

The Diagnosis and Treatment of Allergic Rhinitis During Pregnancy and Lactation

Gary A. Incaudo, MD^{a,b,*}, Patricia Takach, MD^{a,b}

^a*Department of Internal Medicine, University of California, Davis School of Medicine, 4150 V Street, #3100, Davis, CA 95817, USA*

^b*Allergy Associates, 145 Mission Ranch Boulevard, Suite 110, Chico, CA 95926, USA*

Upper airway congestive symptoms during pregnancy have been recognized since the late nineteenth century [1]. Among randomly selected pregnancies, as many as 18% to 30% of patients report substantial symptoms of rhinitis and sinusitis; this percentage may be higher among patients who have pre-existing atopic disease [2–4]. Nasal conditions during pregnancy can take many forms. For example, hormone surges in pregnancy can induce a form of rhinitis, termed “rhinitis of pregnancy,” which presents as congestion (see elsewhere in this volume). This congestion often is difficult to distinguish from other forms of rhinitis that may be present during pregnancy. Furthermore, coexisting and mild forms of rhinitis may be amplified or uncovered by the physiologic changes that are characteristic of pregnancy. Comorbid features of allergic rhinitis during pregnancy, such as sinus disease, asthma exacerbation, and sleep interference, are common because of the understandable reluctance of mothers to undergo diagnostic or therapeutic intervention for something that “can wait” until the pregnancy is completed.

Twenty to forty percent of women in their childbearing years have some form of allergy [5]. Of those pregnant women who have known allergies, some studies suggest that as many as 10% to 30% experience increasing allergic symptoms during their pregnancy and return to their normal prepregnancy state after delivery [5–7]. In addition, increased circulating blood volume and hormonal influences on nasal mucosal secretions that are seen in pregnancy promote nasal

* Corresponding author. Department of Internal Medicine, University of California, Davis School of Medicine, 4150 V Street, #3100, Davis, CA 95817.

E-mail address: gaincaudo@ucdavis.edu (G.A. Incaudo).

vascular engorgement and noticeable nasal congestion [8,9]. It stands to reason, therefore, that pregnancy can amplify any pre-existing nasal condition.

There are limited data regarding the clinical effects of the various forms of rhinitis on pregnancy outcomes. On the surface, it seems unlikely that gestational rhinitis alone would have a deleterious effect on the course of pregnancy; however, uncontrolled allergic rhinitis or sinusitis during pregnancy may aggravate coexisting asthma, and cause a distinct, adverse effect on pregnancy outcome. Furthermore, nasal obstruction may affect the pregnant mother's eating, sleeping, and emotional well being, which indirectly could affect pregnancy adversely. For example, rhinitis during pregnancy may cause snoring, which has been associated with pregnancy-induced hypertension and intrauterine growth retardation [10]. To optimize pregnancy outcome, the health care provider should be knowledgeable about rhinitis during pregnancy, become familiar with potential comorbidities, and use specialists to optimize pregnancy outcome when complications emerge.

The differential diagnosis of nasal symptoms during pregnancy

Nasal pathologies during pregnancy are a compendium of nasal and sinus problems that are typical of that age group, which are enhanced by some of the physiologic changes that are unique to pregnancy. Prominent in the differential diagnosis of nasal symptoms during pregnancy are viral infection or bacterial sinusitis following viral infection, allergic rhinitis, rhinitis medicamentosa, nasal septal or turbinate deformities, nasal polyps, and the "rhinitis of pregnancy." Each of these conditions may exist by itself, occur in various combinations, or emerge to greater prominence because of the hormonal influences on the nasal mucosa and nasal secretions. For example, infectious sinusitis seems to be increased in pregnancy and reportedly complicated as many as 1.5% of pregnancies, a sixfold increase over the frequency that was observed in a nonpregnant population [9]. Pregnant women also may abuse topical nasal decongestants (rhinitis medicamentosa) when relief is required for chronic congestion, likely because of their inclination to favor topical medications over oral medications to protect their fetus [11].

Viral infections

There are no data to suggest that upper respiratory viral infections occur more frequently in pregnant women; however, such viral infections are common and induce direct tissue damage to the nasal mucosa. Some indirect consequences of viral invasion are nasal mucosa hyperactivity and impaired nasal mucociliary clearance. Secondary bacterial invasion is enhanced in these circumstances, especially from the heavily colonized nasal cavity to the sterile paranasal sinuses. Any coexisting nasal conditions, including the physiologic hormonal effects on

the nasal mucosa during pregnancy, complicate the picture and enhance the probability that bacterial sinus disease will evolve. As allergists, we often see women who have chronic sinus disease—the origin of which seems to be related to pregnancy—and who were reluctant to seek intervention.

Atopy

The peak age of child bearing corresponds with the peak age of onset of allergic disease. Foxen and colleagues [12] suggested that nasal allergy can be exacerbated or initiated by pregnancy. Other investigators have refuted this impression, and used the fact that there is no consistent change in serum IgE during pregnancy as evidence [13]. At the very least, pregnancy tends to occur during a period in a woman's life that coincides with the peak age of onset or expression of allergic rhinitis. Furthermore, the physiologic effects of pregnancy on the respiratory tract can influence the clinical expression of any IgE-mediated response. One report found that during pregnancy, nasal symptoms in patients who had known allergic rhinitis improved in 34%, worsened in 15%, and remained unchanged in 51% [5].

Anatomic obstruction

Anatomic variations, such as septal deflections, polyps, and turbinate hypertrophy (primary or secondary due to allergies or rhinitis medicamentosa), can influence nasal obstruction. The degree of obstruction varies according to the extent and location of the anatomic blockage. The pregnant patient who complains of nasal congestion always should be questioned about the use of topical nasal decongestants. Turbinate hypertrophy that is not related to topical decongestant abuse and nasal polyps generally represent the end-product of more severe pre-existing nasal disease, and suggest the need for a thorough investigation following delivery.

Sinusitis

The actual extent and mechanisms that are responsible for the increased incidence of bacterial respiratory infections during pregnancy remain uncertain. There is alteration of maternal cell-mediated immunity during pregnancy, but this seems to be a selective process that does not cause a predisposition to infections [12,14]. Furthermore, most of the available evidence supports normal functioning of humoral maternal immunity during gestation [15]. There are no data to support the notion that the immunologic changes that occur during pregnancy explain the observed increased incidence of purulent sinusitis.

Limited clinical observations have been made concerning bacterial sinusitis in pregnancy. The organisms seem to be the typical *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*, with the peak onset in the second trimester. Of concern to the medical practitioner is that classic symptoms

and signs of sinusitis are absent in nearly half of the women who have documented purulent sinusitis during pregnancy [9]. Even in the nonpregnant state, sinusitis can be notoriously subtle in its clinical presentation, with little in the patient history or physical findings to support a firm diagnosis. Considering the sixfold increased frequency of sinusitis in pregnancy, health care providers should maintain a high degree of suspicion for sinus disease in pregnancy that is marked by persistent nasal symptoms that are unresponsive to conservative measures, such as nasal rinsing and recommended nasal/sinus medications. The diagnosis and management of bacterial sinusitis during pregnancy is described elsewhere in this issue.

Patulous eustachian tubes

Complaints of ear congestion, fullness, or stuffiness are encountered frequently during pregnancy. They may be due to eustachian tube dysfunction that is associated with rhinitis or they may represent a unique condition—patulous eustachian tubes—that occurs most frequently as a consequence of pregnancy. Clinical clues to this disorder are aggravation of symptoms by the upright position, exercise, and nervousness, as well as a sense of disturbed hearing—autophony—which is hearing one's voice as if one were talking in an empty barrel. The frequency of onset of patulous eustachian tubes increases with each trimester, and typically resolves post partum. Derkay [16] described 20 pregnant volunteers who had symptoms of eustachian tube dysfunction, 80% of whom had demonstrable eustachian tube abnormalities by functional testing, such as tympanometry. Nineteen percent (3 of 16) had patulous eustachian tubes as demonstrated by correlating tympanic impedance variation with respiration, which is diagnostic of this disorder. Because this condition is found mostly in pregnancy and in women who take birth control pills, hormonal factors may be important in this disorder; however, a direct cause and effect relationship with any specific hormone has not been established [17]. The differentiation of patulous eustachian tubes from the other aforementioned disorders of the middle ear space is important in that decongestants, typically prescribed for eustachian tube dysfunction, aggravate patulous eustachian tubes, whereas antihistamines or antibiotics have no effect.

Diagnostic approach

General considerations

In evaluating a pregnant patient who has nasal symptoms, the entire differential diagnosis of rhinitis must be kept in mind. A seasonal onset with itching of the nose or palate and paroxysmal sneezing with congestion and a clear watery rhinorrhea suggest allergic rhinitis. Similarly, prolonged nasal congestion and purulent drainage, particularly if lateralized to one nasal passage, is reasonably diagnostic of purulent sinusitis. Bacterial sinusitis, “rhinitis of preg-

Box 1. Common differential diagnosis of rhinitis during pregnancy

Allergic rhinitis*
Infectious sinusitis
Rhinitis medicamentosa
Pregnancy rhinitis
Eosinophilic nonallergic rhinitis*
Nasal polyps*
Structural nasal obstruction*

* History of same often precedes pregnancy.

nancy,” nasal structural problems that are compounded by hormonal mucosa effects, and rhinitis medicamentosa can mimic allergic rhinitis during pregnancy when classic seasonal hay fever is not present (Box 1). Rhinitis medicamentosa is probably encountered more commonly than the in the general population due to a logical preference pregnant women have for topical vs. systemic medications to relieve their nasal symptoms. Structural abnormalities, eosinophilic non-allergic rhinitis, and nasal polyps are also occasionally seen in pregnant women as a pre-existing condition or even evolve during pregnancy, although there is nothing to suggest any predisposing influence from pregnancy.

Based on a questionnaire study, some degree of nasal congestion occurs in at least 22% of pregnant women, although it is not clear how many would seek medical attention for their symptoms [18]. The authors found such “pregnancy rhinitis” is more common in smokers, and it seemed to be independent of concurrent atopy, such as hay fever or asthma. These observations suggest a non-specific reactive mucosa, perhaps from hormonal influences. This syndrome of nasal congestion (discussed in depth elsewhere in this issue) develops most prominently in the second and third trimesters, and usually disappears within 5 days post partum, although any accompanying eustachian tube dysfunction may persist for an additional 4 to 10 weeks. Knowledge of the possible etiologies of rhinitis in pregnancy allows the treating physician to dictate a logical, direct, and cost-effective diagnostic scheme.

Evaluation

The combination of a carefully directed history, physical examination of the nose, and limited laboratory testing commonly suggests the etiology of rhinitis in pregnancy (see Box 1). Some good questions to ask, other than the description of symptoms, include the following:

Has the patient had allergic rhinitis in the past and, if so, is this the usual season?
Does the patient have a history of nasal symptoms before pregnancy and, if so, are they worse now?

- Is there purulence, especially in the morning upon arising?
- Are the symptoms lateralized to one side?
- Is the sense of smell diminished or absent (common in nasal polyps or chronic sinusitis)?
- Is the patient using a decongestant nasal spray?

The physical examination of the nose can be illuminating and often is omitted. Anatomic findings, such as septal deflections, anterior middle meatal polyps, boggy paleness or erythema of the turbinate mucosa, and turbinate hypertrophy, help to define the source of nasal symptoms.

Laboratory testing should be restricted, given the limited nature of pregnancy. Still, an accurate diagnosis allows for more specific and directed therapy, and there are some helpful simple maneuvers. For example, nasal cytology can be an extremely helpful noninvasive approach in pregnancy. Expelling mucus onto a slide, fixing in alcohol, and staining with Hansel's or Wright-Giemsa stain can provide considerable insight into etiologies. The presence of sheets of neutrophils and bacteria suggests purulent sinus disease. The presence of eosinophils in the nasal mucosa or secretions is strong circumstantial evidence for an allergic etiology, eosinophilic nonallergic rhinitis, or polyps, and more accurately directs additional investigative procedures and treatment. If identification of sensitivity to a potential allergen (eg, house dust mite, animal dander) would be useful for formulating avoidance instructions, in vitro methodology, such as selective in vitro (eg, radioallergosorbent test [RAST] or ELISA) testing is useful [19]. Comprehensive allergy skin testing during pregnancy is not recommended because of the small risk of anaphylaxis and subsequent adverse fetal effects [20,21]; however, scratch or prick tests to inhalant allergens carry little risk of anaphylaxis. Under carefully controlled conditions, limited scratch or prick tests to inhalants (eg, animal dander, dust mite) can be preformed in pregnancy [22]. They only should be performed after inconclusive RAST testing, and only when the results cannot wait until the pregnancy is completed and are expected to have substantial therapeutic implications [23].

The presence of purulent nasal discharge, facial pain or discomfort, and nasal congestion strongly suggest purulent sinusitis; however, rhinitis that is unaccompanied by any of these "classic" findings may still be based on sinus disease [24]. In such circumstances, the diagnosis of sinusitis would escape detection unless an imaging study or maxillary antral puncture and culture is pursued. Limited sinus radiographs or maxillary antral washings can be considered when deemed necessary for diagnostic confirmation.

Although physicians are rightfully cautious about ordering radiographs during pregnancy, the threshold dose of pelvic radiation exposure for induction of a congenital defect has been considered to be 0.1 Gy, which is more than 1000-fold greater than the amount of radiation that is received from routine diagnostic radiologic studies [25]. Therefore, the risk of a single radiographic procedure to the developing fetus is small. As with any medical intervention in a patient, the benefit to risk ratio must be weighed carefully. To consider imaging in the

gravid patient, several factors should be considered. These factors include the total amount of radiation exposure during the pregnancy (considering occupational exposure to radiation as found in flight attendants and pilots or frequent airline fliers) and other nonradiation imaging options. Several organizations have commented on radiation risks and limits in the pregnant patient, including the American College of Obstetricians & Gynecologists (ACOG) and the U.S. National Council on Radiation Protection and Measurement (NCRP) [26,27]. The ACOG Committee noted that fetal risks of anomalies, growth restriction, or abortions are not increased with radiation exposure during pregnancy of less than 0.05 Gy [26]. The NCRP, however, recommends a limit of 1 mSv over a 40-week period [28].

Most imaging is far below the 0.05-Gy risk limit. A limited sinus CT in children with 12 to 15 coronal sections 3- to 5-mm thick provides radiation exposure of less than 0.005 Gy [29]. A screening CT scan of the sinus, as done at most facilities with only 4 to 6 sections, decreases the radiation dose even further. The amount of exposure to the fetus from a Waters and Caldwell view of the mother is less than 0.0000007 Gy. The most sensitive time period for central nervous system teratogenesis is between 10 and 17 weeks of gestation. Radiologic testing should be avoided during this time if possible, and alternative diagnostic measures should be pursued. Rare reported consequences of prenatal radiation exposure include a slight increase in the incidence of childhood leukemia and, possibly, a small change in the frequency of genetic mutations [30,31]. Appropriate counseling of patients is mandatory before radiologic studies are performed.

In circumstances in which allergic rhinitis or sinusitis is suspected but the physician or patient is reluctant to undergo additional diagnostic studies, a diagnostic/therapeutic trial of carefully selected medications, such as antihistamines, nasal allergy medications, and broad-spectrum antibiotics, may be pursued.

Treatment

General considerations

Data regarding the safety of allergy and asthma medications during pregnancy are reviewed comprehensively elsewhere in this issue. Information that is particularly relevant to the treatment of allergic rhinitis during pregnancy is reviewed here.

In 1979, the U.S. Food and Drug Administration (FDA) mandated that the package inserts of all drugs that were approved after November 1, 1980 must include all available information about their teratogenic and nonteratogenic effects. A drug classification system was developed using five pregnancy precaution categories: A, B, C, D, and X [32]. The classification system is based on the degree of risk of teratogenic effects on the fetus as shown by animal and

Table 1

Food and Drug Administration format for labeling human prescription drugs

Category	Description of risk
A	Well-controlled human studies have failed to demonstrate risk to the fetus.
B	Either animal studies show no fetal risk and no human data are available, or animal studies show a risk but human studies do not show fetal risk.
C	Either animal studies indicate a fetal risk and there are no controlled studies in humans, or there are no available studies in humans or animals.
D	Studies show fetal risk in humans, but potential benefits may outweigh the potential risk in certain situations.
X	Studies in animals or humans, or based on human experience show definite fetal risk.

human clinical data (Table 1). The safest drugs are those in Category A. No rhinitis medication that has been labeled since 1980 meets the requirements for pregnancy category A: “adequate and controlled” studies in animals and humans show no increased risk. Therefore, product labels suggest that medications for allergic rhinitis, for example, should be avoided in pregnancy because of the lack of data on fetal safety, although most of the agents have human data that refute this conclusion. Such limitations represent a major problem for physicians who treat rhinitis during pregnancy. An effort is being made to replace the current FDA letter ratings with narrative statements that summarize and interpret existing teratogenicity data and provide estimates of potential teratogenic risk.

Data sources for drug safety in pregnancy

To help physicians cope with the lack of adequately controlled data and the difficult medico-legal environment under which most of them practice, several groups recently published guidelines regarding the use of medications to treat rhinitis during pregnancy. One comes from the Motherisk Program at the Hospital for Sick Children, at The University of Toronto concerning the treatment of allergic rhinitis in pregnancy [33]. The second is a position statement concerning the use of asthma and allergy medications during pregnancy from a joint committee of the ACOG and the American College of Allergy, Asthma, and Immunology (ACAAI) [34]. The third comes from the updated NAEPP guidelines for the management of asthma during pregnancy, in which a section on rhinitis treatment is included [35]. The following drug information was derived from these statements and other more recent published reports.

Topical and oral decongestants

Intranasal and ophthalmic decongestants are divided into short-acting agents (phenylephrine), intermediate-acting agents (naphazoline and tetrahydrozoline), and long-acting agents (oxymetazoline and xylometazoline). Each of these drugs carries an FDA category C rating. Data from the Drug Epidemiology Unit of the

Boston Collaborative Perinatal Project and a case-control study reported a statistically significant association between phenylephrine use in pregnancy and the occurrence of congenital malformations [36]. A retrospective cohort study and two case-controlled studies could not confirm such associations [37–39]. These studies also failed to demonstrate adverse effects from the intermediate- and long-acting topical decongestants. Limited data suggest that for the occasional episode of nasal congestion that interferes with sleep, oxymetazoline HCl drops or spray can be used as minimally as possible, preferably after the first trimester and not during labor. Two older reports on the effect of nasal decongestants on fetal circulation must be kept in mind. Baxi and colleagues [40] showed that repeated use of a long-acting sympathomimetic amine, in the form of a nasal spray, was associated with a nonreactive nonstress test and late decelerations in a patient at 41 weeks of gestation. There was a gradual disappearance of the changes 6 hours after the last dose. A later study examined the effects of a single dose of intranasal oxymetazoline on maternal and fetal indices [41]. There were no significant changes in the maternal blood pressures or pulse rates, and blood flow velocities did not change significantly from baseline for the uterine artery, fetal aorta, or umbilical artery circulations. These investigators concluded that no acute changes in the maternal or fetal circulations occurred in uncomplicated pregnancies after a single dose of oxymetazoline. The risk of rhinitis medicamentosa with continued use of this agent beyond 3 to 5 days should be emphasized.

The most commonly used oral decongestant, pseudoephedrine, carries an FDA class C rating. Cohort studies, including 2509 pseudoephedrine exposures, revealed a congenital malformation rate of approximately 2.3%, which was not increased over the expected incidence [42,43]. Recent case-control studies found a statistically significant association between the use of pseudoephedrine or phenylpropanolamine and the risk of developing gastroschisis, a rare disorder that involves failure of closure of the abdominal wall [44]. The joint ACOG and ACAAI committee Position Statement emphasized that, even if the relative increased risk is 10-fold, the rate of gastroschisis is so low (1–2 per 10,000 live births) that the absolute risk in infants who were exposed to oral decongestants during the first trimester would not be greater than 20 per 10,000 live births. Oral decongestants, either alone or in combination with antihistamines, should be avoided in the first trimester “unless the expected benefit is large and unique”.

Pseudoephedrine, 30 to 60 mg every 6 hours or 120 mg time release capsule every 12 hours, can be considered after the first trimester when the risk of gastroschisis and vascular disruption has passed. There is a theoretic risk that oral α -adrenergic agents could induce uterine vascular constriction; however, administration of single doses of pseudoephedrine did not cause any alteration in uterine or fetal Doppler blood flow in one study [45].

There are no specific data available concerning the use of decongestants during lactation. Pseudoephedrine does pass into the breast milk. It is recommended that only the short-acting form be used, and taken just after breastfeeding to minimize the concentration in breast milk. As with any medication that is taken

while breastfeeding, the mother should be advised to look for signs of toxicity in her infant. In the case of decongestants, this typically would be irritability.

Antihistamines

Oral and intranasal

Patients who have known eosinophilic allergic or nonallergic rhinitis that is accompanied by prominent sneezing and rhinorrhea may benefit from antihistamine therapy. In general, there are no human data to suggest that antihistamines, as a group, have any deleterious effect on pregnancy, regardless of when they are taken. Tripelemnamine, 25 to 50 mg as needed every 6 hours to a maximum of 200 mg/d, and chlorpheniramine, 4 to 24 mg/d in divided doses, have been recommended as the “safest” antihistamines for use during pregnancy based on available animal and human studies, FDA class B rating, and the “antiquity” of these drugs [46,47]. More recently, loratadine or cetirizine have been recommended because of reassuring animal and human data [48]. There are few human data reported regarding fexofenadine and none regarding azelastine in pregnancy.

The regular maternal use of first-generation antihistamines at the time of delivery poses a different type of potential risk. Parkin described a 5-day-old infant who had tremulousness and diarrhea following the maternal ingestion of 150 mg of diphenhydramine daily throughout pregnancy [49]. A mother who used 400 mg of hydroxyzine daily throughout her pregnancy gave birth to an infant who demonstrated a transient narcoticlike withdrawal symptom complex [50]. Finally, maternal antihistamine use has been associated with retrolental fibroplasia in infants with a birth weight of less than 1750 g [51]. These data suggest that the regular maternal ingestion of antihistamines, especially in high dosages, should be terminated as soon as possible before delivery in an attempt to minimize neonatal withdrawal risk; it should be avoided altogether in women who are at risk for delivery of very low birth weight infants.

Some adverse effects might be expected from breast milk that contains maternally ingested antihistamines. Rarely has this proven to be the case; irritability is the most common observation in approximately 10% of mothers surveyed [52]. A report incriminated clemastine as the cause of drowsiness and irritability in a nursing 10-week-old infant [53]. Clemastine concentrations in breast milk were 25% to 30% of the maternal serum values, but none could be detected in the infant's serum. The infant showed resolution of symptoms within 24 hours of drug withdrawal. Maternal concentrations of loratadine in breast milk are unlikely to present a hazard to the nursing infant [54].

Ophthalmic antihistamines

The ophthalmic antihistamines, antazoline, azelastine, ketotifen, levocabastine, olopatadine, and pheniramine, carry FDA category C ratings. There are no published data on their safety during pregnancy.

Antihistamine–decongestant combinations

The physician should be aware that many antihistamines come combined with decongestant preparations because the former have little or no effect on congestion. Many patients who have rhinitis would benefit from the addition of pseudoephedrine to the treatment plan after the first trimester, when there is no further risk of gastroschisis (after the fourth month). Similarly, topical decongestants will help “get the red out” as an ophthalmic preparation.

Corticosteroids

Systemic

First-trimester maternal use of oral corticosteroids has been associated with an increased risk for oral clefts [55–57]. In addition, the use of oral corticosteroids in patients who have asthma was associated with an increased risk of preeclampsia and prematurity, although it is difficult to differentiate adverse effects that are due to the drug itself from the effects of the more severe asthma that requires systemic steroids (see the article by Namazy and Schatz elsewhere in this issue). Systemic corticosteroids rarely, if ever, should be needed for the treatment of allergic rhinitis during pregnancy.

Topical

Although published human data on the intranasal use of corticosteroids is sparse, the topical use of poorly absorbed and “first-pass metabolized” corticosteroid derivatives, such as beclomethasone, budesonide, mometasone, triamcinolone, fluticasone, and flunisolide, for allergic rhinitis during pregnancy, especially after the first trimester, seems to be justified. Because of the metabolic characteristics of these drugs, little, if any, would be expected to reach the fetus during maternal intranasal use, but no specific information is available. Certainly, all of the intranasal steroids cause adverse effects when injected into animals. Still, the apparent safety of inhaled budesonide in the management of asthma during pregnancy suggests that the intranasal route of this drug also should be safe [58–60]. Based on these reassuring data, the FDA recently assigned a category B rating to intranasal budesonide. For patients who have significantly symptomatic nasal polyposis or eosinophilic rhinitis, intranasal budesonide should be considered; however, none of the intranasal corticosteroids seems to have significant systemic side effects at therapeutic dosages [61]. This led the joint ACAAI-ACOG committee to state that it is “not unreasonable to continue an intranasal corticosteroid different than beclomethasone or budesonide in a patient who is well-controlled on that drug before pregnancy and continues to require such therapy”.

Lactation

With the exception of extremely high parenteral dosages in status asthmatics, the use of corticosteroids in the lactating mother poses no substantial threat to the infant. A 50-mg dose of prednisone in the lactating mother would transfer, to the

neonate, less than 20% of its daily physiologic corticosteroid requirement [62]. There are no data concerning the passage of topical corticosteroids into the breast milk, but one would not expect substantial breast milk levels or any increase in risk.

Cromolyn sodium

Animal and human data suggest that cromolyn sodium is probably safe in pregnancy, and it carries an FDA category B rating. There are no pregnancy data specifically on intranasal or ophthalmic use. Although no controlled teratogenicity studies have been published specifically with these routes of sodium cromoglycate, three human studies that involved 638 pregnancies failed to demonstrate any increased risk for congenital defects, even if there was exposure to inhaled cromolyn sodium for asthma in the first trimester [63]. Furthermore, little systemic absorption of cromolyn is seen with topical application. For women who have allergic rhinoconjunctivitis, intranasal or ophthalmic cromolyn sodium may be considered a first-line treatment before moving on to more systemic or stronger medications.

Leukotriene modifiers

Zileuton, an inhibitor of 5-lipoxygenase pathway, is an FDA category C drug with adverse effects in animal studies. Montelukast, which selectively binds to CystLT₁ receptors, and zafirlukast, which competitively binds LtD₄ and LtE₄ receptors, are listed as FDA category B based on reassuring animals studies. The package insert now lists montelukast as indicated for treatment of seasonal allergies and asthma, whereas zafirlukast is still only indicated for the treatment of asthma. Although there are reassuring animal studies, human data are inadequate; it is recommended that montelukast or zafirlukast be used in pregnancy only if it is needed (eg, in patients who have recalcitrant asthma who have benefited clearly from the drug). The use of montelukast for allergic rhinitis in pregnancy cannot be supported because there are alternative treatments with equal or greater efficacy that have much more data on human gestational safety.

Montelukast is excreted in rat milk, but there are no comparable human data; therefore, caution is advised. The only human data for lactation in this class of drugs are for zafirlukast; according to the package insert, it reaches a steady-state concentration in the breast milk that is approximately one fifth of the serum concentration.

Ancillary measures: humidification/cleansing, structural modification, and avoidance maneuvers

Nasal irrigation methods deserve mention as a useful nonpharmacologic modality in the treatment of sinusitis during pregnancy. This can take the form of a

topically applied nasal saline mist that is available over the counter, tepid physiologic saline, or hypertonic saline that is washed through the nose, using a bulb syringe, ear syringe, or various squeeze bottles (eg, Sinus Rinse), or more vigorously with a Water Pik and special nasal adapter. There is little consensus regarding a uniform protocol for nasal irrigation. It is clear that these techniques improve nasal hygiene, reduce symptoms of postnasal drainage, and generally are soothing to the nose. There is some evidence that hypertonic saline delivered by way of a standard Teledyne Water Pik (Fort Collins, Missouri) device has advantages of improving mucociliary clearance and sinusitis outcomes [64,65]. Furthermore, there is the suggestion that pulsatile saline delivery using a bulb syringe or Sinus Rinse is more effective in sinusitis cases than is saline delivered by way of a nasal spray, such as Ocean Spray [66,67].

Other nonpharmacologic modalities include the use of an external nasal dilator at night and radiofrequency reduction of turbinate size. The external dilator has been investigated in gestational nasal congestion and was reported to be effective [68]. Radiofrequency ablation, although considered to be a safe and effective procedure, has not been studied in the pregnant population, other than in isolated case reports [69,70]. Nevertheless, this in-office technique should be considered in any pregnant patient who is suffering from sleep disturbance and discomfort, despite all of the other conservative measures that have been enacted, especially if significant rhinitis medicamentosa has occurred.

Avoidance of irritants, such as smog and smoke, by staying indoors on high-risk days or through the purchase and use of an HEPA air filter should be considered, depending on the clinical circumstances. For the pregnant patient who has known allergic disease, allergen avoidance is particularly important. Avoiding known allergens, when possible, will improve maternal well-being and minimize the need for pharmacologic intervention.

If all pertinent allergens have not been identified before the pregnancy in the allergic patient, identification of the offending agents may be of benefit. Because skin testing with potent antigens may be associated with systematic reactions, and because abortions and other adverse fetal effects have been associated with anaphylaxis, it generally should be replaced during pregnancy with in vitro methods, such as RAST or ELISA tests [71,72]. Historical information often can be used to suggest if house dust, mold, animal dander, or pollen may be involved. Avoidance instructions can be given empirically in these circumstances; however, in selected cases, especially when dealing with indoor animals, selected in vitro testing may be necessary to demonstrate the need for more vigorous avoidance maneuvers.

Immunologic management

Allergen immunotherapy is an effective method for treating seasonal and perennial allergic rhinitis. Reduction of the severity of rhinitis or coexisting asthma, and less need for medications is useful in the allergic pregnant patient. Ongoing

allergen immunotherapy can be maintained during pregnancy. Brief studies and anecdotal reports from the 1940s suggested a slight increased risk of spontaneous abortion [34,73]; however, a series of similar reports and studies over the next several decades suggested that the use of pollen and dust immunotherapy was not associated with any adverse fetal outcomes [74–76]. More recently, two retrospective cohort studies failed to detect any negative association between immunotherapy during the first trimester of pregnancy and congenital malformations [77,78].

Immunotherapy can be considered safe for the mother and fetus during pregnancy [21,79]; however, because of the risk of anaphylaxis, the initiation of immunotherapy during pregnancy should be avoided [80]. Most investigators recommend that allergen immunotherapy be continued in patients who become pregnant and have experienced clinical benefit without systematic reactions [81]. To minimize the risk of a future systematic reaction, consideration should be given to decreasing the maintenance dosage and stopping any build-up of antigen dose routinely when the patient and physician become aware of the pregnancy.

Summary

Rhinitis, including allergic rhinitis, in pregnancy represents a challenge to the physician in terms of its diagnosis and therapy. Although several unique influences of pregnancy adversely affect nasal mucosa, there is growing recognition that most symptomatic nasal problems are expressions of diagnostic entities that have been or will be experienced by the patient in the nonpregnant state. In approaching gestational rhinitis, emphasis should be placed on making an early, accurate diagnosis so that limited, specific, and informed medicinal intervention can be used. Simultaneously, the physician should keep in mind that rhinosinusitis in pregnancy is not necessarily a benign clinical problem. It is important to remember that upper airway disease, if uncontrolled, has a significant adverse effect on quality of life and may exacerbate coexisting asthma, which could affect the pregnancy outcome adversely [82]. Specialty consultation with otolaryngology or allergy may be necessary in the symptomatic pregnant woman before an accurate diagnosis and successful therapeutic recommendations can be made.

The medico-legal atmosphere in the United States poses problems in making clinical statements about the absolute safety of medicinal intervention during pregnancy. For physicians who choose to take up this therapeutic challenge, suitable pharmacologic agents are available to manage the pregnant patient who has rhinitis or rhinosinusitis to achieve the desired therapeutic outcome. Suggested guidelines for the treatment of allergic conjunctivitis and rhinitis are summarized in [Box 2](#). In the individual clinical situation, management decisions must be made only after establishing an exact clinical diagnosis, giving full consideration to the therapeutic risks, benefits, and alternatives, and document-

Box 2. Summary of strategies for the treatment of allergic rhinoconjunctivitis in pregnancy^a

All patients: allergen avoidance

Conjunctivitis: ophthalmic cromolyn, supplemented by loratadine or cetirizine as needed

Intermittent rhinitis (symptoms less than 4 days a week or for less than 4 weeks per year)

Mild: loratadine or cetirizine as needed

Moderate-severe (impairment of sleep, daily activities, school or work, or troublesome symptoms): intermittent intranasal budesonide, supplemented by loratadine or cetirizine as needed

Persistent rhinitis (symptoms more than 4 days per week and more than 4 weeks per year)

Mild: intranasal cromolyn supplemented by loratadine or cetirizine as needed

Moderate-severe: regular intranasal budesonide, supplemented by loratadine or cetirizine as needed; immunotherapy^b

^a Classification from the ARIA Workshop Report (Bousquet J, Van Cauwenberge P, et al. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;108(Suppl):S147–334. *J Allergy Clin Immunol* 2001;108:S148).

^b If initiated before pregnancy and successful. Reduce dosage during pregnancy.

ing this in the patient's record. Moreover, the physician's interpretation of the benefit–risk ratio and the therapeutic decisions based thereon must be fully explained to, and approved by, the pregnant patient before intervention is initiated. A significant number of women who suffer from rhinitis of pregnancy are allergic. Under these circumstances, the best first-line approach is avoidance of allergens, which can reduce symptoms significantly. Often, what is chosen first is either a medication or the decision to allow the pregnant patient to suffer the symptoms, which can affect the pregnancy outcome adversely. Limited allergy consultation can be useful under these circumstances to identify pertinent allergens and to direct avoidance effectively. If avoidance is unsuccessful, then, with the informed consent of the patient and documentation in the chart, medicinal intervention can begin as shown (see [Box 2](#)). Although many women and caregivers may choose not to intervene with medications based on fear of teratogenicity, such notions are contradicted by a significant amount of medical evidence. This is especially true of drug intervention for rhinitis and rhinosinusitis after the first trimester.

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