Allergic rhinitis in women

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Allergic rhinitis is a high-prevalence disease that significantly impairs the quality of life. Its pathogenesis is quite well understood, and involves numerous cells, cytokines and mediators, which result in an inflammatory process. The triggering IgE-mediated reaction does not differ between men and women, but in females some aspects, related mainly to the hormonal frame, must be taken into account. In fact, cyclic hormonal changes can affect the severity of rhinitis, as can pregnancy, which may result in a particular form of 'pregnancy rhinitis'. The most important and challenging aspect is the management of allergic rhinitis in pregnancy, which require a careful evaluation of the risk:benefit ratio. This review will examine the aforementioned aspects, with particular regard to the pharmacotherapy of rhinitis in pregnancy.

Allergic rhinitis (AR) is probably the most common immune-mediated disorder and the most prevalent allergic disease. On average it affects 5–15% of the general population worldwide, although with large variations among geographical regions [1,2], with a constantly increasing prevalence. Despite this AR is not a life-threatening disease, but it significantly impairs quality of life, sleep and school and work performance [3–5], thus resulting in significant direct and indirect costs. Today, the pathophysiology of AR is quite well understood and the role of molecules and mediators is known in detail. In addition to allergy, several other disorders can provoke rhinitis symptoms, but a detailed clinical history and some simple tests usually allow for the allergic form to be clearly distinguished and diagnosed. It is reasonable to assume that the IgE-mediated mechanism that initiates AR does not differ between men and women, whereas there are some special aspects in females that deserve particular attention. These distinctive aspects are related mainly to cyclic hormonal changes occurring during the fertility period and during pregnancy, thus a special 'pregnancy rhinitis' has been defined. The most important aspect likely to be related to the treatment strategies of AR in pregnancy, when the safety issues assume primary relevance.

Pathophysiology

AR is defined in an operative way as an inflammation of the nasal mucosa, subsequent to the contact with an allergen to which the subject is sensitized [6]. The inflammation is initiated by immunoglobulins belonging to the E class (IgE), which are bound to specialized cells (mast cells) located in the nasal mucosa. The allergic subject has an imbalance between the 'normal' Th1 lymphocytes (responsible for the defense against pathogens) and the Th2 type (responsible for the atopic response). Therefore, allergic subjects produce high amounts of specific IgE, which are able to precisely recognize the allergens (e.g., pollens, mites and pet dander). The IgEs bind the surface of the mast cells, which reside in the mucosa of the nose (as well as in the bronchial tree, skin and gut). When the allergen comes into contact with its specific IgE, the mast cells are activated and immediately release numerous proinflammatory substances. Histamine is the predominant mediator and provokes the early-phase symptoms (sneezing, nasal itching, watery nasal discharge and obstruction). Following activation, mast cells initiate the synthesis of other inflammatory mediators, which amplify the effect of histamine and recruit inflammatory cells, thus maintaining the inflammatory process. Of note, if exposure to the allergen persists, the nasal inflammation becomes chronic.

The allergens that cause symptoms of AR in allergic individuals are largely present in the environmental air and are innocuous for nonallergic people. They include: house dust mites, tree pollens (e.g., hazelnut, birch and olive), weed pollens (ragweed, mugwort and parietaaria), grass pollens, pet dander (cat, dog and rabbit) and moulds (alternaria, aspergyllus and penycillum). Some allergens are present in the environment throughout the whole year (mites, pets and moulds), and are therefore referred to as perennial. However, pollens that appear only during the period of blossoming are named seasonal allergens.
Clinical aspects & diagnosis

Based on the presence of allergens throughout the year, AR was traditionally subdivided into seasonal AR (SAR or hay fever) and perennial AR (PAR). Nonetheless, this practical classification does not reflect the impact of rhinitis on everyday life. In fact, symptoms may be long lasting and troublesome with seasonal allergens, or largely variable with perennial allergens. Based on these considerations, the classification has been changed recently, taking into account the severity and duration of disease, rather than of the type of allergen. The new classification considers the duration of symptoms and the effect of symptoms on everyday life. Thus, AR can be classified into intermittent and persistent, each with two grades of severity (Figure 1). The new classification results in a stepwise treatment strategy that is based on the severity and duration of symptoms [6].

The typical symptoms of AR are:

- Sneezing
- Itching
- Rhinorrhea
- Nasal obstruction

However these symptoms can have a variable expression. In fact, from a practical viewpoint, patients with rhinitis are often subdivided into ‘sneezers/runners’ and ‘blockers’. Subjects sensitized to perennial allergens (e.g., mites) usually belong to this latter subset, with obstruction as the predominant symptom. A family history of atopy or allergy is strongly suggestive of the atopic nature of the disease, as well as the history of seasonal exacerbations. AR is often accompanied (especially in pollen allergy) by conjunctivitis, which involves conjunctival pruritus, tearing, palpebral edema and redness [7]. There are some ocular and nasal symptoms that are not usually related to the allergic disorder, and therefore require a specificity evaluation (Box 1). Another important aspect is that persistent AR is often associated with asthma [6,8]. This makes the assessment of asthma symptoms mandatory in all subjects who suffer from persistent AR. When AR is suspected, the etiological diagnosis can be made easily by means of the so-called skin-prick test, whereas intradermal tests are not recommended. Skin tests are safe, cheap and provide an etiological diagnosis in 15 min. However, with the skin-prick test technique there is also a remote risk of severe systemic reactions [9,10], thus it is unanimously considered reasonable to postpone skin testing in pregnant women. If an immediate allergy diagnosis is needed in a pregnant woman, then specific IgE assay would be preferred. In selected cases, when skin testing and serum assays do not provide a convincing...
answer, a specific challenge with intranasal or conjunctival administration of the suspected allergen may be discriminative [11].

Special considerations in women
Sex hormones & rhinitis
The initiating pathogenic mechanism of AR (i.e., mast-cell activation and mediator release) is not different in women and men, but in women some special aspects must be considered. First, is the special hormonal situations related to the menstrual cycle and pregnancy. Second, is treatment strategy during pregnancy. In addition to these aspects it has also been shown that, strictly related to the hormonal situation, the perception and reporting of symptoms may differ between males and female [12].

Sex hormones, estrogens in particular, cause smooth-muscle relaxation and vascular engorge-ment in the female genital tract, but they can also exert these actions on the nasal mucosa [13], where sex hormone receptors are well represented [14]. In addition, estrogens may favor inflammation, as demonstrated in vitro [15], and this can be clearly evidenced by the increase of nasal reactivity in the middle menses [16]. In addition, it has previously been shown that in the middle cycle there is an increase of skin reactivity to histamine or allergen prick, independent of the atopic status of the woman [17]. In this case, estrogens seem to be the major factor responsible for the nasal alteration and for the increase of nasal reactivity [18]. Of note, oral contraceptives have no effect on the menstruation-related nasal changes [19]. In summary, if a woman has AR (i.e., inflamed nasal mucosa), an overall worsening of rhinitis symptoms (especially nasal obstruction) may occur during the ovulation period of the menstrual cycle. This usually requires only a temporary increase in symptomatic drug intake. Finally, an intriguing clinical observation on the possible relationship between sex hormones and rhinitis is that hayfever and asthma are significantly associated with irregular menstrual cycles in young females. There is no clear pathogenic explanation for this observation, although it has been hypothesized that there is a common role of insulin resistance for both allergies and irregular menstruation [20].

Rhinitis & pregnancy
In pregnancy there is a general modification in the hormonal asset that may affect the course of respiratory allergy. It is well known that pregnancy induces asthma exacerbation in approximately a third of women and asthma improvement in another third, it has also been shown that the course of rhinitis usually parallels that of asthma [21]. The hormonal changes in pregnancy involve not only estrogens and progesterone, but also other substances such as placental growth factor (PGF), cortisol and others. In fact, an increased level of PGF in women with pregnancy-related nasal congestion has been clearly demonstrated [22]. The changes in the hormonal constellation may lead to congestion and inflammation of the nasal mucosa. This fact has been well ascertained in a study that instrumentally evaluated the nasal patency throughout the pregnancy course [23]. Based on these observations, a specific hormone rhinitis, called pregnancy rhinitis [24,25], has been identified. Pregnancy rhinitis is defined as nasal congestion in the last 6 weeks or more of pregnancy, without other signs of respiratory-tract infection, with no allergic cause and that resolves completely within 2 weeks of delivery [25]. Pregnancy rhinitis has been described to occur in approximately 20% of pregnant women, appearing at almost any

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**Box 1. Typical and nontypical symptoms of allergic rhinitis and conjunctivitis.**

**Allergic rhinitis**

Typical symptoms:
- Watery rhinorrhea
- Sneezing
- Nasal congestion
- Itching
- Conjunctivitis

Symptoms requiring specialty referral:
- Unilateral symptoms only
- Purulent discharge
- Isolated posterior rhinorrhea
- Pain, epistaxis
- Total anosmia

**Allergic conjunctivitis**

Typical symptoms:
- Tearing
- Ocular itching
- Redness
- Palpebral edema
- Concomitant rhinitis

Symptoms requiring specialty referral:
- Unilateral symptoms
- Photophobia/pain
- Ocular burning
- Purulent secretion
- Dry conjunctiva
Nevertheless, a recent clinical study using strict diagnostic criteria reported an overall prevalence of less than 10% of pregnant women [26]. This condition may be troublesome, especially in the last weeks of pregnancy, when the overweight and mechanical displacement of the diaphragm, per se, may alter the respiratory pattern. In addition, it has been shown that approximately a quarter of pregnant women report snoring during the last trimester. Although the study did not specifically deal with AR or pregnancy rhinitis, it was evident that snoring was significantly correlated with fetal growth retardation [27].

There is no specific therapy for pregnancy rhinitis. Owing to safety concerns and the fact that pregnancy rhinitis is self-limiting, aggressive pharmacological treatments are not recommended. Reasonable approaches include nasal lavages with isotonic saline or alar nose dilators. Topical corticosteroids are of marginal benefit, whereas topical decongestants are highly effective in relieving nasal congestion. For this reason, pregnant women tend to overuse them, with the risk of rhinitis medicamentosa (a severe and refractory athrophic rhinitis) [28]. Therefore, it is important that pregnant women are correctly informed and educated regarding the use of decongestant, which must be limited to a few days.

Table 1 summarizes the most common aspects of rhinitis to be considered in pregnancy.

| Condition                  | Action                                      |
|----------------------------|---------------------------------------------|
| Allergic                   | Adjust treatment considering the risk profile of drug |
| Worsens in approximately a third of women, improves in a third |                                  |
| Occupational               | Avoid allergen/trigger                       |
| Aspirin intolerance        | Consider surgery if nasal obstruction is intolerable |
| Mechanical (septum deviation, polyposis, turbinate hypertrophy) | Family/case history, seasonal exacerbation, specific IgE assay |
| Allergic rhinitis not diagnosed before | Treat considering the risk profile of drugs |
| Rhinitis medicamentosa     | Discontinue topical decongestants, treat with nasal corticosteroids |
| Abuse of topical decongestants for a pre-existing rhinitis |                                  |
| Infectious (common cold)   | Only symptomatic treatment                  |
| Accompanied by headache, mild fever, cough, sore throat; lasts few days |                                  |
| Pregnancy rhinitis         | Treat considering the risk profile of drugs |
| Usually not allergic, disappears after delivery |                                  |

Contraceptives

There is another relevant aspect of allergic rhinitis in women – the hypothesized role of oral contraceptives in increasing the risk of atopy in offspring. Indeed, this aspect has been poorly investigated, although the few studies available would suggest that previous use of oral contraceptives slightly increases the occurrence of atopy, asthma or rhinitis in the newborn. In a questionnaire-based survey conducted in Germany in more than 2000 children [29], the maternal use of oral contraceptives before birth was associated with a higher risk of atopic diseases in the offspring compared with children of mothers who had never taken them. The odds ratios were 1.6 for asthma, 1.5 for allergic rhinitis and 2.6 for atopic eczema. The same was seen in a case-control study in 1100 children, where previous use of oral contraceptives before pregnancy increased the risk of allergic rhinitis among offspring with an odds ratio of 1.67 [30].

Owing to the paucity of data and established advantages of oral contraceptives, no change in the recommendations for their use can be made.

Treatment of allergic rhinitis in pregnancy

The most important aspect of allergic rhinitis in women is most likely related to pharmacological treatment, mainly for safety concerns. In general, the recommendations given in international guidelines remain valid in pregnancy, and the therapeutic approach is stepwise, with new drugs to be added according to disease severity.
Allergic rhinitis in women – REVIEW

Allergen avoidance is not practically feasible in the case of pollens, whereas with perennial allergens (mites and pets) some precautions can be taken. Although the more recent reviews indicate that none of the avoidance measures alone are effective [31], the use of mite-impermeable bed covers, frequently washing blankets and removal of pets must still be recommended. The use of chemical acaricides should not be encouraged, due to the poor efficacy and possible irritating effect.

Indeed, none of the drugs used for rhinitis can be considered safe. A US FDA classification is commonly used to grade the level of teratogenic risk of drugs (Table 2) [32], and the majority of the drugs used for rhinitis are classified as grade B or C. Although, concerns regarding the FDA classification have been raised [33,34], it still remains valid as a general guideline in evaluating the fetal safety of drugs.

It is likely that only nasal lavages with saline solutions (isotonic or hypertonic) can be considered totally safe, but their efficacy, which has been proved in other conditions, is often marginal in allergic rhinitis, therefore a drug therapy is usually needed in association. Nasal cromones (sodium cromoglycate and sodium nedocromil) are almost totally devoid of side effects and they are classified as grade B in the FDA list. Cromolyn sodium was formally studied in more than 300 women and showed no increased risk of teratogenicity [35]. A consistent result was found by retrospectively analyzing the occurrence of malformations in a general population and no cluster of risk was observed in women taking cromolyn during pregnancy. The problem with cromones is that they must be given regularly 3–4 times daily, and this usually results in problems of adherence to treatment.

Second-generation antihistamines (topical or systemic) are one of the first-line treatments for allergic rhinitis, although the most abundant data on safety come from the older molecules. Many first-generation antihistamines have been studied extensively and can be reasonably considered devoid of teratogenic risks [36,37]. However, first-generation antihistamines are in general not recommended because of their CNS side effects [6]. Today, there are also data regarding the safety of some of the newer antihistamines, such as loratadine and cetirizine. In fact, those compounds were studied in cohort trials, and both drugs were found to not increase the risk of fetal malformations [38,39]. So far, cetirizine and loratadine are considered the first-choice oral antihistamines [40]. Topical antihistamines (e.g., azelastine) have a moderate efficacy in AR, and multiple daily administrations are needed. There is no formal study in pregnant women, but their absorption rate is very low. They can be considered a reasonable second-choice alternative.

Intranasal corticosteroids are very effective in nasal congestion, where antihistamines usually provide only a marginal benefit. Data on their safety in pregnancy are available for the old molecule beclomethasone dipropionate [41,42] and for the more recent steroid budesonide [43]. Thus, these two nasal corticosteroids can be used when rhinitis is severe and congestion is the prominent symptom. No serious risk with inhaled and nasal corticosteroids has ever been described [44]. A new molecule, named ciclesonide, is to be introduced in clinical practice. This is a steroid prodrug that is activated in the mucosae and is therefore devoid of systemic side effects [45]. In regards to systemic corticosteroids (oral or injected), the data obtained in women with severe asthma, taking high doses of steroids,
would suggest a modestly increased risk of cleft lip and pre-eclampsia [46]. Nonetheless, in AR, systemic corticosteroids are recommended only as short courses (3 days) and only to control intractable obstruction [6]. With this strict limitation, it is likely they can be used safely. Leukotriene modifiers (e.g., montelukast, zafirlukast and zileuton) are almost as effective as oral antihistamines in AR [47] and their safety profile is good. They could be a therapeutic option, especially for rhinitis with concomitant asthma.

The use of nasal decongestants is allowed only for very short periods (<10 days), owing to the well-ascertained risk of rhinitis medicamentosa [6], and also due to sparse reports of safety concerns in pregnancy [48,49]. Systemic decongestants are not recommended at all as first-choice drugs, even outside of pregnancy [6], although they were not associated with fetal malformations [50]. Concerning specific immunotherapy, it is suggested that this can be continued during pregnancy if the patient is in the maintenance phase, the benefit of the treatment is ascertained and there have been no previous severe reactions. However, it is advisable not to begin immunotherapy during pregnancy because the risk for side effects is higher during the phase of increasing doses [51]. Recently, the anti-IgE monoclonal antibody omalizumab has become available. It has been shown to be effective and safe in severe asthma and in allergic rhinitis [52], but there is no systematic study on omalizumab in pregnancy. Owing to the high cost and the lack of safety data, this drug is not recommended for AR in pregnancy.

In conclusion, the use of drugs in pregnancy must be evaluated, taking into account the severity of the disease, the effects of symptoms on quality of life and the available information on the risks of the drugs (Table 3). A stepwise approach is always recommended (Figure 2) [53,54]. It is important to consider that, in the presence of persistent rhinitis (as defined by the Allergic Rhinitis and its Impact on Athsma [ARIA] document), the possible presence of concomitant asthma should be carefully investigated. If asthma is present, an appropriate therapy must be given [55–57] as the risks

### Table 3. Teratogenic risk of drugs used for rhinitis in pregnancy.

| Category               | Molecules                                                                 | US FDA risk category |
|------------------------|---------------------------------------------------------------------------|----------------------|
| Nasal cromones         | Cromolyn sodium                                                           | B                    |
| Intranasal steroids    | Budesonide, fluticasone, flunisolide, mometasone, triamcinolone          | B, C                 |
| Oral antihistamines    | Cetirizine, clemastine, chlorpheniramine, loratadine, diphenhydramine, tripelennamine | B                    |
|                       | Brompheniramine, hydroxyzine, promethazine, triprolidine                  | C                    |
| Nasal antihistamines   | Azelastine                                                                | C                    |
| Nasal decongestants    | Oxymetazoline, pseudoephedrine                                            | C                    |
| Anticholinergic         | Ipratropium bromide                                                       | B                    |
| Antileukotrienes       | Montelukast, zafirlukast, zileuton                                         | B, C                 |

![Figure 2. Summary of the therapeutic options for the treatment of rhinitis in pregnancy.](image)
of uncontrolled asthma in pregnancy always outweigh any possible risk related to pharmacological treatments.

Expert commentary
Allergic rhinitis is a high-prevalence disease, sustained by the IgE-induced inflammation of the nasal mucosa. The classification of AR has been recently changed, taking into account the duration of symptoms and their impact on the quality of life. This implies a new treatment strategy with a stepwise approach, based on that classification. This stepwise approach obviously also applies to women, although some particular aspects have to be taken into account, that is, the effects of the hormonal cycle on inflammation and the effects of pregnancy. For this reason, it is important to provide a detailed diagnosis in order to distinguish, for example, a typical AR from a pregnancy rhinitis or a hormonal rhinitis. Another aspect that has been recently evidenced is the strict correlation between rhinitis and asthma, thus making mandatory a careful evaluation for asthma in all patients suffering from persistent rhinitis. This latter aspect is of primary importance in pregnancy, where the treatment of rhinitis and asthma needs particular attention and a careful choice of the drugs to be used.

Future perspective
Although the pathophysiology of AR is quite well known, the details of the hormonal influences on allergic inflammation still need to be clarified. This would allow to better define, under the diagnostic and therapeutic viewpoint, many aspects of rhinitis in women and especially in pregnancy. In this regard, it is unlikely that in vivo clinical research on the safety of drugs in pregnancy will be carried out, owing to the well-known ethical limitations. On the other hand, the advances in pharmaceuticals are expected to provide new and safer treatments for rhinitis (and asthma) in women in general and in pregnancy in particular.

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**Executive summary**

**Definition of allergic rhinitis**
- A symptomatic disorder of the nasal mucosa following an IgE-mediated reaction.
- It is classified as intermittent or persistent and mild or moderate/severe.

**Typical symptoms**
- Sneezing, itching, rhinorrhea and congestion.
- Conjunctivitis may also occur, especially in pollinosis.
- Unilateral symptoms, pain, anosmia and purulent discharge are not typical and require special investigations.

**Burden of allergic rhinitis**
- Affects quality of life.
- Impairs sleep and work/school performance.
- In the persistent form, is often associated with asthma.

**Special aspects in women**
- Rhinitis may worsen in the middle cycle owing to hormonal changes.
- Pregnancy may exacerbate or trigger rhinitis in approximately a third of cases and improve it in another third.
- The management of rhinitis in pregnancy deserves a special attention (drug-related fetal risks).

**Management of rhinitis in pregnancy**
- Allergen avoidance.
- Nasal lavage/douche.
- Nasal cromoglycate (first choice).
- First-generation oral antihistamines or intranasal antihistamines.
- Loratadine or cetirizine.
- Nasal budesonide or beclometasone.
- Topical decongestants must be used only for very short periods (<10 days).
- Consider leukotriene modifiers if asthma coexists.

If persistent rhinitis is present, the possible coexistence of asthma must be investigated.

**Future perspective**
- Despite the ethical concerns, controlled studies on the safety of new molecules would expand the therapeutic choice and provide more options for the effective control of symptoms.
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