

Prevention and Treatment of Allergic Asthma in Pregnancy: From Conventional Drugs to New Therapeutical Approaches

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Abstract: Different conventional anti-asthmatic and anti-allergic drugs are commonly used in pregnancy, including inhaled corticosteroids, long- and short-acting β -agonists, leukotriene modifiers, cromolyn, and theophylline. Alternatively, immunotherapy with allergens before and during pregnancy is accepted as a causal treatment of allergies, but the allergy specificity and severity in combination with a variety of application protocols and procedures cause wide heterogeneity of this treatment principle. Furthermore, the pharmacokinetic characteristics and the US Food and Drug Administration (FDA) classification of conventional anti-allergic drugs and immunological implications of immunotherapy are summarized in this review, and insights on fetal programming of allergies are introduced. We propose a potential perspective of treatment with anti-inflammatory and pro-resolving mediators, such as lipoxins, resolvins and protectins; these are lipid mediators physiologically generated during the immune response from arachidonic acid, eicosapentaenoic acid and docosahexaenoic acid. This proposal fits with the recently appreciated approaches to allergy prevention for the newborn child by a balanced maternal nutrition and omega-3 long-chain polyunsaturated fatty acid consumption.

Keywords: Allergic asthma, anaphylactic reaction, anti-allergic drugs, immunotherapy, lipid mediators, omega-3 polyunsaturated fatty acid, pregnancy, resolvins.

INTRODUCTION

Allergy is a disorder of the immune system that occurs due to hypersensitivity to normally harmless environmental substances known as allergens. Aside from these ambient allergens, allergic reactions can result from insect stings, food, and reactions to medications that, in particular, may produce a systemic and life-threatening allergic response that is called anaphylaxis. In general, common allergic reactions include eczemas, hives, hay fever, asthma attacks, food allergies, and reactions to the venom of stinging insects such as bees and wasps [1].

Risk factors for allergies can be classified into host and environmental factors, with genetic host factors being highly significant. Treatments and strategies for the prevention of allergies presented in this review cannot completely overcome such well-established risk factors, such as the heritable component, but may be able to reduce the risk of children to develop allergies, especially in high risk individuals. Epigenetic mechanisms have been of great interest in recent years, as they are believed to imprint the activity state of specific gene loci, such as an environmentally induced phenotype that becomes inheritable. It is becoming increasingly accepted that exposure to environmental factors during

pregnancy can significantly modulate the susceptibility of children to develop chronic diseases in later life [2, 3]. In basic science [4] and clinical [5] studies, prenatal stress challenge has been identified as a potent environmental factor, which programs the fetus to become more likely to develop asthma. Also, the risk for allergies can be reduced as early as pregnancy; as shown in children born by mothers living in a rural environment [6].

For this review, we considered the prevention and management of allergic asthma and anaphylactic reactions during pregnancy, because of their severity and potential risk for the mother and fetus. We focused on the management with pharmacological drugs, and the alternative option of immunotherapy with allergens that not only work on the mother, but that also may prevent the development of allergies in the child by intervention during the period of fetal programming. Finally, we present a proposal for a potential therapeutical approach with anti-inflammatory and pro-resolving polyunsaturated fatty acid-derived lipid mediators that are endogenously produced by the immune system, and that might represent a very interesting alternative to the prevention and treatment of allergies and other inflammatory reactions via dietary complementation with ω -3 polyunsaturated fatty acids (PUFA).

ALLERGIC ASTHMA AND PREGNANCY

Allergic asthma is a heterogeneous disorder of the airways involving chronic airway inflammation and tissue re-

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modeling; chronic inflammation is associated with airway hyper-responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing [7].

Asthma is considered the most common respiratory problem in women of reproductive age, and probably the most common potentially serious medical alteration that occurs during pregnancy. Between 1997 and 2001, the asthma prevalence was approximately 3.7% to 8.4% of pregnant women in the United States [8]. The severity of asthma may improve, worsen, or remain unchanged during pregnancy. Women with severe and uncontrolled asthma have been reported to have a higher risk of several complications during pregnancy, including preeclampsia, preterm birth, infants with low birth weight or intrauterine growth restriction, infants with congenital malformations and perinatal death. Conversely, women with well-controlled asthma and appropriate treatment have little or no increased risk of adverse maternal or fetal outcomes [9, 10].

Current medical management for asthma emphasizes the treatment of airway inflammation in order to decrease airway responsiveness and prevent asthma symptoms. In pregnant women, the final aim of asthma therapy is the prevention of hypoxic episodes in the mother and the maintenance of adequate oxygenation of the fetus. Integral management of asthma during pregnancy includes objective monitoring of lung function, avoidance or control of allergen or asthma triggers, education of patients, and individualized pharmacological therapy [9].

Conventional drugs used for asthma are divided into long-term controller medications that prevent the manifestations of asthma (inhaled corticosteroids, long-acting β -agonists, leukotriene modifiers, cromolyn, and theophylline) and rescue therapy that provides quick relief of symptoms (mainly short-acting inhaled β -agonists). Oral corticosteroids can either be used as a form of rescue therapy to treat an asthma exacerbation, or as long-term control therapy for patients with severe, persistent asthma [7, 9]. In Table 1, several characteristics of these drugs are described [11]. No medications for the management of asthma have been rated by the US Food and Drug Administration (FDA) as Pregnancy Category A (controlled studies show no risk to the fetus); the requirement for a well-controlled study in pregnant women, which may not always be ethically or financially feasible, limits the number of drugs that will be rated Category A. Most of the drugs used to treat asthma are rated Pregnancy Category B (no evidence of risk in humans) or Category C (risk cannot be ruled out) [10].

To understand the pharmacokinetics of these medications in pregnant women, it is necessary to highlight some of the physiological changes occurring during pregnancy: a) reduced gastric drain and intestinal motility with alterations in bioavailability parameters; b) increased water body and fat percentage within the body which creates a larger volume of distribution for hydrophilic and lipophilic drugs, respectively; c) decreased plasma protein binding that might increase the concentration of free drugs in the plasma that may cross the placenta; d) increased metabolic capacity of phase I and II enzymes (for example, CYP3A4, CYP2D6, CYP2C9 and CYP2A6 of the cytochrome P450 family or the conjugating enzyme UGT1A4 and UGT2B7) and decrease in

CYP1A2 activity; e) an increase in renal blood flow with accelerated elimination of polar drugs, while the elimination of lipophilic drugs may be retarded [12-14].

Drugs and different chemical compounds cross the placenta mainly through passive diffusion. Other possible mechanisms of transport also found in the placenta are active transport, facilitated diffusion, pinocytosis and phagocytosis [15]. Passive diffusion represents the permeation of a molecule down its concentration gradient without expenditure of energy. The amount of drug that crosses the placenta by passive diffusion in a given time is dependent on the concentration of the drug in the maternal circulation and its physicochemical properties such as molecular weight, pKa, lipid solubility and protein binding capacity. Low molecular weight (below 500 Da) and lipid soluble drugs, are favored in its passage through the placenta [16]. Most of the anti-asthmatic drugs described in Table 1, meet these criteria.

During the past years, several placental transporter proteins have been identified and their relevance for selective drug transfer through the placenta is currently under investigation. Some of these active transporters prevent the entry of xenobiotics into the feto-placental unit while several transporters facilitate the passage of drugs to the fetal compartment. Nonetheless, published studies of human placental transporters for the above mentioned anti-asthmatic drugs are very limited [16-19].

Although placental metabolism is more restricted than liver metabolism, placental enzymes are capable of metabolizing several drugs and it seems that the placenta expresses a wider variety of enzymes during the first trimester than at term [16]. In the particular case of anti-asthmatic drugs it is important to highlight the placental expression of CYP1A2 and UGT2B7, which are involved in the metabolism of theophylline and formoterol respectively (Table 1).

ANAPHYLACTIC REACTION IN PREGNANCY

The cascade of events in anaphylaxis is initiated by the introduction of a foreign substance into the maternal circulation, triggering the release of mediators such as histamines, bradykinins, cytokines, prostaglandins, leukotrienes, thromboxane, and many other mediators of inflammation that are responsible for the hemodynamic collapse in systemic anaphylaxis. In the classical form, mediator release occurs when the antigen (allergen) binds to antigen-specific immunoglobulin E (IgE) attached to basophils and mast cells [20].

Anaphylaxis in pregnancy may present uterine cramping, abdominal pain, vomiting, diarrhea, oropharyngeal or labial edema, and respiratory compromise. Subsequent cardiovascular collapse may occur, and uterine vessel vasoconstriction may lead to fetal bradycardia, fetal hypoxia, and subsequent poor neurological outcome or fetal death [21].

The treatment of anaphylactic reactions in the pregnant female is essentially the same as in non-pregnant women. In general, immediate intervention includes assessment of airway function, breathing, circulation, and level of consciousness; as well as the administration of epinephrine, H1 and H2 histamine antagonists, and systemic corticosteroids according to the physician's discretion [20].

Table 1. Pharmacokinetic Characteristics of Some Traditional Drugs Used in the Management of Asthma During Pregnancy

Drug	FDA Category	Bioavailability	Properties Hydrophilic/Lipophilic	Metabolism Phase I/Phase II	Molecular Weight in Dalton	Excretion	Half-life (Hours)
Inhaled corticosteroids • Budesonide • Fluticasone (propionate)	B C	B: 39 % (aerosol inhalation) F: almost complete (aerosol inhalation)	B: practically insoluble in water; freely soluble in chloroform F: no data	B: liver by CYP3A4 F: liver, extensive hydrolysis by CYP 3A4	B: 430.5 F: 500.5	B: renal, 60%; F: feces, 95%	B: 2 to 3 F: 7.8
Long-acting β -agonist • Salmeterol • Formoterol	C C	S: no data F: virtually undetectable plasma concentration	S: freely soluble in methanol; sparingly soluble in water. F: no data	S: liver, extensive hydroxylation F: glucuronidation involving UGT1A1, 1A8, 1A9, 2B7, and 2B15 enzymes, and O-demethylation involving CYP2D6, CYP2C19, CYP2C9, and CYP2A6 enzymes.	S: 415.6 F: 344.4	S: feces, 25% to 60%. F: renal, 1.1% to 28%	S: 5.5 F: 10
Cromolyn	B	After inhalation about 8% of the drug reaches the lungs and is absorbed	Soluble in water and the resulting solution is neutral	Not metabolized	468.4	Renal: 30% to 50%. Feces: 80% to 87%	1.5
Theophylline	C	Around 96%	Slightly soluble in water at pH: 7; the water solubility increases with increase in pH	CYP1A2 is the major isoenzyme metabolizing theophylline after 3 years of age.	180.2	Renal: 10 to 13% in adults.	1.2 to 7, children; 6 to 12, adults.
Leukotriene-receptor antagonists • Montelukast • Zafirlukast	B B	M: 60% to 78% Z: not determined.	M: Soluble in ethanol, methanol, and water, Z: Practically insoluble in water.	M: <i>in vitro</i> studies indicate metabolism is by cytochromes CYP 3A4 and CYP2C9. Z: hydroxylated via the CYP2C9 pathway.	M: 568.2 Z: 575.7	M: renal, less than 0.2%; feces, 86%. Z: renal, 10%; <u>feces</u> , 90%.	M: 2.7 to 5. Z: 8 to 16
Short-acting β -agonists • Salbutamol • Terbutalina	C B	S: less than 20% (nebulized inhalation) T: 10 to 50% (oral).	S: soluble in ethanol; sparingly soluble in water; very soluble in chloroform. T: soluble in water, slightly soluble in methanol, chloroform.	S: metabolized by sulphotransferase (SULT1A3). T: first pass metabolism is about 69%.	S: 239.3 T: 225.3	S: renal, 80% to 100%. T: renal, 24% to 60%,	S: 4.6 to 6. T: 11 to 26, Pregnant patients had a half life of 3.7.

Unfortunately, there are very severe anaphylactic events that do not respond to therapy and resuscitation efforts. For this reason, preventive measures should be employed when possible, and desensitization with immunotherapy is an accepted and effective option.

CURATIVE TREATMENT OF ALLERGIES: SPECIFIC IMMUNOTHERAPIES AGAINST ALLERGIES BEFORE AND DURING PREGNANCY

For many decades, immunotherapy has been a well established treatment for allergies. Immunotherapies are also able to prevent asthma in allergic individuals and to improve or even cure established allergic asthma [22]. Preparations for immunotherapies are based on the respective allergen itself. Treatment starts with the application of a low allergen dose, which does not induce allergic symptoms. During the initial phase, which may vary from a few days to several months, doses increase up to a maintenance dose which should then be given for approximately three years. The classical route for application is subcutaneous injection, but during the last 20 years, alternative routes, mainly sublingual administration, have become increasingly popular. Subcutaneous injections are given in intervals of several weeks, while sublingual preparations are usually applied in a daily rhythm. Immunotherapy is the only accepted causal treatment of allergies [22]. Severe, including lethal, side effects have been reported for subcutaneous application, but the standardization of preparations has strongly improved safety [23]. The exact mechanism is not yet completely understood, but immunotherapies induce a shift from a Th2 prone towards a Th1 prone immune response [24]. This shift is strongest in immunotherapies against insect venom allergies. Furthermore, although very controversially discussed for many years, immunotherapies seem to induce the production of allergen specific IgG4 which may have allergy protective effects [25]. Immunotherapies are not generally contraindicated in pregnancy, but it is recommended not to initiate such therapies during pregnancy, especially not for insect venom allergies [26].

Immunotherapy Before Pregnancy

Several mouse studies indicate that an active allergic disease of the mother, and especially allergen exposure and symptoms during pregnancy, increase the baby's risk of developing an atopic predisposition [27]. In humans, allergic women have high levels of specific IgE, low levels of specific IgG4 and, during exposure, high levels of acute allergy mediators. In numerous different studies, IgE has been detected in cord blood or in human or animal fetuses [28]. It can also be expected that acute allergy and inflammation mediators, especially in cases of systemic reactions, may influence the physiological cytokine cocktail in the placenta, which may then influence the prenatal programming of the fetus. Early initiation and termination of immunotherapies before pregnancy may change this situation. The fetus will receive higher doses of allergen-specific IgG4 and lower doses of inflammatory mediators [24]. This switch may prevent exposure of the fetus to substances which may program it for future allergies. Therefore, it may be concluded that curative treatment of allergies in young women by immuno-

therapies may be a novel strategy to reduce the risk of the fetus becoming atopic in childhood.

In some cases, as in severe insect venom allergies, which may induce dangerous to lethal symptoms, the completion of immunotherapy before pregnancy should be indispensable. Many studies have proven long-term efficacy of subcutaneous and sublingual immunotherapies [29]. The importance of dampening or possibly even curing an allergic disease before pregnancy is mirrored in animal studies which have disclosed that the absence of allergies, and especially of allergic symptoms, during pregnancy reduces the risk for the newborns of developing new allergies later in life [27].

Immunotherapy During Pregnancy

As mentioned earlier, immunotherapies may lead to a shift in maternal immunoglobulin and cytokine expression, which may influence the immunological placental equilibrium and thereby affect the transfer of immunoactive substances from the mother to the fetus. In addition, the applied allergen itself may cross the placenta and the fetus may be exposed artificially. The major allergen fraction is held back by the placenta, but due to the high number of immune cells therein which are able to react, significant amounts of immunoactive factors may reach the fetal organism [30]. The relevance of these effects depends on a) the applied allergen, b) the time interval of treatment before pregnancy, c) the application route, and d) the composition and nature of the preparation.

- a) The immunogeneic capacities vary between different allergens. The strongest and fastest Th2 to Th1 shift is induced by subcutaneous immunotherapies against insect venom allergies. Therefore, this treatment should not be initiated during pregnancy, but before it. Although the expected immunological shift is lower and slower for other specific immunotherapies, the general recommendation is to start them well before pregnancy [31].
- b) The strongest immunological shift, best observed upon venom allergy therapy, occurs during the early phases of immunotherapies. A longer treatment period before pregnancy may increase safety, compared to shorter periods or even initiation during pregnancy [32].
- c) Subcutaneous immunotherapies induce faster and stronger detectable immunological reactions than sublingual applications, although the clinical effects appear to be similar in most studies. Local and systemic side effects occur more frequently than in sublingual immunotherapy. Therefore, subcutaneous immunotherapies in particular should be applied very carefully, and only as strictly indicated, during pregnancy [33].
- d) Most immunotherapy preparations contain pure, mainly recombinant allergens, but some use modified allergens (allergoids) or adjuvants (e.g. m monophosphoryl lipid A – MPL) to enhance the Th1 shift, which has been shown to be not toxic in reproduction [34]. Nonetheless, immunologic stimulation in several organs has been detected and may be interpreted as being potentially harmful in pregnancy and, therefore, should be avoided. Due to their structural differences to native allergens, aller-

goids should not bind to allergen specific IgE and, therefore, not induce mast cell degranulation [35]. Since mast cells are also present in the placenta [36], it can be expected that allergoids may be safer for the conceptus. On the other hand, nothing is yet known about their passage into the fetal circulation.

PERSPECTIVE OF THE POTENTIAL USE OF ANTI-INFLAMMATORY AND PRO-RESOLVING POLY-UNSATURATED FATTY ACID-DERIVED LIPID MEDIATORS AS A THERAPEUTICAL APPROACH FOR PREVENTION OR TREATMENT OF ALLERGIES

A number of endogenously formed PUFA-derived lipid mediators are now known to function as potent anti-inflammatory compounds that regulate the extent and pace of the inflammatory response, and stimulate the resolution of inflammation. These endogenous counter-regulatory lipid mediators are formed from the ω -6 PUFA arachidonic acid (AA) and from ω -3 PUFAs such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) by the enzymatic actions of lipoxygenase and cyclooxygenase enzymes.

The best studied anti-inflammatory lipid mediator, lipoxin A₄ (LXA₄), is formed during a process termed transcellular biosynthesis, characterized by the sequential oxygenation of AA by the actions of two lipoxygenases, each present in a different cell-type [37, 38]. For example, neutrophils carrying 5-lipoxygenase can oxygenate AA to form leukotriene A₄, which in turn is oxygenated to LXA₄ by a different cell-type with 15-lipoxygenase activity. Especially, when neutrophils interact with other cell types such as endothelial cells, epithelial cells or platelets, transcellular biosynthesis of anti-inflammatory lipid mediators seems to be very active. Furthermore, granulocytes from eosinophilic donors constitute an efficient source of LXA₄ [39].

LXA₄ is a potent anti-inflammatory compound which acts as an autacoid; following generation it acts locally in a tissue, and is thereafter rapidly degraded by enzymatic pathways [38]. LXA₄ stimulates a number of cellular actions which are mediated by binding to a G-protein coupled receptor, FPR2/ALX [40]. One important action is the down-regulation of neutrophil migration from the circulation to the inflamed tissues. This is achieved by the inhibition of neutrophil chemotaxis and decreased adherence to endothelial cells *via* the down-regulation of adhesion molecules. Furthermore, LXA₄ reduces pro-inflammatory cytokine and chemokine release, and reduces neutrophil activation (decreased degranulation and oxidative burst). LXA₄ also effectively reduces the migration of eosinophils in experimental allergy [41]. Thus, LXA₄ actively diminishes neutrophilic and eosinophilic inflammation. On the other hand, LXA₄ stimulates monocyte recruitment to an inflamed tissue and promotes the phagocytosis of apoptotic neutrophils by monocytes/macrophages [42]; this type of phagocytosis is non-phlogistic and limits further inflammatory cell recruitment and activation. In addition, LXA₄ can stimulate host-defense by stimulating the formation of bactericidal/permeability-increasing protein (BPI) from epithelial cells [43]. Taken together, LXA₄ exerts immunomodulation *in vivo*, and

acts on several cell types to counter-regulate inflammation and promote resolution [44].

Aspirin specifically triggers the endogenous formation of 15-*epi*-LXA₄, a LXA₄ isomer that carries one hydroxy group at carbon-15 with a different stereospecificity (*S* in LXA₄ and *R* in 15-*epi*-LXA₄) [45]. This is brought about by aspirin-mediated acetylation of the cyclooxygenase-2 active site, thereby inhibiting its activity as a cyclooxygenase but permitting the introduction of one oxygen molecule into AA with an altered stereospecificity forming 15*R*-hydroxy-eicosatetraenoic acid. This product can be oxygenated by 5-lipoxygenase to form 15-*epi*-LXA₄. 15-*epi*-LXA₄ is similar in activity to LXA₄, but its enzymatic inactivation is not as rapid, affording a significantly enhanced endogenous potency. The insight that a small change in the chemical structure can lead to an increased potency has spurred the development of chemical analogues of LXA₄ and aspirin-triggered 15-*epi*-LXA₄, which resist enzymatic degradation and can display enhanced pharmacological properties as anti-inflammatory drugs [46].

Recently, a number of novel anti-inflammatory and pro-resolution lipid mediators derived from ω -3 PUFA, EPA and DHA have been identified. EPA-derived mediators include resolvin E1 (RvE1) and RvE2 (so called E-series resolvins). RvE1 was the first identified pro-resolving mediator derived from ω -3 PUFA, and activates the G-protein coupled receptor CMKLR1. The DHA-derived mediators include D-series resolvins, protectin D1, and maresins [47, 48]. These compounds are also formed by lipoxygenase-catalyzed oxygenation reactions [49, 50]. Exposure to aspirin can trigger the formation of RvE1 and the aspirin-triggered (AT) D-series resolvins, in an analogous fashion to the formation of 15-*epi*-LXA₄. The resolvins, protectins and maresins are potent endogenous agonists for counter-regulating inflammation, stimulating resolution, and enhancing tissue protection [50, 51].

LXA₄ and 15-*epi*-LXA₄ have been shown to reduce allergen-induced eosinophil trafficking and promote the resolution of allergic inflammation in airways [41, 52, 53]. LXA₄ can also counter-regulate signalling by granulocyte-monocyte-colony stimulating factor in eosinophilic granulocytes, likely reducing eosinophil activation [54]. LXA₄ inhibits the binding of the cysteinyl-leukotriene D₄ (LTD₄) to its cognate receptor CysLT1, thereby reducing the cellular actions of LTD₄, a mediator often involved in allergic reactions [55]. In addition, a recent study has revealed the potent immunomodulatory actions of LXA₄ in allergic airway responses [56]. Of further interest, LXA₄ biosynthesis is compromised in severe asthmatics and in aspirin-intolerant asthmatics [57]. In a murine model of allergic asthma, RvE1 has been recently shown to promote the resolution of allergic airway inflammation through the down-regulation of interleukin (IL)-17, a cytokine important for maintaining allergen-induced airway inflammation [58]. RvE1 also down-regulated the cytokines IL-6 and IL-23, which are important in stimulating Th17-type responses. The topical application of the LXA₄ stable analogue ATLa2 has been shown to be efficacious in reducing trimellitic anhydride-induced allergic delayed-type hypersensitivity, a model for a T-lymphocyte-dependent allergic inflammation of the skin [59].

Dietary supplementation with ω -3 PUFA has been shown to afford protective actions in experimental settings of allergic inflammation; studies in humans have only recently been initiated [60, 61]. An interesting avenue for research will therefore be to establish whether ω -3 PUFA-derived resolvins and protectins exert anti-allergic actions in humans [62]. Given the endogenous roles of LXA₄ and ω -3 PUFA-derived lipid mediators in regulating the pace and extent of the inflammatory response, the delineation of their involvement in the counter-regulation of allergy during pregnancy is of interest. The potential therapeutic benefits of these lipid mediators, as well as metabolically stable analogues, are of significant value in addressing these innovative approaches to treating allergic inflammation. The possible influence of ω -3 PUFA and its derivatives on pregnancy and fetal programming is still being actively discussed. Nonetheless, it can be summarized that the intake of ω -3 appears to have a substantial impact on allergy manifestation [63].

CONCLUSION

Asthma affects approximately 5% of pregnancies in industrialized countries. Besides the classical and established drug-based therapies, new methods for prevention and treatment come into the focus. Immunotherapy is a curative treatment, which can be recommended to apply before pregnancy in regard of avoiding asthma-related problems during pregnancy, but also to reduce the risk of fetal programming for allergies in later life. Finally, anti-inflammatory and pro-resolving mediators, including lipoxins, resolvins and protectins as well as nutritional factors, such as ω -3 long-chain polyunsaturated fatty acid, are currently under investigation and may also have the potential to prevent allergies in the newborn.

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