                                                                                                     |                                                                                                     |                                                                                                     |                                                                                                     |
|                                | Triamcinolone         |                                                                                                     |                                                                                                     |                                                                                                     |                                                                                                     |
|                                | Ciclesonide           |                                                                                                     |                                                                                                     |                                                                                                     |                                                                                                     |
| **Inhaled bronchodilators**    | Albuterol             | Albuterol/salbutamol are the preferred and most studied beta-agonists for the treatment of asthma. Current available human data of albuterol/salbutamol is reassuring and safe in pregnancy, and the abovementioned malformations might be confounded by asthma severity or by chance findings |
|                                | Formoterol            | Based on experimental animal studies, inhalation therapy of asthma with formoterol is not anticipated to increase the risk of congenital malformations. Limited human data are reassuring                                                                                                   |                                                                                                     |                                                                                                     |                                                                                                     |
|                                | Salmeterol            | Based on experimental animal studies and human experience, salmeterol therapy during pregnancy is not expected to increase the risk of congenital anomalies                                                                                                                                                                        |                                                                                                     |                                                                                                     |                                                                                                     |

(Continues)
the nasal mucosa can worsen allergic rhinitis. The most important steps to treat allergic rhinitis are trigger avoidance and treatment with the appropriate medications: nasal corticosteroids and antihistamines, combinations thereof, and oral antihistamines. Chronic rhinosinusitis (CRS) is a prevalent disease, and women are more often affected than men. Specifically, CRS with nasal polyps is a Type 2 inflammatory disorder of the paranasal sinuses and linings of the nasal passages, which can aggravate during pregnancy. Therefore, accurate management is crucial to avoid asthma exacerbations. Treatment during pregnancy is similar to the non-pregnant population, and the use of add-on therapy with biologicals (omalizumab and dupilumab) for CRS with nasal polyps (CRSwNP) during pregnancy is described below.

7 | MANAGEMENT OF ANAPHYLAXIS

Anaphylaxis is a life-threatening event for both the mother and fetus. First-line treatment in pregnancy is similar to the general population, with early recognition and immediate administration of epinephrine. Recommendations specific to pregnant women are (1) positioning on the left side to avoid compression of the aortocaval vessels by the gravid uterus, (2) maintaining adequate uteroplacental perfusion by keeping the systolic blood pressure >90 mHg, and (3) monitoring fetal heart rate and status while applying treatment to the mother.

Key points such as adequate oxygen supply, intravenous fluid resuscitation, and use of adjunctive therapies apply to pregnant women in the same ways as to the normal population. Considerations have been described above regarding the use of adjunctive therapies like bronchodilators, antihistamines, and corticosteroids. Pregnant women with an established diagnosis of food, venom, and/or drug allergy require information about the safety of epinephrine and anti-allergic treatment and (re)education, ensuring that they are informed and recognize symptoms of anaphylaxis early on. This allows a timely intramuscular injection of epinephrine. As recommended for any patient with an epinephrine auto-injector, an anaphylaxis emergency action plan should be provided, and information on allergen avoidance and long-term prevention should be refreshed and assessed at every clinic visit.

8 | ANTI-ALLERGIC TREATMENT IN PREGNANCY

8.1 | Treating allergic diseases in pregnancy—evidence and considerations regarding the safety of medication

In order to discuss and inform about the safety of medications for the treatment of allergic disease for women of reproductive age and during pregnancy, the baseline risk of congenital malformations (e.g., cleft lip, neural tube defects, and heart defects) in the general population has to be outlined. This risk to deliver a baby with a congenital malformation is considered 3%-5% in the general population. Genetic and environmental risk factors must be individually addressed. Most importantly, the known risk of treated and untreated medical conditions during pregnancy must be discussed. The aspects that require consideration to effectively counsel women of reproductive age diagnosed with allergic diseases are summarized in Box 1.

8.2 | Antihistamines

Antihistamines are widely prescribed during pregnancy for various indications. A systematic evaluation of 54 studies assessing antihistamine use during pregnancy reported that the literature regarding antihistamine safety, especially congenital malformations, is reassuring. Non-sedating, second-generation antihistamines are recommended for treatment. First (old) generation antihistamines (H1 Antihistamines) are chlorpheniramine, diphenhydramine,
hydroxyzine, and ketotifen are not recommended for the treatment of allergic rhinitis due to their pregnancy independent safety profile. In the case of prescription, no increased rates of congenital malformation have been reported. Chlorpheniramine has been recommended as the first choice for first-generation antihistamines. The drugs of choice of second (new) Generation H1 Antihistamines with less sedating properties are Cetirizine and Loratadine.55

8.3 | Leukotriene antagonists

The leukotriene receptor antagonists (LTRAs), montelukast, and zafirlukast are prescribed for asthma control and maintenance therapy. Animal studies have not shown any teratogenic effect. A study on leukotriene receptor antagonists (LTRAs) (72 montelukast; 22 zafirlukast; and two on both) did not show any association with major congenital malformations or adverse perinatal outcomes.56 A study evaluated 166 pregnant women who used montelukast during the 1st trimester, and 56 (31.1%) used it throughout pregnancy. Out of 180 montelukast exposed pregnancies, there have been 160 (87.4%) live births with three sets of twins, 20 (10.9%) spontaneous abortions, three elective abortions, and one major malformation.57 A post-marketing surveillance report stated six reports of limb reduction defects (four of the retrospective and two prospective; from 1997 till 2006). A health insurance claims database study sponsored by the manufacturer did not report an association between limb defects and montelukast prescriptions to the mother.58 Given the limited data available, if better-tested treatment options fail, LTRAs can be considered second-line therapy during pregnancy. Recent black box warnings on mental health side effects related to montelukast should be mentioned during the counseling process even if the pregnancy-related data did not show an increased risk (https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-boxed-warning-about-serious-mental-health-side-effects-asthma-and-allergy-drug).

8.4 | Theophylline

Theophylline might be an alternative but not preferred add-on treatment for asthma in pregnancy. The ESR/TSANZ task force statement 2020 considers theophylline compatible with pregnancy. No evidence for an increased risk of congenital malformations after theophylline exposure was found in humans.59 Theophylline crosses the placenta, and serum levels in the therapeutic range can be found in the infant serum. Transient tachycardia, vomiting, and irritability have been reported in newborns of mothers treated with theophylline.55 During pregnancy, pharmacokinetics changes of theophylline include an increase in the volume of distribution, reduced clearance, and an increase in the half-life of the drug. These changes can lead to toxicity; therefore, the National Asthma Education and Prevention Program (NAEPP) expert panel recommends: “Theophylline use during pregnancy requires careful titration of the dose and regular monitoring to maintain the recommended serum theophylline concentration range of 5–12 µg/mL”.60

8.5 | Allergen immunotherapy

One randomized controlled trial on the safety of sublingual immunotherapy in pregnancy and several retrospective studies have reported that maintenance therapy during pregnancy does not lead to unfavorable outcomes.61,62

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**BOX 1  Counseling pregnant women with allergic disease**

| Preconception counseling and assessment | Assessment and monitoring during pregnancy |
|----------------------------------------|--------------------------------------------|
| Preconception baseline assessment (spirometry, skin test, questionnaire) | Disease activity assessment |
| Disease activity assessment | Frequency depending on the allergic disease and baseline assessment, e.g., asthma every 4–6 weeks |
| Assessment of medication knowledge, self-management skills, adherence, and inhalation techniques | Reassessment of adherence, medication knowledge, self-management skills, inhaler technique |
| Discuss trigger factors and smoking cessation | Reassessment of comorbidities |
| Assessment of comorbidities | Provide information about vaccination during pregnancy (influenza, COVID-19 and pertussis and the benefit for mother and child) |
| Discuss educational resources | Reassess written emergency management plan |
| Provide a written treatment and emergency plan | Medication Written treatment plan and emergency plan |

- Emphasize the importance of adherence to prescribed medication
- Discuss stepwise treatment approach
- Be cautious with a step-down approach during pregnancy
- Personalized treatment plan, that is, inflammation-based management in asthma patients
- Provide a written birth plan in case of long-term systemic corticosteroids
Given the lack of data and the existing, albeit very rare, risk of treatment-associated anaphylaxis, the initiation of allergen-specific immunotherapies or dose increase steps should be avoided during pregnancy. In the case of a hymenoptera allergy, the decision needs to be made on an individual basis, and the risk versus benefit has to be discussed with the patient. If well tolerated and effective, allergen immunotherapy should be maintained during pregnancy. 55,63

8.6 Biologicals for the treatment of allergic disease

In moderate-to-severe asthma disease phenotypes, biologicals are considered when conventional asthma treatment approaches are poorly tolerated or ineffective. 64,65 The currently approved biologicals for the treatment of allergic diseases are either an IgG1 (omalizumab, benralizumab, and mepolizumab) or IgG4 (dupilumab, reslizumab) isotype (Table 2). 67-75 Animal data are reassuring, however, published human data are rare. The largest prospective, observational study reported the outcomes of 250 women exposed to omalizumab during pregnancy and compared them to 1153 women with moderate-severe asthma. The authors reported no increased risk of malformations compared to the disease-matched control population. 76 Due to placental transport, maternal IgG levels and with moderate- severe asthma. The authors reported no increased risk of malformations compared to the disease-matched control population. 76 Due to placental transport, maternal IgG levels and consequently biologicals of the respective isotype in the fetal circulation increase after week 13. Levels reach 50% at weeks 28–32 and may exceed maternal levels after week 35. 77,78 Therefore, future studies on long-term data on fetal exposure are required. The placental transport is dependent on the Fc portion, and the efficacy of transport is as follows: IgG1 > IgG4 > IgG3 > IgG2. 77 The precise IgG levels in a fetus depend on the IgG levels of the mother. The educated healthcare provider should advise in continuing or discontinuing biologicals during pregnancy by discussing the benefit versus risk of maternal and fetal well-being.

In addition to type 2 asthma, dupilumab is the approved biological for atopic dermatitis by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) and also for chronic rhinosinusitis with nasal polyps (Table 2). Dupilumab is an IgG4 isotype antibody and directed against the anti-IL-4Ralpha antibody. In monkeys, dupilumab therapy has not been shown to increase the risk of birth defects. Currently, only case reports are available on the use of dupilumab during pregnancy. 79,80 ETFAD does not recommend dupilumab use during pregnancy, on the other hand, the EMA states that women have to be counseled that the potential benefit associated with biological exposure during pregnancy has to be balanced against the risks to the fetus. 46 In line with EMA recommendations, the EAACI position statement supports the patient’s information on existing evidence and creates an informed decision process that outweighs benefits against potential risks. 71

In conclusion, during pregnancy biologicals can be considered after informed and shared decision-making, as suggested by current position statements. 55,71

9 IMMUNOSUPPRESSANTS

9.1 Azathioprine

ETFAD 46 suggests that azathioprine might be continued if already initiated before pregnancy. Azathioprine use during pregnancy is well studied in inflammatory bowel disease patients. Based on the available data, there is no evidence that azathioprine exposure is associated with an increased incidence of congenital malformations. Risks of adverse pregnancy outcomes such as prematurity have been reported. 81 It is important to note that most of the reports concerning azathioprine involve concomitant maternal medications and women with underlying autoimmune/chronic inflammatory diseases, which may affect pregnancy outcomes.

9.2 Cyclosporine

Cyclosporine can be considered as first-line treatment if long-term management for disease control is required. 46 Reassuring pregnancy data on cyclosporine use are available from transplant patients and

| Biologicals | Target and antibody type | Animal data | Pregnancy data |
|-------------|---------------------------|-------------|----------------|
| Benralizumab 71,73,124 | IL-5Ra Humanized IgG1/κ | No adverse effects in animal studies (monkeys), suppression of eosinophil counts in the exposed offspring | No published data from trials, one case report with an unknown outcome |
| Dupilumab 68,71,73,124 | IL-4Ra Full human IgG4 | No adverse effects in animal studies (monkeys) | No published data from trials |
| Mepolizumab 71,124 | IL-5 Humanized IgG1/κ | No adverse effects in animal studies (monkeys) | No published data |
| Omalizumab 67,71,73,76,124 | IgE Humanized IgG1 | No adverse effects in animal studies (monkeys) | Published data |
| Reslizumab 71,124 | IL-5 Humanized IgG4 | No adverse effects in animal studies (mice and rabbits) | No published data |
other chronic systemic medical conditions. Studies have not shown increased congenital malformations rates. Adverse pregnancy outcomes such as fetal growth retardation, prematurity, or preeclampsia are probably related to the mother’s underlying medical condition rather than drug therapy. It is recommended to watch maternal blood pressure and kidney function.

9.3 | Systemic corticosteroids

Corticosteroids have been used and needed for a variety of chronic conditions during pregnancy, including allergic diseases. Generally, corticosteroids cross the placenta; however, the extent of concentrations in the fetus may vary by metabolisms at the maternal site and the placenta (significantly lower levels in the fetus: prednisolone, methylprednisolone; readily transferred: cortisone, hydrocortisone, prednisone, triamcinolone, betamethasone, dexamethasone). Both human and animal studies have suggested increased rates of cleft palate, prematurity, low birth weight, stillbirths, preeclampsia, and gestational diabetes. The severity of the underlying maternal disease and inflammation is significant confounders that need to be considered when interpreting these results. A recent meta-analysis (12 studies) evaluated the relationship between maternal corticosteroid use and orofacial clefts. The authors concluded that even if corticosteroid use during the first trimester is genuinely associated with cleft lip with or without cleft palate, the absolute risk remains very small (baseline risk 1/1000, exposed pregnancies 1.2/1000). Since the palate formation is completed by 12 weeks of fetal life, therapy later in pregnancy is no longer a concern for anomalies.

Systemic corticosteroids are applied as maintenance therapy to treat severe asthma during pregnancy if other treatment options fail to succeed. Short courses of systemic corticosteroids are indicated to treat exacerbations during pregnancy. The increased risk of untreated disease, recurrent exacerbations, associated maternal, and fetal mortality should weigh against the potential increased risks of the medication for mom and fetus. According to the NICE and BTS/SIGN guidelines, a stress dose of steroids should be considered for women on long-term oral corticosteroids (eg, 5–7.5 mg or more prednisolone daily for more than 3 weeks) during labor. Hydrocortisone (intravenous or intramuscular), at least 50 mg, every 6 h from the first stage of labor until 6 h after delivery is recommended.

10 | INHALED THERAPEUTICS

10.1 | Inhaled beta-agonists and inhaled corticosteroids

Albuterol/salbutamol is the preferred and most studied beta-agonist used for the treatment of asthma. Few studies suggested an increased risk of malformations in the context of beta-agonists exposure. A case-control study, using data from the National Birth Defects Prevention Study (NBDPS) reported that salbutamol use was associated with an increased risk for both cleft lip (OR 1.79, 95% CI 1.07–2.99) and cleft palate (OR 1.65, 95% CI 1.06–2.58). Another case-control study using data from the NBDPS could not find any association between maternal asthma medication use and individual major congenital malformations (NTDs, esophageal atresia, small intestinal atresia, anorectal atresia, limb deficiencies, diaphragmatic hernia, and omphalocele). The reported associations were for bronchodilator use and isolated esophageal atresia (OR 2.39, 95% CI 1.23–4.66), anti-inflammatory use and isolated anorectal atresia (OR 2.12, 95% CI 1.09–4.12), and combination medication (betamimetics and inhaled steroids) use and omphalocele (OR 4.13, 95% CI 1.43–11.95). The authors of both studies commented that reported associations might result from maternal asthma severity and associated fetal hypoxia or chance alone rather than the respective medication use.

In summary, given current data, treatment with albuterol/salbutamol is reassuring and considered safe during pregnancy in the absence of prospective intervention studies. The mentioned malformations might be confounded by asthma severity or by chance findings.

Long-acting beta-agonists are anticipated to have a similar safety profile as albuterol/salbutamol due to similar pharmacology and toxicology. A retrospective population-based cohort study using the linkage of three administrative databases from Quebec found no association of major congenital malformations with LABA (formoterol and salmeterol, n = 165) exposure during the first trimester of pregnancy adjusted OR 1.31 (95% CI, 0.74–2.31). A cohort study from Quebec, linking two healthcare administrative databases, compared the relative perinatal safety of a sub-cohort of asthmatic women using LABAs and inhaled corticosteroids (ICSs), fluticasone, and budesonide during pregnancy. The sub-cohorts included 547 LABA (385 salmeterol and 162 formoterol) pregnancies. There were no statistically significant differences regarding low birth weight (LBW) (OR 0.91; 95% CI, 0.44–1.88), preterm birth (PB) (OR 1.11; 95% CI, 0.56–2.23), and small for gestational age (SGA) (OR, 1.16; 95% CI, 0.67–2.02) in newborns between women exposed to salmeterol versus formoterol. The authors concluded that this study did not provide evidence of superior perinatal safety for one LABA over the other. The sub-cohorts included 3798 ICS (3190 fluticasone and 608 budesonide) pregnancies. There were no statistically significant differences between women exposed to fluticasone versus budesonide for low birth weight (LBW) (OR, 1.08; 95% CI, 0.76–1.52), preterm birth (PB) (OR, 1.07; 95% CI, 0.78–1.49), and small for gestational age (SGA) (OR, 1.10; 95% CI, 0.85–1.44). The authors concluded that this study did not provide evidence of greater perinatal safety for one ICS over the other. No human safety data are available for ciclesonide and mometasone. Therefore, the ICS mentioned above are preferred. However, if a pregnant woman is long-term well controlled with, for example, ciclesonide, one should be cautious with switching ICS because of the risk of provoking uncontrolled asthma. Pregnant women should be informed about the available evidence. The aim is to create a situation where an informed
decision is possible. In line with the standard approach of asthma, physicians should aim for the lowest effective dose to be applied to maintain asthma control.55 GINA 2021 guidelines advise toward a cautious approach placing a low priority on a step-down approach during pregnancy, and ICS should not be stopped during periconceptional care or pregnancy (www.ginasthma.org).

In conclusion, data on the inhaled corticosteroids budesonide, beclomethasone, and fluticasone are reassuring.94–97 The most used medication for the treatment of asthma, controller (ICS; ICS/LABA), and rescue (SABA) medication, are safe during pregnancy and breast feeding.98

11 | NASAL SPRAYS

11.1 | Nasal corticosteroids

Corticosteroid nasal sprays are the most effective single maintenance therapy for allergic rhinitis. Safety data on ICS are reassuring, especially for budesonide, which can be considered the first choice for nasal application. One case report described the delivery of an intrauterine growth restriction (IUGR) offspring after topical corticosteroid use and suggested linkage.99 Subsequent research in a population-based prospective cohort study including 912 women with first-trimester exposure to fluticasone, 1127 with first-trimester exposure to mometasone was compared with 318 triamcinolone exposed women. This dataset showed that maternal exposure to intranasal triamcinolone during pregnancy was not associated with an increased risk of congenital malformations, especially oral clefts. Budesonide, ciclesonide, fluticasone, and mometasone have been considered probably safe.55

Nasal Antihistamines (eg, Olopatadine, Azelastine): Based on animal data, the use is not expected to increase the risk of congenital anomalies; however, no human data are currently available.

Cromoglicic acid: The available data on Cromoglicic acid in animals did not report increased rates of congenital malformations. In a study reporting 151 pregnant women diagnosed with asthma and treated with intranasal, inhaled, and ophthalmic Cromoglicic acid in the first trimester,96 although limited, these human data are reassuring.

12 | TOPICAL TREATMENT

12.1 | Topical corticosteroids

Topical corticosteroids are the first-line treatment for the management of atopic dermatitis if moisturizers are not sufficient. Systemic absorption after topical corticosteroid application does occur, particularly when applied to larger surface areas to inflamed or injured skin.101 A Cochrane review (including14 publications) assessed the safety of exposure to topical corticosteroids during pregnancy and reported no increased risk of congenital malformations. However, 3 of the 14 studies suggested an increased risk of low birth weight using potent and very potent corticosteroids.102 If more potent topical corticosteroids are needed, the exposure should be limited to a short period.103

The current recommendation is that mild to moderate topical corticosteroids are the first choice over potent to very potent corticosteroids.103

12.2 | Topical calcineurin inhibitors

There are no studies on the use of topical calcineurin inhibitors (CNI) in pregnant women available. The most used are tacrolimus and pimecrolimus. Published data on oral tacrolimus do not suggest an increased risk for major congenital malformation above the general population’s baseline risk. The bioavailability of topical tacrolimus is low, and due to the large size of tacrolimus, systemic absorption is very low (0/1%–0.03%).46 Therefore, topical formulations are only expected to be absorbed in minimal amounts, which should not affect the fetus. The ETFAD recommends that the use of topical CNIs during pregnancy is justified due to the known outcomes after oral intake.46

Pimecrolimus: There are no adequate and well-controlled studies on its use in pregnant women. Similar to tacrolimus, there is low systemic absorption. Information on pimecrolimus exposure in pregnancy is too limited to determine the safety of its use during pregnancy. Thus, topical usage of tacrolimus is recommended over pimecrolimus during pregnancy.46

12.3 | Topical PDE-4 inhibitor

The topical phosphodiesterase-4 inhibitor (PDE-4 Inhibitor) Crisaborole is used to treat mild to moderate AD. Due to lack of human data and approval, the use is not recommended preconception or during pregnancy.46

13 | CONTRAINDICATED MEDICATIONS IN PREGNANCY

Methotrexate is a folic acid antagonist and inhibits dihydrofolate reductase. Hence, methotrexate inhibits DNA synthesis; it is associated with congenital malformations in the offspring. Craniofacial abnormalities (hydrocephaly, meningoeencephalocele, encephaly, parietal craniostenosis, cleft lip and/or palate, hypo- or retrognathia), limb defects (syndactyly, club hands/feet), intrauterine growth retardation, and mental retardation have been reported after methotrexate intake. Preconception data after inadvertent low-dose exposure reported a dissimilar risk; therefore, a joint, informed decision should
be applied. Methotrexate is contraindicated during pregnancy, and different preconception recommendations have been proposed. To summarize, the ETFAD states: “The ETFAD acknowledges the discrepancy between the EULAR/EADV/EDF recommendations (1- to 3 months prior desired time of conception) and the EMA label (6-month waiting period) and recommends therapy must be stopped six months prior to the desired time of conception if no local/national guideline exists.”

Mycophenolate mofetil is a purine synthesis inhibitor. The most common malformations described in the context of mycophenolate are abnormal ear development, facial clefts, ocular, skeletal, and heart defects. Increased rates of spontaneous abortions and preterm delivery have also been reported in women exposed to mycophenolate mofetil. Mycophenolate mofetil is teratogenic, strictly contraindicated in pregnancy, and treatment must be stopped at least 3 months before planned conception. Therefore, women of reproductive age have to be informed about the teratogenicity of the drug. If women are planning a pregnancy, mycophenolate mofetil should not be prescribed by the healthcare providers.

14 | GENERAL CONSIDERATIONS—PRECONCEPTION COUNSELING AND ASSESSMENT

Preparedness, awareness, and education of patients and healthcare providers are the cornerstones of preconception counseling (Box 1). Family planning provides a valuable window of opportunity to review the diagnosis and perform a baseline evaluation, especially for women with a prior event of anaphylaxis, venom allergies, asthma, adverse drug reactions, and severe atopic dermatitis. In addition, the impact of comorbidities on pregnancy, such as obesity, should be reviewed and education about the harmful effects of smoking, alcohol, and drug abuse should be given. When patients discuss pregnancy planning with their healthcare provider, this is also an opportunity to (re-) educate patients, for example, on avoidance of allergens and other triggers, adherence to therapy, and inhalation techniques. In addition, women at risk of anaphylaxis should be (re)trained on how to use an epinephrine auto-injector, and an updated prescription should be provided.

Information regarding the benefits and risks of each pharmacologic treatment for both mother and fetus needs to be provided and reviewed before starting or switching medications. Reassurance is often needed to avoid unnecessary discontinuation by fear of teratogenicity. The benefits of pursuing allergen immunotherapy should be assessed prior to pregnancy, and the importance of disease control for maternal and fetal health needs to be outlined. The risks of an uncontrolled disease during pregnancy should be explained and balanced with the actual risk of the treatment.

Depending on allergic disease and severity, regular monitoring is recommended during pregnancy. Skin prick tests are not contraindicated in pregnancy, but in vitro tests are preferred over allergy skin tests since systemic reactions have been reported. Intra-dermal tests have a slightly higher risk of systemic reactions and may only be applied if needed to assess specific drug reactions.

14.1 | COVID-19 (coronavirus infectious disease 2019)

COVID-19 (coronavirus infectious disease 2019) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Based on available cohort studies and meta-analysis from different parts of the world, patients with asthma do not appear to have more severe COVID-19 than the general population. Surprisingly, patients with (mild) asthma may even be less susceptible to severe COVID-19 infection. However, as asthma is a heterogeneous disease, different asthma phenotypes may have different outcomes. Some studies suggest that neutrophilic (T2low) inflammation and non-atopic asthma may be related to more severe COVID-19. Of particular interest is the finding that eosinopenia is a marker of potentially severe COVID-19 while eosinophilia both in patients with and without asthma was associated with better outcomes.

Pregnant women with COVID-19 are at increased risk of adverse maternal and pregnancy outcomes. A meta-analysis of 77 studies showed that pregnant women with COVID-19 were at increased risk of hospitalization, intensive care treatment, and higher preterm birth rates. Consequently, pregnant women should be informed about the facts, and COVID-19 vaccines should be made available for pregnant women. In most studies, asthma was not associated with an increased risk for severe COVID-19 in pregnant patients.

Studies reporting on COVID-19 during pregnancy in patients with other allergic diseases, especially AD or CRS, are limited.

According to current asthma guidelines, pregnant patients with asthma should be encouraged to continue ICS and biologicals during this COVID-19 pandemic. Asthma exacerbations can be treated with systemic corticosteroids, but biologicals should be stopped during active SARS-CoV-2 infection. Many aspects concerning COVID-19 infection in pregnant patients with allergic diseases are still unclear. For now, it seems appropriate to treat patients with allergic diseases and COVID-19 during pregnancy, with special attention for maintaining good disease control. Future registry trials could be helpful to address the gaps in our knowledge.

15 | CONCLUSION

Allergic diseases are among the most common chronic diseases during pregnancy. The principle of pharmacological treatment should be similar to other non-pregnant patients of the same age and disease group. Management of allergic diseases during pregnancy has to be well-defined to ensure the best outcome for mother and child. Healthcare professionals are encouraged to inform women of reproductive age and pregnant women about potential risks and existing/lack of evidence, and they should create a situation where
an informed decision is possible. Therefore, frequent education of healthcare providers and pregnant women about the maternal and fetal risk of allergic disease in pregnancy is required. This will most likely contribute to better treatment adherence, better disease control, and, consequently, better outcomes.

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