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Treatment of Allergic Rhinitis During Pregnancy

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Abstract

Allergic rhinitis is a frequent problem during pregnancy. In addition, physiological changes associated with pregnancy can affect the upper airways. Evidence-based guidelines on the management of allergic rhinitis have recently been published, the most recent being the Allergic Rhinitis and its Impact on Asthma (ARIA) – World Health Organization consensus. Many pregnant women experience allergic rhinitis and particular attention is required when prescribing drugs to these patients. Medication can be prescribed during pregnancy when the apparent benefit of the drug is greater than the apparent risk. Usually, there is at least one drug from each major class that can be safely utilised to control symptoms.

All glucocorticosteroids are teratogenic in animals but, when the indication is clear (for diseases possibly associated, such as severe asthma exacerbation), the benefit of the drug is far greater than the risk. Inhaled glucocorticosteroids (e.g. beclomethasone or budesonide) have not been incriminated as teratogens in humans and are used by pregnant women who have asthma. A few histamine

H_1-receptor antagonists (H_1-antihistamines) can safely be used as well. Most oral decongestants (except pseudoephedrine) are teratogenic in animals. There are no such data available for intra-nasal decongestants. Finally, pregnancy is not considered as a contraindication for the continuation of allergen specific immunotherapy.

1. Allergic Rhinitis

Rhinitis is often a problem during pregnancy since nasal obstruction may be aggravated by pregnancy itself.[1-4] Persistent hormonal rhinitis may develop during the last trimester of pregnancy in otherwise healthy women and symptoms disappear at delivery. Pre-existing rhinitis usually remains stable during pregnancy,[5,6] but can become aggravated or improve in 30–45% of patients.

The management of allergic rhinitis includes allergen avoidance, pharmacological treatment, specific immunotherapy and education. Evidence-based guidelines have recently been published, the most recent being the Allergic Rhinitis and its Impact on Asthma (ARIA) – World Health Organization workshop report.[7] Caution should always be taken when administering a drug to a pregnant woman, as most medications cross the placenta. The risk of malformation of the fetus represents a major fear and is highest during the first trimester. Concerning human teratogenicity, the following factors do not formally eliminate toxicity in a fetus: (i) the chemical structure of a drug; (ii) animal reproductive studies; (iii) the apparent safety of medication in healthy adults; and (iv) the absence of case reports involving teratogenicity, even with drugs which have been on the market for a number of years. Moreover, for most available drugs, only limited studies on small groups without long-term analysis have been performed. However, for some drugs, it would appear that, based on birth registries and registries of congenital malformations, the possibility of fetal harm is remote. Nevertheless, prescribing a drug to a pregnant woman enlists the responsibility of the doctor and the benefit/risk ratio, for the mother and for the fetus, should always be considered.

2. Drugs Available for the Control of Allergic Rhinitis

2.1 Glucocorticosteroids

Intra-nasal glucocorticosteroids (beclomethasone, budesonide, flunisolide, fluticasone propionate, mometasone and triamcinolone) are currently the most potent medication available for the treatment of allergic[7,8] and non-allergic rhinitis[7] with a few exceptions, including pregnancy rhinitis.[9] They can suppress many stages of the allergic inflammatory process. The rationale for using intranasal corticosteroids (instead of systemic corticosteroids) in the treatment of allergic rhinitis is that high drug concentrations can be achieved at receptor sites in the nasal mucosa, with minimal risk of systemic adverse effects. Systemic absorption may occur following the nasal administration of corticosteroids but, although more data are required, clinically relevant adverse effects do not generally occur at therapeutic doses.[7,10]

All corticosteroids[11] are teratogenic in animals (principally harelip but also cardiovascular malformations) and, although a significant risk of abnormalities with systemic corticosteroids has been found in humans, some debate exists. Moreover, there is only one study concerning the risk of intranasal corticosteroids during pregnancy.[9] In this trial, 26 pregnant women received fluticasone propionate aqueous nasal spray for 8 weeks without any deleterious effects for either the mother and the

Table I. US FDA pregnancy rating for allergic rhinitis medications

Categories	Description of the risk	Interpretation	Examples
A	Animal studies *and* well controlled human studies exclude teratogenicity	No risk	
B	Animal studies do not show teratogenicity *but* no well controlled human studies are available *or* animal studies show teratogenicity but well controlled human studies exclude teratogenicity	No evidence of risk	Budesonide, cetirizine, cromoglycate, dexchlorpheniramine, diphenhydramine, ipratropium bromide, loratadine, nedocromil, pseudoephedrine
C	Animal studies show teratogenicity or are not available *and* no well controlled human studies are available. However, potential benefits may justify the potential risk	Risk cannot be ruled out	Other corticosteroids, azelastine, brompheniramine, fexofenadine, hydroxyzine, all other decongestants
D	Well controlled human studies show teratogenicity *but* apparent benefit of the drug may be greater than the risk in certain circumstances	Evidence of risk	
X	Well controlled human studies show an increased risk of teratogenicity which always exceeds that of the clinical benefit	Contraindication	

fetus.[9] Nevertheless, inhaled corticosteroids (e.g. beclomethasone or budesonide) have not been incriminated as teratogens in humans and are used by pregnant women who have asthma. Greenberger and Patterson[12] did not find any materno-fetal adverse effects in 40 pregnant asthmatic women who were treated with beclomethasone. The Michigan MedicAid registry did not find any excess of risk of congenital malformation in 395 new borns who were exposed to beclomethasone during the first trimester.[13] The US FDA recently approved a revised labelling for budesonide inhalation powder which upgrades its pregnancy rating to Category B. All other inhaled corticosteroids are classified as a pregnancy Category C (table I). The US FDA based the label change on a review of data from the Swedish birth and congenital malformation registries.[14] No increased risk for congenital malformations was observed from the use of inhaled budesonide during early pregnancy. However, when considering systemic corticosteroids administered during the first trimester, there is an increased risk of about 3 to 5 of harelip (with or without cleft palate). The power of such studies remains poor and many confounding factors persist.[15] Nevertheless, when the indication is clear (not for allergic rhinitis but for diseases possibly associated, such as severe asthma exacerbation), the benefit of the drug is far greater than the risk. There is no other increased risk of teratogenicity.

In the case of prolonged systemic corticosteroid therapy, the increased risk of growth retardation *in utero*, first demonstrated by Reinisch et al.[16] seems to be related more to a severe underlying maternal pathology than to the corticosteroid therapy itself.[17] However, the increased risk of preeclampsia is observed even after controlling for other potential confounders.[5,17] The initially described risk of adrenal insufficiency in newborns in the perinatal period has not been confirmed.[18] As an example, in 36 pregnant asthmatic women treated with prednisone, Snyder and Snyder[19] did not note any pathological pregnancy-related or medical problem in the children born and observed during a 2-year period.

2.2 Chromones

The action of these drugs (sodium cromoglycate and nedocromil) is linked to the cell wall of the mast cell[20] and/or to the intracellular events that follow the allergen binding to IgE.[21] However, the exact mechanism of action remains unclear. With regard to the pharmacokinetics of chromones, cromogly-

cate and nedocromil are virtually not absorbed through mucosal surfaces, and the swallowed portion is also poorly absorbed from the gastrointestinal tract and excreted in the faeces.

No teratogenic effect has been found in animals. To this day, no adverse effect has been shown in humans[22] but there are no prospective studies available. However, neither the Michigan MedicAid registry[13] nor Schatz et al.[17] found any excess of risk of congenital malformation in 191 and 151 asthmatic women, respectively, exposed to inhaled sodium cromoglycate during the first trimester. Schatz et al.[17] then proposed the use of sodium cromoglycate as a first-line treatment for allergic rhinitis in pregnant women.

2.3 Antihistamines

Antihistamines or histamine H_1-receptor antagonists or H_1-antihistamines block the effect of the major mediator involved in the pathophysiology of allergic rhinitis, that is, histamine. First-generation antihistamines induce sedation and are no longer recommended in developed countries.[7] The newer generation compounds are mostly devoid of central nervous system adverse effects,[23] and are therefore a first-choice treatment for allergic rhinitis in these countries.[7]

Some first-generation antihistamines (e.g. azelastine, chlorpromazine, diphenhydramine, hydroxyzine and promethazine) were shown to be teratogenic in animals.[24-26] Because they have been on the market for more than 50 years, chlorphenamine (chlorpheniramine)[27] and dexchlorpheniramine[28] are favoured by some authors, but they are sedative and no longer recommended by guidelines on allergic rhinitis.[7] Second-generation antihistamines do not appear to be teratogenic in animal reproductive studies. Once again, the absence of controlled trials in humans and the fact that they cross the placental barrier means it is necessary to avoid prescribing them during pregnancy. However, a small, prospective, matched-case control study of hydroxyzine and cetirizine was carried out in 43 and 33 pregnant women, respectively, and no adverse effects to either the fetus or the mother were found.[29] This is the reason why French Pharmacovigilance Centres recommend cetirizine. In addition, no increased risk of total congenital malformations was found with loratadine in infants of 292 exposed mothers from the Swedish Medical Birth Registry.[30] A causal relationship between hypospadias and use of loratadine from that registry could neither be confirmed nor excluded by the European Agency for the Evaluation of Medicinal Products – Committee for Proprietary Medicinal Products (EMEA – CPMP).[31,32] In a small, prospective, multicentre study, no significant difference in the number of malformations or other outcomes were seen between 161 loratadine-exposed pregnant women and an equal number of unexposed controls.[33] Although there are differences in regulations between countries, examples of the US FDA categories for antihistamines are given in table I.

2.4 Anticholinergic Agents

Intranasal ipratropium bromide, a quaternary derivative of isopropyl noratropine, is poorly absorbed by the nasal mucosa because of a low lipid solubility and does not cross the blood-brain barrier.[34] It acts on rhinorrhoea by blocking the muscarinic receptors of the seromucinous glands.[34] It is effective in controlling watery nasal discharge, but it does not affect sneezing or nasal obstruction.

There are no existing records of teratogenicity in animals with this class of drugs. Atropine passes through the placenta and can be prescribed to pregnant women. The prescription of its derivatives also seems to be without danger, but once again, it is advisable because of the lack of extensive studies, to avoid these during the first trimester.

2.5 Decongestants

The decongestant (or vasoconstrictor) drugs affect the sympathetic tone regulation of blood vessels by acting on adrenergic receptors and provoking vasoconstriction.[35] They may be administered topically or systemically. In both allergic and non-allergic rhinitis, intra-nasal decongestants such as oxymetazoline, xylometazoline and naphazoline are very effective in the treatment of nasal obstruction in the short-term.[36] Their prolonged use (>10 days) may lead to tachyphylaxis, a rebound swelling of the nasal mucosa, and 'rhinitis medicamentosa'.[37] Oral decongestants such as ephedrine, phenylephrine and especially pseudoephedrine are the most commonly used systemic nasal decongestants.[38] They act on nasal obstruction only. In many countries, combinations of oral antihistamines and decongestants (pseudoephedrine) are marketed and frequently available over the counter.

Most oral decongestants (except pseudoephedrine) are teratogenic in animals. There are no such data available for intra-nasal decongestants. Pseudoephedrine has been shown to increase the risk of gastroschisis by a factor of 2 to 3.[39] No increased adverse outcomes compared with controls were reported in 2509 pregnant women exposed to pseudoephedrine.[40,41] Avoidance of decongestants only during the first trimester has been previously recommended.[4] Because extensive studies are lacking, we consider that intra-nasal decongestants cannot be safely administered to pregnant women even after the first trimester.

2.6 Specific Immunotherapy

Allergen specific immunotherapy (SIT) is the practice of administering gradually increasing quantities of an allergen extract to an allergic individual in order to ameliorate the symptoms associated with the subsequent exposure to the causative allergen. SIT has a place in selected patients with demonstrable IgE-mediated diseases who either have a long duration of symptoms or in whom pharmacotherapy is not effective or induces adverse effects. Guidelines and indications for SIT with inhalant allergens have been published regularly over the past years, in particular by the WHO.[7,42]

There are no teratogenicity data for SIT available in animals. Metzger et al.[43] showed the safety of SIT in a study in 115 pregnant women each receiving SIT for allergic rhinitis. Therefore, pregnancy is not considered as a contraindication for the continuation of immunotherapy; however, it is advisable not to increase the dosage during pregnancy in order to avoid any possibility of an anaphylactic accident. It is also advisable not to begin SIT for allergic rhinitis during pregnancy.[7,42]

3. Treatment Strategy for Allergic Rhinitis

3.1 Development of Guidelines for Allergic Rhinitis

Evidence-based guidelines for the treatment of allergic rhinitis have been published. In the most recent ARIA – WHO guidelines,[7] a new subdivision of allergic rhinitis was proposed: intermittent (for symptoms lasting <4 days a week or <4 consecutive weeks a year) versus persistent (for symptoms lasting >4 days a week and >4 consecutive weeks a year). These two terms replace seasonal and perennial, respectively. The severity of allergic rhinitis has been classified as 'mild' and 'moderate/severe' depending on the severity of symptoms and quality of life outcomes. Depending on the subdivision and severity of allergic rhinitis, a stepwise therapeutic approach has been proposed. The treatment of allergic rhinitis combines allergen avoidance (when possible), pharmacotherapy and immunotherapy. It is recommended to consider allergic rhinitis as a risk factor for asthma, especially in patients with persistent allergic rhinitis, and therefore to evaluate for asthma by history, chest examination and, if poss-

ible and when necessary, assessment of airflow obstruction before and after administration of a bronchodilator. If both allergic rhinitis and asthma are present, a strategy considering efficacy and safety issues should be considered to combine the treatment of both the upper and lower airway disease.

3.2 Pharmacological Management of Allergic Rhinitis

For mild intermittent allergic rhinitis, the ARIA – WHO recommendations[7] for treatment are: oral or intranasal H_1-antihistamines, intranasal decongestants (<10 days and not more than twice a month) and oral decongestants. For moderate/severe intermittent and mild persistent allergic rhinitis, the options for treatment are: oral or intranasal H_1-antihistamines, oral H_1-antihistamines and decongestants, intranasal corticosteroids and chromones. For moderate/severe persistent allergic rhinitis, it is advisable to use intranasal corticosteroids as a first-line treatment. If the nose is very blocked, a short course (e.g. 1–2 weeks) of oral corticosteroids may be added or intranasal decongestants for <10 days.

The patient should be re-assessed after 2–4 weeks and if the patient does not improve reasons for failure should be considered. Reasons include inadequate compliance, patient or doctor misunderstanding of the dose and frequency of administration of intranasal corticosteroids, prevention of drug delivery as a result of nasal obstruction (nasal polyps or nasal septal deviation), heavy persistent allergen exposure and wrong diagnosis. If none of the above reasons are found, the following options are proposed: (i) double the dose of intranasal corticosteroid if the major symptom is nasal blockage; (ii) add an H_1-antihistamine if the major symptoms are sneezing, itching or rhinorrhoea; (iii) add ipratropium bromide if the major symptom is rhinorrhoea; and/or (iv) add an oral H_1-antihistamine combined with an oral decongestant. Referral to a specialist may be considered at this point.

Table II. Possible treatment options for allergic rhinitis during pregnancy, first trimester included[4,6,7,17]

Anti-inflammatory drugs
Cromoglycate
Beclomethasone
Budesonide
Prednisone or prednisolone (only if clearly needed)
Anti-allergic measures
Allergen avoidance
Cetirizine
Loratadine
Specific immunotherapy

If the patient improves, a step down approach should be used and low-dose intranasal corticosteroids may be required as a maintenance treatment to control symptoms.

3.3 Management of Allergic Rhinitis During Pregnancy

The management of allergic rhinitis in pregnant women should follow the same guidelines as for other patients. A firm diagnosis is needed as well as an assessment of the severity of the rhinitis. Although allergen avoidance is the treatment of choice, especially during pregnancy, it is not possible to avoid outdoor allergens. The real challenge is to create a low allergen environment in patients' homes but, unfortunately, the majority of single interventions have failed to achieve a sufficient reduction in allergen load to lead to a clinical improvement.[7] Nasal saline drops or spray can help to clear the nose, in particular before eating and sleeping,[44] and may be of interest in pregnancy. When the disease is severe enough and allergen avoidance has failed to control symptoms, drugs are necessary. Although the choice of agents should partly be based on the evidence of fetal safety, the issue of maternal health also needs to be considered to provide optimal management. This is particularly the case when a systemic corticosteroid is needed, which should very seldom be the case for allergic rhinitis. At least one drug of each major class

utilised to control symptoms can be given safely[4-7,17,28] in moderate to severe allergic rhinitis (table II).

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