Treating allergic diseases in pregnancy

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Abstract

Allergic diseases like asthma, allergic rhinitis, or food allergy have a high prevalence in women of childbearing age and may affect up to 30% of this age group. A multitude of immunological changes characterizes pregnancy to create the optimal milieu for the unborn child. Both these immunological changes and pre-conceptional, sub-optimal disease control may affect the severity of the respective allergic disease manifestations during pregnancy and pose a risk for mother and child.

Due to apparent limitations in conducting clinical trials, safety data on anti-allergic drugs during pregnancy are limited. This lack of clinical evidence demands to counsel between potential and known risks and benefits of anti-allergic drugs. This includes the potential of disease aggravation in the absence of treatment. By doing so, informed decisions and shared decision making is facilitated. In particular, in patients with severe asthma, education about the risk of uncontrolled asthma for mother and child should be part of regular care. This review focuses on the management of allergic diseases during pregnancy, maternal counseling, and available information/evidence regarding allergic diseases' management and treatment during pregnancy. Furthermore, we discuss the challenges of treating patients with allergic diseases and covid-19 during pregnancy.

Introduction

Allergic diseases are among the most prevalent diseases in industrialized countries, affecting 18% to 30 % of women of childbearing age.[1,2] While the risk of allergic diseases is higher in males during childhood, there is a shift during adolescence towards females.[3] In particular allergic rhinitis, asthma, and atopic dermatitis represent the most important allergic phenotypes. Severe asthma and allergic diseases in pregnancy have been associated with increased adverse perinatal outcomes, such as preterm birth, low birth weight, and preeclampsia.[4-6] Thus, adequate disease control and education of patients and health care providers is essential to ensure the best care of both 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, specifically in patients with allergic diseases.

Immunologic during pregnancy regarding allergic disease

Immunologic changes in pregnancy ensure a coordinated balance between effective immune defenses against infections and subtle immune modulation specific to every pregnancy stage. It was previously suggested that maternal immunological tolerance must prevail throughout pregnancy to prevent rejection of the paternal antigens expressed in the fetus.[7,8] However, implantation and placentation, fetal growth, and parturition are distinct processes that each require a specific immune environment.[8] Implantation and placentation require the presence of immune cells and involve the creation of 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 are considered to be critical for placental perfusion. Dysregulation may be a key factor in the development of preeclampsia. An effective cross-talk between maternal decidual immune cells and fetal trophoblast cells is needed for the depth of trophoblast invasion and spiral arteries remodeling.[7-9] 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.[8] In the third trimester, a switch towards 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.[8] The extensive exchange of factors between and the mother and the child does not involve IgE. IgE does not cross the placenta, but there is limited knowledge on the potential role of IgE in pregnancy on IgE receptor-positive maternal effector cells. IgE levels are mildly elevated, but this is most likely not of clinical relevance. In line with the type 2 response promoting periods, an increase in IgE levels is observed.[10-12] The clinical significance and impact of IgE levels on pregnancy outcomes remain unclear.

General considerations - Preconception counseling and assessment

Preparedness, awareness, and education of patients and health care providers are the cornerstones of preconception counselling (Figure 1). It provides a valuable window to review the diagnosis and for a baseline evaluation especially for women with a prior event of anaphylaxis, venom allergies, asthma, adverse drug reactions, and severe atopic dermatitis. Aggravating comorbidities should be reviewed (co-existing food allergies, environmental allergies, chronic rhinosinusitis…), and information about the adverse effects of smoking, alcohol consumption (co-factor) given.[14-16] [17] Immunization status should be updated.
It also is an opportunity to (re-) educate patients, for example on avoidance allergens and trigger factors or inhalation techniques. Women at risk of anaphylaxis should be (re)trained on how to use an epinephrine auto-injector, and an updated prescription should be provided.
The treatment needs to be reviewed and optimized. Information regarding benefits and risks of each pharmacologic treatment for both mother and fetus need to be provided. The benefits of ongoing allergen immunotherapy should be assessed prior to pregnancy, and the importance of disease control for maternal and fetal health needs to be outlined. [18] Medication should not be withdrawn in preparation for pregnancy and lactation. The risks of an uncontrolled disease during pregnancy should be explained and balanced with the actual risk of the treatment.[19]

Depending on allergic disease and severity, regular monitoring is recommended during pregnancy. [20] Skin prick tests are not contra-indicated in pregnancy, but *in vitro* tests are preferred over allergy skin tests since systemic reactions have been reported.[21] Intra-dermal tests have a slightly higher risk of systemic reactions and may only be applied if needed to assess specific drug reactions.

Asthma and pregnancy: Counselling, risk factors, outcomes, and management

One of the most common chronic medical conditions in pregnancy is asthma. It represents the best-studied allergic disease in pregnancy. Uncontrolled, severe asthma puts mother and baby at risk. If the asthma is not controlled, it poses an increased risk of preeclampsia, cesarean delivery, preterm delivery, low-birthweight, and small for gestational age babies. [22-25] It also increases the risk of early-onset asthma in the offspring compared to offspring from non-asthmatic mothers and is more pronounced if the asthma is non-controlled early on in pregnancy. [19]
Hormonal, immunological, and physiological changes are responsible for differences in the course of asthma during pregnancy. Sex hormones such as estrogens, progesterone, and prostaglandin E are known to have broncho-dilating effects, while hormones such as prostaglandin F promote broncho-constrictive effects.[14] Another critical factor to consider is immunological changes during pregnancy, which may enhance Type 2 phenomena that favor airway inflammation.[26] This adaptation of immune responses also increases susceptibility for viral respiratory tract infections [27,28] in pregnant women, which are the most common triggers for asthma exacerbations. [29] [30] Preconception counseling should, therefore, also include the recommendation to receive influenza vaccinations annually. 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. It is generally accepted that asthma control and symptoms can change during pregnancy. Traditionally about 30% of pregnant women suffer from asthma deterioration, 30% will improve, and the remaining 30% will experience no change in asthma control. This is based on data from the 1990s and early 2000. [15] [16] [17] A recent Italian study indicates a lower risk for asthma deterioration in pregnancy of 18.8%. This data is based on extensive questionnaires, including the Asthma Control Test. [31] 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. GERD (gastroesophageal reflux disease) is common in pregnant women because of decreased oesophageal sphincter tone and decreased gastric motility.[32] Rhinitis occurs in about 65% of pregnant women with asthma and can be of the allergic and non-allergic type. [15] Obstructive sleep apnoea syndrome (OSAS) may be a reason for poor asthma control. [33] Increased blood volume, adipose tissue, rhinitis, and edema during pregnancy contribute to upper airway narrowing. [34]. Assessment of these comorbidities before and during pregnancy has the potential for preventive strategies to improve mother's and their offspring's health.

Exacerbations during pregnancy are a significant clinical problem and may be related to poor pregnancy outcomes and are associated with an increased risk of pregnancy-induced hypertension, low birth weight, and preterm babies. [35] Asthma exacerbations occur in 20 to 50% of patients with asthma during pregnancy. Exacerbations that require oral corticosteroid treatment affect approximately 10% of pregnant asthma patients. [36,37] Most exacerbations occur in the second and beginning of the third trimester, with a decrease in asthma-related symptoms during the last weeks of pregnancy. [38] Viral infections of the upper respiratory tract are the most common triggers of asthma exacerbations during pregnancy. [39] Treatment of acute exacerbations is similar to non-pregnant asthmatic women with special attention for adequate oxygenation. [38] Inflammation-based asthma management via inhaled steroids is demonstrated to reduce exacerbations and may also improve pregnancy outcomes. [40]

The course of asthma is unpredictable during pregnancy, and regular monitoring is decisive. Risk factors for uncontrolled asthma or exacerbations during pregnancy include pre-existing poor lung function, severe asthma prior to pregnancy, smoking, and obesity.[41] [42] [43]. Enrolment in an asthma management program[44] with regular monitoring of disease activity and reassessment of inhaler use and techniques leads to improved medication adherence and asthma self-management[14].

Treating allergic diseases in pregnancies – Evidence and considerations regarding safety

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, heart defects) in the general population has to be outlined. This risk of developing congenital malformation in an unselected population is considered 3-5%[45]. Genetic and environmental risk factors have to be individually addressed.

Most importantly, the known risk of a medical condition treated and untreated on pregnancy outcomes has to be discussed. The aspects that require mentioning and consideration effectively counsel management of women of reproductive age with allergic diseases are summarized in Figure 1.

Management and pharmacological treatment of asthma

The management plan for asthma in pregnancy aims the same goals as in the non-pregnant population: to define the optimal treatment in accordance with severity, which is maintaining control and avoiding exacerbations. A conventional step-up approach proposed, e.g., by the GINA guidelines, is used [17]. Consequently, medications encompass short-acting beta-agonists, inhaled corticosteroids, long-acting beta-agonists, leukotriene receptor antagonists, tiotropium, oral steroids, 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 [40] and the risk of asthma in offspring, as reported in 140 mother – children pairs with children followed up to the age of six. [46] Again, this data supports the importance of a close follow up and the need to control asthma-related inflammation.

Inhaled Beta-agonists and Inhaled Corticosteroids

Albuterol/salbutamol is the preferred and most studied beta-agonist used for the treatment of asthma. Few studies raised questions about the increased risk of malformations due to exposure to beta-agonists. 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). [47] Another case-control study using data from the NBDPS could not find any association between maternal periconceptional asthma medication use and individual major congenital malformations (NTDs, esophageal atresia, small intestinal atresia, anorectal atresia, limb deficiencies, diaphragmatic hernia, and omphalocele). The only associations found 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 due to fetal hypoxia or due to chance alone rather than medication use[48]. In a "case-malformed control study," odds ratios (ORs) for exposure to various groups of asthma medications were calculated for ten malformations when compared with non-chromosomal, non-signal malformations (control registrations) by analyzing congenital anomalies from 13 EUROmediCAT registries encompassing 76.249 patients. The first-trimester use of inhaled β2-agonists was associated with increased odds of cleft palate (OR, 1.63; 95% CI, 1.05-2.52) and gastroschisis (OR, 1.89; 95% CI, 1.12-3.20). The OR of exposure to inhaled salbutamol was also increased compared to controls (cleft palate: OR, 1.63; 95% CI 1.02-2.60; gastroschisis: OR, 2.01; 95% CI, 1.18-3.44). The authors report that a large number of comparisons were performed, and therefore the increased risks reported may be a chance finding as they were most likely only able to correct for a limited number of potentially confounding factors [49].

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 (LABA) are anticipated to have a similar safety profile to albuterol/ salbutamol due to similar pharmacology and toxicology. A retrospective population-based cohort study using the linkage of three administrative databases from Québec 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)[50]. A cohort study from Quebec, linking two health care 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 for 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) newborns between women exposed to salmeterol vs formoterol. The authors concluded that this study did not provide evidence of greater perinatal safety for one LABA over the other[51]. The sub-cohorts included 3,798 ICS (3,190 fluticasone and 608 budesonide) pregnancies. There were no statistically significant differences 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) newborns between women exposed to fluticasone vs. budesonide. The authors concluded that this study did not provide evidence of greater perinatal safety for one ICS over the other.[51] No human safety data are available for ciclesonide and mometasone, so the aforementioned ICS 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 existing and lack of evidence and create a situation where an informed decision is possible.

Following the standard approach in asthma management, the lowest effective dose to maintain asthma control should be applied [52].

In conclusion, data on the inhaled corticosteroids fluticasone and budesonide are reassuring[50,51,53-55] with no evidence for a difference in safety profile. If ICS are initiated during pregnancy, budesonide will be the first choice due to the largest amount of available data. In addition, data on long-acting beta-agonists combined with ICS are reassuring and prescribed during pregnancy.

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 transfer may vary by steroid (poorly crossing: prednisolone, methylprednisolone; readily crosses: cortisone, hydrocortisone, Prednisone, Triamcinolone, Betamethasone, Dexamethasone). Both human and animal studies have suggested increased rates of cleft palate [56], prematurity, low birth weight [57] and stillbirths, preeclampsia[58] and gestational diabetes. The severity of the underlying maternal disease and inflammation are significant confounders that need to be considered when interpreting these results. A recent meta-analysis

(12 studies included) 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). [59]

Systemic corticosteroids can be needed as maintenance therapy to treat severe asthma during pregnancy when other treatment options fail to succeed [6014,16,61] Short courses of systemic corticosteroids are indicated for the treatment of exacerbations during pregnancy. There is a relatively small risk for oral clefts due to systemic corticosteroids (in comparison, the incidence of oral clefts in the general population is about 1 in 1000). Since the palate formation is completed by 12 weeks of fetal life, therapy after this time is no longer a concern for anomalies[59]. The increased risk of untreated disease, exacerbations, and maternal and fetal mortality should weigh against the potential increased risks for mom and fetus.

The occurrence of transient neonatal adrenal insufficiency following long term use of oral corticosteroids during pregnancy has been described [62], but is unusual. A stress-dose of steroids should be anticipated for women on long-term oral corticosteroids (comparable to 5 mg or more prednisolone daily for more than three weeks). The NICE guidelines recommend giving intravenous or intramuscular hydrocortisone (at least 50mg) every 6 hours from the first stage of labor until 6 hours after delivery. [63]

Leukotriene antagonists and Cromoglicic acid

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.[64] 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[65]. A post-marketing surveillance report stated six reports of limb reduction defects (4 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.[66] 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). 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 [54], although limited, these human data are reassuring.

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. [52] No evidence for an increased risk of congenital malformations after theophylline exposure was found in humans[68]. 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[52]. 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 mcg/mL" [69].

Biologicals for the treatment of asthma

In moderate-to-severe disease phenotypes, biologicals are considered when conventional treatment approaches are poorly tolerated or ineffective. [70,71] The currently approved biologicals for the treatment of allergic diseases are either IgG1 (omalizumab, mepolizumab, and benralizumab) or IgG4 (reslizumab and dupilumab [72]) isotype (Table 2). [73-81] Animal data are reassuring, however, published human data is 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 patients and reported no increased risk of malformations compared to the disease matched not exposed women. [82] Due to placental transport, IgG levels in the fetal circulation increase after week 13, reach 50% at weeks 28-32, and may exceed maternal levels after week 35 [83,84] and, therefore, future studies on long-term data on fetal exposure is required. For the treatment of allergic diseases during pregnancy, the information is still limited in humans. A personalized benefit versus risk of maternal and fetal wellbeing has to be provided by the educated health care providers.
In conclusion, during pregnancy biologicals can be considered after informed and shared decision-making, as suggested by current position statements. [52,77]

COVID-19 (coronavirus infectious disease 2019) and pregnancy

In contrast to more common viral respiratory infections, such as rhinovirus or influenza, the impact of COVID-19 (coronavirus infectious disease 2019) on asthma exacerbations is less clear.
COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It is not yet clear whether patients with asthma are at increased risk of severe COVID-19 infection. [85-87] Based on available studies from cohorts from China, Europe, and the US, patients with asthma do not appear to have more severe COVID-19 than the general population [88] [89,90]. The most important risk factors for severe covid-19 are increased age, male gender, and comorbidity related factors such as obesity, diabetes mellitus, and hypertension. [91] However, as asthma is a heterogeneous disease, different asthma phenotypes may have different outcomes. Some studies suggest that neutrophilic (Th1 predominant) inflammation

in asthma may be related to more severe COVID-19. [92,93] This may depend on variable angiotensin-converting enzyme -2 (ACE2) receptor expression determined by different types of inflammation. ACE2 serves as the receptor for SARS-CoV-2, through which it gains entry to the host's cells. In addition, because COVID-19 is characterized by a Th1/Th17 inflammatory response, patients with non –atopic asthma might show an increased Th1 response, possibly related to more severe clinical outcomes. Critical gaps remain in our current knowledge and understanding of immune responses to SARS-CoV-2. A Korean study suggests that especially non-allergic asthma is associated with increased susceptibility to SARS-CoV-2 infection and more severe clinical outcomes of COVID-19 [93]. Another study analyzed data from three different cohorts of children and adults [94]. In children, allergic sensitization was inversely correlated with ACE2 expression. In adults, allergen exposure led to significant reductions in ACE2 expression. The authors conclude that modulation of ACE-2 expression by type 2 inflammatory processes likely has a role in COVID-19 pathogenesis. Together, these findings imply a potential mechanism of reduced COVID-19 severity in patients with atopic diseases. Currently, atopic diseases do not seem to be an important risk factor for severe covid-19. This may slightly differ in patients with severe disease manifestations.

Pregnancy itself does not increase the risk of acquiring SARS-CoV-2 infection, but pregnant women with COVID-19 are at increased risk of adverse maternal and pregnancy outcomes. [95,96] [97] 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. Another prospective cohort study in French Guiana also found a higher risk of intrauterine fetal death in pregnant women infected with SARS-CoV-2. [98] Surprisingly, this also applied to asymptomatic women. Of note is that it has not yet been established whether COVID-19 infection is an independent risk factor for adverse neonatal outcomes.

Interestingly, in most studies, asthma was not found to be associated with increased risk for severe COVID-19 in pregnant patients, in contrast to widely accepted risk factors like older age, obesity, and diabetes mellitus[95] [98] Only one systematic review from Hessani et al. [99] found co-morbid asthma as a risk factor for maternal and fetal mortality. The studies included in this review, however, had very low patient numbers.

Given the impact of physiological changes during pregnancy on the respiratory system, it is most likely that pregnant women with COVID-19 are at risk and should be monitored carefully. Studies reporting on COVID-19 during pregnancy in patients with atopic diseases are limited. [99] [100] [101] The precise, complex interaction of pregnancy-induced alterations in the immune system with the immune response by COVID-19 infection is poorly clarified. Overall, COVID-19 infection is accompanied by major changes in the immune system. [92] [102] [76] These changes most likely interfere with physiologic immunologic changes during pregnancy, especially in patients with atopic diseases. [77]

Regarding the treatment of COVID-19 in pregnant patients with atopic diseases, studies are lacking. Most trials for the treatment of COVID-19 exclude pregnant women. For now, it seems appropriate to treat patients with atopic diseases and COVID-19 during pregnancy like non-pregnant patients with special attention for a multidisciplinary approach and adequate oxygenation. According to current asthma guidelines, pregnant patients with asthma should be encouraged to continue ICS during this COVID-19 pandemic, and asthma exacerbations

can be treated with systemic corticosteroids. Biologicals targeting type 2 inflammation should be continued, preferably by self-administration or in-home treatment. [76] [103] In case of active SARS-CoV-2 infection, withholding biologicals for a minimum of 2 weeks is advised. Finally, as some of the signs of COVID-19 are similar to physiological symptoms during pregnancy or overlap with symptoms of atopic diseases (e.g., dyspnea, nasal congestion, fatigue), clinicians should be extra alert when pregnant women present with these symptoms. [104]

Management of allergic rhinitis in pregnancy

The treatment of allergic rhinitis in pregnancy is similar to the general population. The most important steps are trigger avoidance and treatment with the appropriate medications: nasal corticosteroids and antihistamines, combinations thereof, and oral antihistamines.

Inhaled 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. [105] 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 has been compared with 318 triamcinolone exposed women. This dataset showed that maternal exposure to intranasal triamcinolone during pregnancy was not associated with an elevated risk of overall congenital malformations, spontaneous abortions, or small for gestational age infants. [106] Overall, the limited data on the safety of intranasal corticosteroids during pregnancy does not suggest an increased risk of congenital malformations, especially oral clefts. Budesonide, ciclesonide, fluticasone, and mometasone have been considered probably safe. [52]

Oral Antihistamines

Antihistamines are widely prescribed during pregnancy for various indications.[107,108] A systematic evaluation of 54 studies assessing antihistamine use during pregnancy reported that the literature regarding antihistamine safety, especially congenital malformations, is reassuring. [109]

Non-sedating second-generation antihistamines are recommended for treatment, whereas first (old) generation antihistamines (H1 Antihistamines) are chlorpheniramine, hydroxyzine, and ketotifen are not recommended for the treatment of allergic rhinitis in general due to their pregnancy independent safety profile. In the case of prescription, the latter reported leading to no increased rates of congenital malformation. Chlorpheniramine has been recommended as the first choice for this group.

The drugs of choice of second (new) Generation H1 Antihistamines with less sedating properties are Cetirizine and Loratadine[52]. However, physicians should be aware of potential withdrawal syndromes and irritability or drowsiness of the infant.

In conclusion, the preferred antihistamines during pregnancy are Cetirizine and Loratadine.

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. [110,111]

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 hymenoptera allergies, the decisions need to be made on an individual basis, and the risk versus benefit has to be discussed with the patient. In the case of effectiveness and if it is well-tolerated, immunotherapy should be maintained during pregnancy[52,112].

Management of atopic dermatitis in pregnancy

The European task force on atopic dermatitis (AD) on the treatment of atopic dermatitis (ETFAD) during pregnancy proposed the following stepwise approach during pregnancy: the first step consists of emollient usage, which is extended in the next step by the application of topical corticosteroids class II or III for two weeks or a maximum of 200g total. If sufficient control is not reached, narrow-band UVB should be added. In case of control but re-lapse within a week, a pro-active interval therapy or the addition of topical calcineurin inhibitors. 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 health care providers should discuss in an informed shared process of systemic treatment. Detailed recommendations regarding the current evidence for applying a paramount of medications used to treat AD in pregnancy are provided. [113,114]

Topical Corticosteroids

Topical corticosteroids are the first-line treatment for the management of atopic dermatitis. Systemic absorption after topical corticosteroid application does occur, particularly when applied to larger surface areas, to inflamed or injured skin. [115] A Cochrane review (including14 publications) assessed the safety of exposure to topical corticosteroids during pregnancy and reported no increased risk of congenital malformations. However, 3/14 studies suggested an increased risk of low birth weight with the use of potent and very potent corticosteroids. [116] If more potent topical corticosteroids are needed, the exposure should be limited to a short period. [117]

The current recommendation is that mild to moderate topical corticosteroids are the first choice over potent to very potent corticosteroids. [117]

Topical calcineurin inhibitors

There are no studies on the use of topical calcineurin inhibitors in pregnant women available. The current most commonly used are tacrolimus and pimecrolimus. Published data on oral **tacrolimus** does 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, the systemic absorption is very low (0/1%-0.03%). [113] Therefore, topical formulations are only expected to be absorbed in minimal amounts, which should not

affect the fetus. The ETFAD recommends that the use during pregnancy is justified due to the known outcomes after oral intake. [113]

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, current recommendations for topical calcineurin inhibitors are to use tacrolimus over pimecrolimus during pregnancy. [113]

Topical PDE-4 Inhibitor

The topical phosphodiesterase-4 inhibitor (PDE-4 Inhibitor) Crisaborole is marketed as Eucrisa to treat mild to moderate AD. Due to a lack of human data and approval, the use is not recommended preconceptionally or during pregnancy. [113]

Systemic treatment of atopic dermatitis

Cyclosporine is proposed as first-line treatment if long-term management is required or systemic corticosteroids for short-term rescue treatment. Reassuring pregnancy data on cyclosporine use is available from transplant patients and 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 mothers' underlying medical condition rather than drug therapy. [118] It is recommended to watch maternal blood pressure and kidney function.

ETFAD[113] suggests that **azathioprine** might be considered to 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 azathioprine exposure is associated with an increased incidence of congenital malformations. Risks of other adverse pregnancy outcomes such as prematurity [119] have been reported. It is important to note that most of the reports concerning azathioprine involve concomitant maternal medications and women who have underlying auto-immune/chronic inflammatory diseases, which may affect pregnancy outcome.

Systemic corticosteroids use during pregnancy is discussed above.

Biologicals

Dupilumab is currently the only approved biological by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) for the use in atopic dermatitis (Table 2). Dupilumab is an IgG4 isotype antibody and directed against the anti-IL-4Ralpha antibody. IgG levels in the fetal circulation increase after week 13, reach 50% at weeks 28-32, and may exceed maternal levels after week 35 (Figure 1). [83,84] The precise IgG levels in a fetus depend on the IgG levels of the mother. The placental transport is dependent on the Fc portion, and efficacy is as follows: IgG1>IgG4>IgG3>IgG2[83] In monkeys, dupilumab therapy has not shown to increase the risk of birth defects. Currently, only case reports are available on the use of dupilumab during pregnancy[120,121]. 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. [113] 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. [77]

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, meningoencephalocele, anencephaly, 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. Preconceptionally, data after inadvertent low-dose exposure reported a dissimilar risk; therefore, a joint, informed decision should be applied[122]. Methotrexate is contraindicated during pregnancy, and different preconception recommendations have been proposed. To summarize, the ETFAD states; "The EFTAD 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." [113]

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[123]. Increased rates of spontaneous abortions and preterm delivery have also been reported in women exposed to mycophenolate mofetil. [123] 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 health care providers. [113]

Conclusions

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. The goals of management of allergic diseases during pregnancy have to be well-defined to ensure the best outcome for mother and child. Health care professionals are encouraged to inform pregnant patients about potential risks, existing/lack of evidence, and create a situation where an informed decision is possible. Therefore frequent education of health care 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 and consequently, better outcomes.

Table 1 Medication for the treatment of allergic disease and pregnancy

Drug class	Drug	Adverse Fetal/Neonatal outcomes
Oral Antihistamines		
First (old) Generation: In general, the second (new) generation antihistamines should be preferred	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.
	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 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. Not human data 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.

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Intranasal antihistamines		
	Azelastine	Based on animal data, the use is not expected to increase the risk of congenital anomalies. No human data available.
	Olopatidine	Based on animal data, the use is not expected to increase the risk of congenital anomalies. No human data available.
Inhaled/ Intranasal Corticosteroids		
	Budesonide	The most human data available for budesonide.Due to the reassuring studies, this medication is the preferred ICS for the treatment of asthma during pregnancy.
	Beclomethasone Fluticasone Mometasone Triamcinolone	Inhaled beclomethasone, fluticasone, mometasone, Triamcinolone have been recommended for the treatment of asthma during pregnancy.
Anticholinergic Agent		
	Ipratropium	Based on experimental animal studies, ipratropium therapy during pregnancy is not expected to increase the risk of congenital malformations. No human data available.
	Montelukast	Based on experimental animal data, montelukast is not expected to increase the risk of congenital anomalies.
	Zafirlukast	Based on experimental animal studies and a small number of human pregnancy exposures, zafirlukast therapy is not expected to increase the risk of adverse pregnancy outcomes.
Inhaled bronchodilators		
Short-acting bronchodilators	Albuterol	Albuterol/salbutamol is the preferred and most studied beta-agonist used in 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.
Long-acting bronchodilators	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.
Systemic Corticosteroids		

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Placental transfer		
Poorly crosses	Prednisolone	Corticosteroids do not represent a major teratogenic risk in humans; there is a small increased risk for oral clefts (in comparison incidence of oral clefts in the general population is about 1 in 1000). Since the palate formation is completed by 12 weeks of fetal life, therapy after this time is no longer a concern for anomalies. The increased risk of untreated disease, exacerbation, and maternal and fetal mortality should weigh against the potential increased risks for mom and fetus
	Methylprednisolone	
Readily crosses	Cortisone	
	Hydrocortisone	
	Prednisone	
	Triamcinolone	
	Hydrocortisone	
	Prednisone	
Theophylline		Human reports have not shown an increase in malformations associated with theophylline therapy during pregnancy, although the neonate might show jitteriness, tachycardia, and vomiting. Theophylline during pregnancy requires careful titration of the dose and regular monitoring to maintain the recommended serum theophylline concentration range of 5-12 mcg/mL.
Leukotriene antagonist (LTRA)	Montelukast Zafirlukast	Based on the available human data LTRAs can be considered as second-line therapy during pregnancy

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Table 2 Biologicals and allergic disease

Biologicals	*Target and Antibody type*	*Animal data*	*Pregnancy data*
Benralizumab	IL-5 Rα 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	IL-4Rα Full human IgG4	No adverse effects in animal studies (monkeys)	No published data from trails
Mepolizumab	IL-5 Humanized IgG1/ κ	No adverse effects in animal studies (monkeys)	No published data
Omalizumab	IgE Humanized IgG1	No adverse effects in animal studies (monkeys)	limited
Reslizumab	IL-5 Humanized IgG4	No adverse effects in animal studies (mice and rabbits)	No published data

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Figure 1 Counselling pregnant women with allergic disease

Preconception counseling and assessment	**Assessment and monitoring during pregnancy**
- Preconception counseling and assessment - Baseline assessment (spirometry, skin test, questionnaire) - Assessment of medication knowledge, self-management skills, and inhaler technique - Discuss triggers and smoking cessation - Assessment of comorbidities - Discuss educational resources - Provide a written treatment plan, if needed medical identification	- Assessment of medical condition during pregnancy - Frequency depending on allergic disease, e.g., asthma every four weeks - Reassessment of medication knowledge, self-management skills, inhaler technique - Assessment of comorbidities - Provide information about vaccination during pregnancy (influenza and pertussis and the benefit for mother and child) - Reassess written management plan, if needed medical identification
Outcomes - Increased risk of adverse maternal and fetal/ neonatal outcomes and the importance of controlled atopic disease to reduce these adverse outcomes - Risk factors for adverse outcomes like disease severity, uncontrolled and or exacerbated disease - Impact/effect of uncontrolled maternal disease on long-term outcomes or future child health, such as asthma or atopy in offspring	**Medication** - Written treatment plan - Importance of adherence to prescribed medication - Stepwise treatment approach discussed - Caution of step=down approach during pregnancy - Personalized treatment plan, e.g., inflammation-based management in asthma patients - Provide a written birth plan in case of high-dose systemic corticosteroids

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