

Diagnosis and Treatment of Allergic Rhinitis and Sinusitis During Pregnancy and Lactation

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Abstract

Upper airway congestive symptoms during pregnancy have been recognized since the late 19th century (1). Among randomly selected pregnancies, as many as 18–30% of patients will report substantial symptoms of rhinitis and sinusitis, and this figure may be higher among patients with pre-existing atopic disease (2–4). “Rhinitis of pregnancy” can take many forms. In another chapter in this review, Dr. Elergard discusses a form of rhinitis in pregnancy that occurs as a result of physiologic changes specific to pregnancy. This is to be distinguished from other forms of rhinitis coincident sometimes aggravated by pregnancy such as allergic rhinitis and sinusitis.

The incidence of allergic conditions is 20–30% among women of childbearing years (5). Of those pregnant women with known allergies, some studies suggest that as many as 10–30% will experience increasing allergic symptoms during their pregnancy returning to their normal pre-pregnancy state after delivery (5–7). Postulated causes include those responsible for “rhinitis of pregnancy” such as increased circulating blood volume giving rise to nasal vascular engorgement and hormonal influences on nasal mucosal secretions and have been discussed in another chapter of this review (8,9).

Index Entries

Chronic rhinitis; pregnancy; upper airway congestion; viral infections; nasopathology.

Introduction

Other rhinitis presentations in pregnancy include the various forms of chronic sinusitis, rhinitis medicamentosa and the “rhinitis of pregnancy” aggravating pre-existing structural and sinus problems. Infectious sinusitis

is a particularly difficult problem and may be increased in pregnancy. It has been reported to be as high as 1.5%, which represents a six-fold increase over the frequency observed in a non-pregnant population (9). Pregnant women also tend to develop rhinitis medicamentosa

complicating other rhinitis syndromes, probably because of their congestive tendency from hormonal changes and the inclination to favor topical over-the-counter (OTC) medications over oral medications to protect their fetus (10).

There is little data regarding the clinical effect of the various forms of rhinitis on pregnancy. On the surface, it seems unlikely that gestational forms of rhinitis would have a deleterious effect on the course of pregnancy. However, uncontrolled allergic rhinitis or sinusitis during pregnancy may aggravate coexisting asthma, which can have a distinct adverse effect on pregnancy outcome. Furthermore, the quality of life impact from sinusitis and allergic rhinitis may adversely affect the pregnant mother's eating, sleeping, and emotional well-being. This suggests that rhinitis during pregnancy, whatever the cause, should be actively evaluated and treated to optimize pregnancy outcome.

Nasal Pathophysiology During the Childbearing Years

A brief listing of nasal pathologies in pregnancy is simply a compendium of nasal and sinus problems typical of that age group, enhanced by some of the physiological changes unique to pregnancy. Therefore, the clinical approach to any pregnant patient with rhinitis is no different from the non-pregnant patient except for the addition of diagnostical and therapeutic limitations and the physiological changes inherent in the former. Common causes of nasal pathology in pregnancy are viral infections, allergic reactions to inhalant aeroallergens, chronic inhalation of ambient air pollution, anatomic deformities obstructing air and mucous flow, abuse of topical vasoconstrictive drugs, and bacterial infections of the paranasal sinuses. More unusual and unique to pregnancy involving the nasopharynx is patulous eustachian tubes, which are briefly discussed.

Viral Infections

Common viral infections induce direct tissue damage to the nasal mucosa with resultant inflammation and its consequences. Some indirect consequences of viral invasion are nasal mucosa hyperactivity through alteration in receptor responsiveness 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. More significant nasal pathophysiology, such as concomitant allergic rhinitis, chronic sinus disease, and rhinitis medicamentosa may complicate viral invasions.

Atopy

Women during the childbearing years commonly experience the full expression of their IgE-mediated respiratory disease. Foxen et al. suggested that nasal allergy can be exacerbated or initiated by pregnancy (11). Others have refuted this, using as evidence that there is no consistent change in serum IgE during pregnancy (12). At the very least, pregnancy tends to occur during a period in a woman's life, which coincides with the peak age of onset or expression of allergic rhinitis. Furthermore, the proposed effect on the respiratory tract of physiological changes unique to pregnancy in some women can clearly influence the clinical expression of any allergic airway response. One report found that nasal symptoms in allergic rhinitis pregnant patients tended to improve in 34%, worsen in 15%, and remain unchanged in the remaining 51% (5).

Air Pollution

A number of factors are important in explaining the overall increase in airway disease over the last several decades. Among them are cigarette smoke, formaldehyde, ozone, diesel particulates, and sulfur dioxide. Inhalation of various environmental pollutants, such as diesel exhaust particles, is capable of inducing

nasal hyperactivity and inflammation. The increasing frequency of women smoking, of synthetic material use, of women in the workplace, of energy conservation measures indoors, and the generally deteriorating ambient air quality in our cities, homes, and workplaces are all relevant issues to air pollution and its effects on women during the childbearing years.

Anatomic Obstruction

Anatomic findings, such as septal deflections, polyps, and turbinate hypertrophy, all serve as potential additional sources of nasal obstruction in the pregnancy age group. The degree of obstruction induced will vary according to the extent and location of the anatomic blockage. Turbinate hypertrophy and polyps generally represent the end product of more severe nasal disease and suggest the need for a thorough investigation following delivery. Boggy, pale turbinates with a clear mucoid discharge generally suggest the eosinophilic forms of rhinitis, of which IgE-mediated disease is the most common example. This presentation can be visually confused with "rhinitis of pregnancy" however. A careful examination of the decongested nasal passageway for obstruction, a nasal smear for eosinophils and/or a total IgE and selected radioallergosorbent (RAST) tests can help distinguish each of these entities and direct treatment more efficiently.

Sinusitis

The actual extent and responsible mechanisms for the increased incidence of bacterial respiratory infections during pregnancy remain uncertain. There is alteration of maternal cell-mediated immunity during pregnancy, but this appears to be a selective process and not of a profound degree (12,13). The majority of evidence supports normally functioning humoral maternal immunity during gestation (14). There are, as yet, no immunological reasons defined to explain the observed increased incidence of purulent sinusitis during preg-

nancy with congestion from hormonal effects on the nasal mucosa being the leading suspect.

Limited clinical observations have been made concerning bacterial sinusitis in pregnancy. The organisms do not appear to be different from those found in the non-pregnant state. The peak onset is in the second trimester. Of concern to the medical practitioner is the fact that classic symptoms and signs of sinusitis are absent in nearly half of the women with documented purulent sinusitis during pregnancy (9). Even in the non-pregnant 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, there should be a high degree of suspicion of sinus disease in any pregnancy marked by persistent nasal symptoms unresponsive to conservative measures such as nasal rinsing and selected medications (see Tables 1 and 2).

Patulous Eustachian Tubes

Complaints of ear congestion, fullness, or stuffiness are frequently encountered during pregnancy. The differential diagnosis includes acute or subacute otitis media, serous otitis media, eustachian tube obstruction, and patulous eustachian tubes. This latter condition, although not unique to pregnancy, is found most frequently during pregnancy. Clinical clues to this disorder are aggravation of symptoms in the upright position, by exercise, and by nervousness, as well as a sense of disturbed hearing due to autophony. The frequency of onset of patulous eustachian tubes increases with each trimester and typically resolves postpartum. Derkay described 20 pregnant volunteers with symptoms of eustachian tube dysfunction, 80% of whom had demonstrable eustachian tube abnormalities by functional testing (15). Nineteen percent (3 of 16) demonstrated patulous eustachian tubes as evidenced by impedance variation synchronous with respiration. Hormonal factors may be signifi-

Table 1
Summary of Strategies for the Treatment of Allergic Rhinoconjunctivitis in Pregnancy

	1st Trimester	Second–Third Trimester	Intrapartum
First Line	Avoidance of allergens		→
	Immunotherapy ^a		→
	Nasal saline rinse/mist		→
	Intranasal cromolyn		
	First Generation antihistamines		→
	Tripelennamine, chlorpheniramine		
Second Line		Second Generation antihistamines	
		Loratadine ^b	
		Cetirizine ^b	
		Intranasal corticosteroid ^c	
		Beclomethasone	
		Budesonide	
		Topical decongestants ^d	

^aIf initiated prior to pregnancy and is successful. Reduce dosage during pregnancy.

^bConsider if first generation antihistamines cause undue sedation or cannot control patient with other first line remedies and ? topical corticosteroid agents.

^cCould be used during the first trimester for severe eosinophilic rhinitis or nasal polyps.

^dFor acute relief only. Caution as to rhinitis medicamentosa potential.

Table 2
Summary of Strategies for the Treatment of Rhinitis (Vasomotor) of Pregnancy or Post-Nasal Drip in Pregnancy

	1st Trimester	Second–Third Trimester	Intrapartum
First Line	Nasal dilating strips		→
	Nasal saline rinse/mist		→
	First Generation antihistamines		→
	Tripelennamine, chlorpheniramine		
Second Line		Topical decongestants hs	
		Radiofrequency turbinate reduction	

cantly correlated with this disorder as evidenced by its frequency both in pregnancy and in women who take birth control pills. However, a direct cause-and-effect relationship remains to be established (16). The differentiation of patulous eustachian tubes from the other disorders of the middle ear space mentioned above is important in that decongestants, typically prescribed for eustachian tube dysfunction, aggravate this clinical problem, and antihistamines and antibiotics have no effect.

Diagnostic Approach

General Considerations

Allergic rhinitis, bacterial sinusitis, "rhinitis of pregnancy," and rhinitis medicamentosa appear to be the most common causes of rhinitis requiring medical attention during pregnancy (see Table 3). A seasonal onset with itching of the nose and/or palate and paroxysmal sneezing allow for the examining physician to be reasonable secure in an allergic rhinitis diagnosis. Similarly, prolonged purulent nasal congestion and drainage, particularly if lateralized to one nasal passage, is

Table 3
Causes of "Rhinitis of Pregnancy"

Allergic rhinitis*
Infectious sinusitis*
Rhinitis medicamentosa*
"Vasomotor" rhinitis
"Post-nasal drip" of pregnancy
Structural nasal obstruction
Eosinophilic nonallergic rhinitis (NARES) with or without nasal polyposis

*Most common.

reasonably diagnostic of purulent sinusitis. Rhinitis medicamentosa is encountered more commonly than the general population due to a logical preference pregnant women tend to have for topical vs systemic medications to relieve their nasal symptoms and is evident from the history of drug dependency. Structural abnormalities, eosinophilic nonallergic rhinitis, and nasal polyps are also occasionally seen in pregnant women and, along with allergic rhinitis and sinusitis, increase the likelihood of rhinitis medicamentosa developing.

Some degree of nonspecific increased nasal congestion during pregnancy has been reported in 22% of pregnant women based on a questionnaire study, although it is not clear how many of these women would seek medical attention for their symptoms (17). Such "pregnancy rhinitis" was more common in smokers but not related to the occurrence of hay fever or asthma. This syndrome of nasal congestion, alluded to in an earlier chapter, develops most prominently in the second and third trimesters in this disorder and usually disappears within 5 d postpartum, although any accompanying eustachian tube dysfunction may persist for an additional 4–10 wk. Schatz and Zeiger have subcategorized this gestational form of rhinitis into two overlapping, nonallergic, noninfectious, noneosinophilic forms which they term "nonspecific post nasal drip" and "vasomotor rhinitis" (5). They feel that the former is a gestational hormonal effect on nasal mucosal glands whereas the latter more "stuffy" disorder rep-

resents the nasal vascular effects described previously. It is the knowledge of these prevalent etiologies of rhinitis in pregnancy that allows the physician to dictate a logical, direct, and cost-effective diagnostic scheme.

Diagnosis

The combination of a carefully obtained history, physical exam, and limited laboratory testing commonly suggests the etiology of rhinitis in pregnancy (Table 3). Anatomic findings, such as septal deflections, anterior middle meatal polyps, boggy paleness or erythema of the turbinate mucosa, and turbinate hypertrophy all help in defining the source of nasal obstruction. The examining physician can proceed as usual in investigating the differential diagnosis of nasal congestion with some limitations and specific recommendations. Nasal cytology is generally underutilized but can be an extremely helpful noninvasive approach in pregnancy, particularly considering how "noninvasive" it is. The simple expelling of mucous onto a slide, fixed in alcohol, and stained with Hansel's or Wright-Giemsa stain can add 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 and more accurately directs additional investigative procedures and treatment. If the identification of a potential allergen would be useful for formulating avoidance instructions, in vitro methodology such as selective RAST or ELISA testing is preferable (18). Routine skin testing during pregnancy is not recommended due to the small but still present risk of anaphylaxis and subsequent adverse fetal effects (19,20). However, selected scratch or prick tests to inhalant allergens carry little risk of anaphylaxis. Under carefully controlled conditions scratch or prick tests are considered safe in pregnancy (21). Nevertheless, they should only be performed in a very limited fashion and only when the results cannot

wait until the pregnancy is terminated and only if the results are expected to have substantial therapeutic implications (22).

The presence of purulent nasal discharge, facial pain or discomfort, and nasal cytology demonstrating neutrophils with phagocytized bacteria in the nasal mucous strongly suggest purulent sinusitis. However, rhinitis unaccompanied by any of these "classic" findings may still be based on sinus disease (23). In such circumstances, the diagnosis of sinusitis would escape detection unless a sinus radiograph and/or maxillary antral puncture and culture is pursued. Limited sinus radiographs and/or maxillary antral washings should be considered when 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 10 rads, more than 1000-fold greater than the amount of radiation received from routine diagnostic radiological studies (24). The risk of a single radiographic procedure to the developing fetus, therefore, is quite small. The accepted maximum cumulative dose of ionizing radiation during pregnancy is 5 rads. No single diagnostic study exceeds this maximum. For example, the amount of exposure to the fetus from a Waters and Caldwell view of the mother is less than 0.00007 rads. The most sensitive time period for central nervous system teratogenesis is between 10 and 17 wk of gestation. Radiological testing should be avoided during this time if at all possible and alternative diagnostic measures pursued. Rare reported consequences of prenatal radiation exposure include a slight increase in the incidence of childhood leukemia and, possibly, a very small change in the frequency of genetic mutations (25,26). Appropriate counseling of patients before radiological studies are performed is mandatory.

A-mode ultrasonography has been suggested as a safe and efficacious screening

modality for sinus pathology and is commonly available in the obstetrical office (27,28). Unfortunately, if negative, it is not sufficiently sensitive compared to radiography to be used as a substitute for radiography in diagnosing sinus disease and cannot be recommended (29,30).

In circumstances where sinusitis is suspected but the physician and/or patient is reluctant to undergo additional diagnostic studies, a therapeutic trial of carefully selected broad-spectrum antibiotics may be pursued as a diagnostic test. However, prolonged antibiotic therapy is not justifiable without confirmatory studies.

Treatment

General Considerations

The catastrophic abnormalities observed in newborns exposed to thalidomide in the 1960s raised the public and medical awareness of the potential harmful effects of medications on the developing fetus. Furthermore, it has become evident that medication taken intrapartum may adversely affect labor and delivery. Still, only an estimated 2–3% of fetal abnormalities in the United States can be traced to maternal medication usage (31). Even with such public awareness, one-third to two-thirds of all pregnant women will take at least one medication during pregnancy (32). When any medication therapy is contemplated in pregnancy, the goal should be that the medication dosing offers maximum therapeutic benefit and minimal risk to the mother and fetus. Effective drugs that are generally considered safe are preferable to new therapeutic alternatives with less-known biological activity in pregnancy. Furthermore, drugs should be dosed at the lower end of the therapeutic range initially and adjusted as necessary to optimize therapeutic outcome.

In 1979, the FDA mandated that all drugs approved after November 1, 1980 must include in the package insert all available information about the teratogenic and nonteratogenic effects

of the drug during pregnancy. A drug classification system was developed using five pregnancy precaution categories: A, B, C, D, and X (33). The classification system is based on the degree of risk of teratogenic effects on the fetus as shown by animal and human clinical data (see Table 4). The safest drugs are those in category A. No rhinitis medication labeled since 1980 meets the requirements for pregnancy category A where adequate controlled studies show no risk. As a consequence, product labels suggest that medications for allergic rhinitis, for example, should be avoided in pregnancy because of lack of fetal safety data, even though the majority of the agents have human data which refute this conclusion. Such limitations represent a major problem for the physicians treating rhinitis conditions during pregnancy. As a consequence, there is an effort being made to replace the current FDA rating with narrative statements summarizing and interpreting existing teratogenicity data and provide estimates of potential teratogenic risk.

Data Sources for Drug Safety in Pregnancy

The information available regarding the safety of drugs used in the treatment of rhinitis during pregnancy is derived from two major studies as well as from sporadic case reports, small uncontrolled retrospective series, and small prospective studies describing the outcome of using a given drug in pregnancy. The first major work on drug therapy and pregnancy was the Collaborative Perinatal Project (CPP) which involved 50,282 women studied at 12 centers during 1959 to 1965 (34). "Standardized relative risk" values were derived using the ratio of malformation rates in exposed to nonexposed mother-child pairs. A relative risk greater than 1.5 was considered suggestive of a cause and effect relationship. However, despite the large number of women examined, this study suffered from the fact that the number of mothers exposed to any single therapeutic agent was small, creating a prob-

Table 4
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.

lem in defining true toxicity or safety to the satisfaction of all. A second large investigation analyzed pharmacy records of 6837 pregnant women who delivered between July 1977 and December 1979 and 6509 pregnant women who delivered between January 1980 and July 1982 (35). Termed, the Group Health Co-Operative (GHC) study, it equated prescriptions filled as long as 3 mo prior to conception with drug exposure (36). This approach has drawn criticism and clouded interpretation of their data (37). Both of these are observational studies of inadvertent exposures in early pregnancy and a determination of the overall rate of major congenital malformations compared with the baseline risk of major congenital malformations is made (baseline is 1–5% of pregnancies typically) (34).

Finally, there are many newer drugs being used for rhinitis since these studies were published. Agents such as nasal cromolyn, topical beclomethasone, fluticasone, budesonide, mometasone, and flunisolide, as well as the H1-selective antihistamines terfenadine (withdrawn from market), astemizole (withdrawn

from market), fexofenadine, cetirizine, loratadine, des-loratadine, and astelazine all are commonly used for rhinitis and, yet, data is sparse or lacking. Because of the observational nature and complexities in analyzing the data from these older studies, there remains no adequately confirmed published safety data for the commonly used agents. All current information should be regarded as a hypothesis still requiring independent review and duplication.

To help physicians cope with the lack of adequately controlled data and the difficult medical-legal environment under which most physicians practice, two major statements have been recently published by three prestigious groups summarizing available drug safety data and serving as a "position statement" to guide physicians. One comes from the Motherisk Program at the Hospital for Sick Children, The University of Toronto concerning treatment of allergic rhinitis in pregnancy (38). The other is a position statement concerning the use of newer asthma and allergy medications during pregnancy from a joint committee of the American College of Obstetricians and Gynecologists (ACOG) and the American College of Allergy, Asthma, and Immunology (ACAAI) (39). The following drug information was derived from these statements and other more recent published reports.

Breastfeeding

The transfer of maternally ingested medications into breast milk has been extensively reviewed, although not all the medications used in the treatment of rhinitis are mentioned (40,41). Nearly all drugs pass into the breast milk. This fact, however, does not presuppose an adverse effect on the newborn since many drugs will have already been inactivated, remain unabsorbed, or be destroyed in the infant's gut. The newborn, especially if premature, may be more sensitive to the negative effects of certain therapeutic agents because of a greater blood-brain barrier permeability, poorer enzyme con-

jugating capacity, diminished protein-binding capability, and decreased glomerular filtration rate (42). In general, if a drug is released for use in infancy, it can be safely administered to the lactating mother. Therefore, only a minority of medications are contraindicated during lactation, while the vast majority are considered either safe to use or the risk vs benefit considerations clearly favor use with continuation of breastfeeding. For those drugs that may pose a potential concern to the newborn, there are practical suggestions and precautions that can be taken to minimize risk. These include such interventions as selection of alternative effective drug regimens with safer profiles in breastfeeding, timing of drug dosing to minimize accumulation in the breast milk, surveillance for newborn or infant symptomatology that may be a sign of toxicity, or even the determination of drug levels in the infant's circulation if available (43,44).

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 a FDA class C rating. The CPP and a case-control study reported a statistically significant association between phenylephrine use in pregnancy and the occurrence of congenital malformations (34,45). However, a retrospective cohort study and two case-controlled studies could not confirm such associations (35). These studies also failed to demonstrate adverse effects from the intermediate and long-acting topical decongestants (46,47).

Available data suggests that, for the occasional episode of nasal congestion which may be interfering with sleep, oxymetazoline HCL drops or spray used as minimally as possible may suffice and preferably used after the first trimester and not during labor. The risk of rhinitis medicamentosa with continued use of

this agent beyond 3–5 d should be emphasized. Although there may be little or no appreciable absorption of topical oxymetazoline at recommended doses, overdose of topically applied imidazolines carries the risk of hypertension nonreactive followed by rebound hypotension and shock (48). There has also been a report of late decelerations during labor suggestive of placental insufficiency in a patient at 41 wk gestation using topical decongestants (49).

The most commonly used oral decongestant, pseudoephedrine, carries a FDA class C rating. Cohort studies including 2509 pseudoephedrine exposures revealed a congenital malformation rate of approx 2.3%, which was not increased over the expected incidence (34,35,50,51). 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 involving failure of closure of the abdominal wall (46,52). 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), the absolute risk in infants exposed to oral decongestants during the first trimester would not be higher than 20 per 10,000 live births. Should nasal obstruction require further therapy, oral decongestants, either alone or in combination with antihistamines should be avoided “unless the expected benefit is large and unique” (39).

Pseudoephedrine 30–60 mg every 6 h or 120 mg time-release capsule every 12 h can be considered after the first trimester when the risk of gastroschisis and vascular disruption has passed. A study of 6837 maternal–infant pairs demonstrated a less than expected incidence of malformations with the use of pseudoephedrine in conjunction with brompheniramine (53). However, caution is still advised since α -adrenergic agonists have been conflictingly associated with increased risks of fetal malformation or the risks remain unknown. Furthermore, all these agents can theoretically induce

uterine vascular constriction. Still, studies of the administration of single doses of pseudoephedrine or oxymetazoline have not found any alteration in uterine or fetal Doppler blood flow (54,55).

There is 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 breast feeding to minimize the concentration in breast milk. As with any medication taken while breast feeding, the mother should be advised to look for signs of toxicity in her infant. In the case of decongestants, this would typically be irritability.

Antihistamines

Oral, Intranasal

Patients with known eosinophilic allergic or nonallergic rhinitis accompanied by prominent sneezing and rhinorrhea may benefit from antihistamine therapy. Human cohort data regarding the occurrence of congenital malformations in infants of women with first trimester exposure to antihistamines compared to controls is summarized in Table 5. In general, there is no human data to suggest that antihistamines, as a group, have any deleterious effect on pregnancy regardless of when they are taken. Tripeleennamine, 25–50 mg PRN every 6 h to a maximum of 200 mg per day and chlorpheniramine 4–24 mg/d in divided doses has been recommended as the “safest” antihistamine for use during pregnancy based on available animal and human studies, FDA class B rating, and the “antiquity” of this drug (34,35,56,57). More recently, Claritin has received category B rating and is available OTC in the United States helping it emerge as the drug of choice in pregnancy along with the prescription antihistamine cetirizine. Other OTC antihistamines have had mixed reviews but overall are generally considered “safe” if given after the fourth month of pregnancy. The CPP reported statistically significant associations

Table 5
Human Data Regarding Antihistamines and Congenital Malformations^a

Classification	FDA Class	Exposed ^b	Control ^c
<i>First Generation</i>			
Alkylamines			
Brompheniramine	C	5.9%/271	5.9%
Chlorpheniramine	B	6.9%/1388	5.1%
Triprolidine	C	1.4%/628	1.4%
Dexchlorpheniramine	B	4.6%/1080	4.0%
Pheniramine	—	8.2%/831	6.4%
Ethanolamines			
Diphenhydramine	B	5.0%/2687	4.5%
Clemastine	C	NHD ^d	NHD
Carbinoxamine	C	NHD	NHD
Ethylenediamine			
Tripelemamine	B	6.0%/100	6.5%
Phenothiazines			
Promethazine	C	5.2%/1718	5.7%
Piperazines			
Hydroxyzine	C	5.9%/995	5.3%
Piperidines			
Azatadine	C	NHD	NHD
Cyproheptadine	B	NHD	NHD
<i>Second Generation</i>			
Astemizole ^e	C	1.8%/114	1.8%
Azelastine	C	NHD	NHD
Cetirizine	B	6.1%/33	5.3%
Fexofenadine	C	NHD	NHD
Terfenadine ^e	C	4.6%/1099	4.3%
Loratadine	B	NHD	NHD
Desloratadine	C	NHD	NHD

^aAdapted from Mazotta et al., Michigan Medicaid Study, and Loebstein et al.

^bIncidence of fetal malformations in the infants of mothers exposed to drug/total number of exposed mothers.

^cIncidence of fetal malformations in the infants of mothers *not* exposed to drug.

^dNHD—No significant human data.

^eVoluntarily discontinued by the manufacturer.

between brompheniramine and total congenital malformations, while chlorpheniramine was associated with an increased risk of ear and eye malformations and inguinal hernia (34). A later study by Jick et al. did not substantiate this finding with brompheniramine (50). An increased risk with diphenhydramine was also noted in the CPP and extended specifically to cleft lip and palate in a Finnish study (58). Animal teratogenicity in several species treated with hydroxyzine prompted particular concern for this drug with additional

suggestive risk emerging from the CPP data (56). However, no unusual congenital malformation prevalence was seen in another study of 74 women given hydroxyzine in the first trimester for gestational nausea and vomiting (59). A more recent cohort study confirmed the lack of association between hydroxyzine exposure during pregnancy and birth defects (60).

Reassurance that antihistamines, as a group, are safe in pregnancy is suggested from data of Nelson and Forfar. These authors found significantly less antihistamine use in a group of

mothers of infants with congenital malformations compared to matched controls (61). However, the Michigan Medicaid record linkage study reported a somewhat higher rate of malformations in children of women exposed to a number of antihistamines used to treat allergic rhinitis (51). These agents were diphenhydramine (5.5%), hydroxyzine (5.8%), and promethazine (5.1%). Because the data collected did not take into account other maternal diseases or concurrent drug use, these data should not be considered sufficient to incriminate these antihistamines as potential teratogens. Still, these data taken together suggest that, if first generation H-1 antihistamines other than tripeleminamine or perhaps chlorpheniramine are needed during pregnancy, they are best used after the first 4 lunar months only.

Among the second-generation antihistamines, cetirizine and loratadine carry a FDA class B rating, and fexofenadine and azelastine a FDA class C rating. Animal studies have been reassuring for cetirizine and loratadine but not for astemizole, azelastine, fexofenadine, or terfenadine. In animal studies with rats and rabbits, exposure to 75–150 times the maximal human daily oral dose of loratadine revealed no evidence of teratogenicity (*see* package insert). Similar animal studies using cetirizine with mice, rats, and rabbits exposed to 40, 180, and 220 times respectively the maximum recommended oral daily dose for humans revealed no increase in birth defects (*see* package insert). On the other hand, fexofenadine (based on terfenadine data) induced a dose-related decrease in weight gain and survival in rats given three times the normal human bioavailable dosage (*see* package insert).

There are no human studies reported using fexofenadine or azelastine in pregnancy. However, there are reassuring data for cetirizine and loratadine. In a prospective controlled study using hydroxyzine and cetirizine in pregnancy, no increase risk of teratogenicity was noted in 53 and 39 live births respectively

(60). A recent prospective study of 161 exposed women to loratadine revealed no difference in the number of malformations compared to a control group of equal number (62). These data suggest that, if a nonsedative antihistamine is necessary during pregnancy, it is best to use it after the first trimester. Loratadine and cetirizine appear to be the best choices under these circumstances (63).

The regular maternal use of first generation antihistamines at the time of delivery poses a further set of potential clinical mishaps. Parkin described a 5-d-old infant with tremulousness and diarrhea following the maternal ingestion of 150 mg of diphenhydramine daily throughout pregnancy (59). Another mother was reported who used 400 mg of hydroxyzine daily throughout her pregnancy and gave birth to an infant who demonstrated a transient narcotic-like withdrawal symptom complex (64). Finally, maternal antihistamine use has been associated with retrolental fibroplasia in infants with a birth weight of less than 1750 g (65). These data suggest that the regular maternal ingestion of antihistamines, especially in high dosages, should be terminated as soon as possible prior to delivery in an attempt to minimize neonatal withdrawal risk or avoided altogether in women at risk for delivery of very low-birth-weight infants.

Some adverse effects might be expected from breast milk containing maternally ingested antihistamines. This has, in fact, rarely proven to be the case, with irritability being the most common observation in approx 10% of mothers surveyed (66). A report incriminating clemastine as the cause of drowsiness and irritability in a nursing 10-wk-old infant has been described (67). Clemastine concentrations in breast milk were 25–30% of the maternal serum values, but none could be detected in the infant's serum. The infant in this report showed resolution of symptoms within 24 h following drug withdrawal.

The above data deserves a summation. Taken together, if an antihistamine is necessary

in the first trimester, with informed consent, tripeleennamine and chlorpheniramine are the safest alternatives. Both loratadine and cetirizine remain attractive alternatives after the first trimester in the pregnant patient. It is preferable to withdraw all antihistamines prior to delivery at least 3 d for first-generation and 5 d for second-generation agents. The short-term effects, if any, of most antihistamine medications on breastfed infants are mild and pose little risk (68).

Ophthalmic Antihistamines

The ophthalmic antihistamines, antazoline, astemizole, ketotifen, levocabastine, olopatadine, and pheniramine all carry FDA category C rating. There is very little human data on these drugs other than ketotifen, which has been used in asthma for over 25 yr outside the United States with no reported adverse effects in 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 rhinitis patients would benefit from the addition of pseudoephedrine to the treatment plan after the first trimester, when there is no further risk of gastrochesis (after the fourth month). Similarly, topical decongestants will help “get the red out” as an ophthalmic preparation. The risk factors associated with the use of these drugs have been previously discussed.

Corticosteroids

Animal studies have suggested that corticosteroids may have adverse effects on the developing fetus when taken systemically (FDA class C). Particular attention has been paid to cleft palate, although intrauterine growth retardation, placental insufficiency, fetal resorption, and spontaneous abortion have also been described (69,70). The overall data concerning the use of systematic corticosteroids during human pregnancy is not so ominous. In fact, a

large body of data on humans published in the past 30 yr has not confirmed the fears generated by animal studies when corticosteroids are given after the first trimester. This is particularly true when consideration is given to adverse fetal affects that may occur from the primary disease for which the corticosteroids are being administered. There is data associating first trimester use of oral corticosteroids with an increased risk of cleft lip with or without cleft palate and with a small increase in the risk of major malformations (71–73). Oral corticosteroids should thus be used during the first trimester only if the benefit for treating a severe, steroid responsive disease would outweigh the risk.

Even though published human data 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 justified. Because of their metabolic characteristics, very little if any of these drugs 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 beclomethasone and budesonide in the management of asthma during pregnancy suggests that the intranasal route of this drug also should be safe (74–76). In addition, a recent study by Ellegard using fluticasone propionate nasal spray (Flonase Rx) in 53 women with pregnancy rhinitis, revealed no detectable differences on maternal cortisol levels, or ultrasound measures of fetal growth or pregnancy outcome (77). Interestingly, there was no therapeutic benefit as compared to placebo in this form of rhinitis in pregnancy. For patients with significantly symptomatic nasal polyposis, or eosinophilic rhinitis not responsive to antihistamines or nasal cromolyn, intranasal beclomethasone or budesonide should be considered,

especially after the first trimester, since human asthma data during pregnancy is available. In a quirk of the FDA, budesonide by turbuhaler now carries a category B rating for asthma while the intranasal form of the same drug still carries a category C rating. Taken together, it would seem reasonable to favor intranasal budesonide (Rhinocort Rx) in the pregnant allergic patient. However, none of the intranasal corticosteroids appear to have significant systemic side effects at therapeutic dosages. This has 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 prior to pregnancy and continues to require such therapy" (39).

With the exception of extremely high parenteral dosages in status asthmatics, the use of corticosteroids in the lactating mother poses no substantial threat in the infant. A 50-mg dose of prednisone in the lactating mother would transfer to the neonate less than 20% of its daily physiological corticosteroid requirement (78). There is no data concerning the passage of topical corticosteroids into the breast milk but one would not expect any increase in risk.

Cromolyn Sodium

Animal and human data suggest that cromolyn sodium is probably safe in pregnancy and carries a FDA class B rating. There is no pregnancy data specifically on intranasal or ophthalmic use. Although no controlled teratogenicity studies have been published specifically with these routes of sodium cromoglycate, two human studies involving nearly 500 pregnancies failed to demonstrate any increased risk for congenital defects even if exposed to inhaled cromolyn sodium for asthma in the first trimester (56,79). Furthermore, very little systemic absorption of cromolyn is seen with topical application. For women with allergic rhinoconjunctivitis, intranasal and/or oph-

thalmic cromolyn sodium may be considered a first line treatment of choice before moving on to more systemic medications.

Ancillary Measures: Humidification/Cleansing, Structural Modification, and Avoidance Maneuvers

Nasal irrigation methods deserve mention as a useful nonpharmacological modality in the treatment of sinusitis during pregnancy. This can take the form of a topically applied nasal saline mist available OTC or tepid physiological saline or hypertonic saline washed through the nose using either a bulb syringe, ear syringe, or various squeeze bottles (Sinus Rinse-Rx) or more vigorously with a Water Pik(Rx) 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 post-nasal drainage, and are generally soothing to the nose. There is some evidence that hypertonic saline delivered via a standard Teledyne Water Pik (Fort Collins, MO) device has advantages of improving mucociliary clearance and sinusitis outcomes (80,81). Furthermore, there is the suggestion that pulsatile saline delivery using a bulb syringe or Sinus Rinse (Rx) is more effective in sinusitis cases than saline delivered via a nasal spray such as Ocean, etc. (82,83).

Other nonpharmacological 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 has been reported to be effective (84). However, radiofrequency ablation, although considered a very safe and effective procedure, has not been studied in the pregnant population other than an isolated case report (85,86). Nevertheless, this in-office technique should be considered in any pregnant patient who is suffering from sleep disturbance and discomfort despite all other conservative measures enacted, espe-

cially 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 also be considered depending on the clinical circumstances. For the pregnant patient with known allergic disease, allergen avoidance is particularly important. Avoiding known allergens, when possible, will not only improve maternal well being, but also minimize needs for pharmacological intervention.

If all pertinent allergens have not been identified prior to the pregnancy in the allergic patient, identification of the offending agents may be of benefit. Because skin testing with potent antigens may be rarely associated with systematic reactions, and since abortions and other adverse fetal effects have been associated with anaphylaxis, skin testing should be replaced with *in vitro* methods such as RAST tests to identify pertinent allergens (87,88). Historical information can often be used to suggest if house dust, mold, animal dander or pollen is potentially involved. Avoidance instructions can be empirically given in these circumstances. However, in selected cases, especially when dealing with indoor animals, selected RAST testing may be necessary to demonstrate the need for more vigorous avoidance maneuvers.

Immunological Management

Allergen immunotherapy is a very effective method of treatment for seasonal and perennial allergic rhinitis. It is always useful for the allergic pregnant patient to reduce the severity of rhinitis or coexisting asthma and to reduce the use of medications that are less desirable during pregnancy. Allergen immunotherapy can be used as such a tool safely. Brief studies and anecdotal reports from the 1940s suggested a slight increased risk of spontaneous abortion (34,89). However, a series of similar reports and studies over the next several decades suggested that the use of pollen and dust immunotherapy was unassociated with any

adverse fetal outcomes (90–92). More recently, two retrospective cohort studies each failed to detect any negative association between immunotherapy during the first trimester of pregnancy and congenital malformations (93,94).

Immunotherapy can be considered safe for both the mother and fetus during pregnancy (21). Still, because of the risk of anaphylaxis, the initiation of immunotherapy during pregnancy should be avoided (95,96). For ongoing immunotherapy patients who become pregnant and who have experienced clinical benefit without systematic reactions, most authors recommend that allergen immunotherapy be continued (97). Consideration should be given to lowering the maintenance dosage routinely to minimize the risk of a future systematic reaction.

Antibiotics

Antibiotics remain the treatment of choice for bacterial sinusitis in pregnancy or lactation. Placental transfer of antibiotics has been documented (98). With a few notable exceptions, most antibiotics can be used with relative safety during pregnancy (98–101). Moreover, none of the antibiotics to date has been shown to be teratogenic, although tetracycline may cause discoloration and hypoplasia of the deciduous teeth when administered late in pregnancy and during lactation and has reportedly produced impaired bone growth when administered early in pregnancy (102). Maternal hepatic injury has also been reported with tetracyclines when used during pregnancy (99). While trimethoprim-sulfamethoxazole is an excellent antibiotic choice for sinusitis, especially in the penicillin-allergic patient, sulfonamides may induce bilirubin toxicity by competing for albumin binding sites if present in the immediate newborn period. Furthermore, the folic acid antagonistic properties of trimethoprim may induce anemia (103).

The drugs of choice for the treatment of bacterial sinusitis in pregnancy and during lactation are ampicillin or amoxicillin. Clavulanic

acid, a β -lactamase inhibitor, has been added to amoxicillin and marketed as Augmenten. Clavulanic acid carries a category B FDA rating with no evidence of teratogenicity in animals; however, virtually no human pregnancy data concerning teratogenicity is available. Although Augmenten may be a superior combination for the treatment of bacterial sinusitis, its use during pregnancy should be reserved for resistant infections with known β -lactamase producing bacteria. Since decreased serum levels of penicillins, cephalosporins, and erythromycin have been observed in pharmacokinetic studies of pregnant women, larger dosages of these drugs are recommended (104).

Erythromycin is commonly mentioned as an alternative drug in the treatment of sinusitis in the penicillin-allergic setting. However, an increased incidence of persistent sinus disease due to erythromycin-resistant strains of *Haemophilus influenza B* has been reported, limiting its usefulness. If it can be documented that the penicillin-allergic patient had used cephalosporins safely subsequent to the penicillin reaction, Cefaclor or Cefuroxime may be considered. A prospective cohort study of Cefuroxime exposure in the first trimester and a 18 mo retrospective follow-up exam analysis of infants exposed to Cefuroxime during a mixture of first to third trimesters failed to reveal any increased risk of malformations or abnormalities of physical and mental development (105,106).

A suspected penicillin-allergic patient with proven or suspected sinusitis due to a β -lactamase producing organism in whom cephalosporin tolerance has not been satisfactorily documented may be treated with an alternative macrolide such as clarithromycin or azithromycin. Azithromycin (FDA category B) would be chosen over clarithromycin (FDA category C) based on the animal studies. In a study of 157 women, 122 of whom were exposed to clarithromycin in the first trimester, no significant increase in major or minor malformations was found. Spontaneous abor-

tion rates in the exposed group were, however, significantly higher (14% vs 7% in the control group, $p = 0.04$), suggesting further study is necessary before a firm recommendation can be made on this drug (107). A later retrospective surveillance study of clarithromycin in 143 mothers and 149 infants exposed in the first trimester revealed no evidence of statistically significant increase in major or minor malformations (108). Very limited human experience with azithromycin suggests a similar lack of teratogenicity (109).

Another alternative drug class in the β -lactam allergic patient is the fluoroquinolones. The parent compound, ciprofloxacin is not embryotoxic or teratogenic in animals. However, it carries a FDA class C rating because arthropathies in immature animals have been reported. Fluoroquinolones are thus considered to be contraindicated in pregnancy and lactation (110). Several retrospective studies suggest that the use of the quinolones during the first trimester of pregnancy does not appear to be associated with an increased risk of malformations or musculoskeletal problems (111–114). However, there are no longterm follow-up studies using magnetic resonance imaging of the joints to exclude subtle cartilage and bone damage.

In summary, antimicrobial agents are prescribed in pregnancy for various specific indications related to pregnancy *per se* (e.g., chorioamnionitis), for infections otherwise unrelated to but complicating pregnancy (e.g., sinusitis, bronchitis, pneumonia), and prophylactically for conditions which, if untreated, would have an adverse outcome for the pregnancy (e.g., asymptomatic bacteriuria). The selection of an agent will depend on the likely pathogen, stage of pregnancy, special pharmacokinetic factors related to the stage of pregnancy, safety of the drug and cost. Some classes of antibiotics can be taken throughout the three trimesters (e.g., β -lactams), while others can be used with caution (e.g., second-generation macrolides) or are completely contraindicated

(e.g., tetracyclines and possibly the fluoroquinolones). Still others are to be avoided in certain trimesters (e.g., sulfonamide in the third trimester). The choice of an appropriate antimicrobial agent must be based on the potential adverse outcome of a particular infection, the drug safety and spectrum of activity. The β -lactam antibiotics (Amoxicillin with or without Clavulanic acid, Cefuroxime) remain the treatment of choice for the pregnant patient suffering from sinusitis, with trimethoprim-sulfameth-oxazole (in the first or second trimester) or macrolides (probably azithromycin) as alternatives (with the patient's informed and documented consent) in the β -lactam allergic patient.

Conclusion

Rhinitis and sinusitis in pregnancy represents a challenge to the physician both in terms of its diagnosis and therapy. Although there are several unique influences of pregnancy which adversely affect nasal mucosa, there is growing recognition that most symptomatic nasal problems are, in fact, expressions of diagnostic entities which have been or will be experienced by the patient in the nonpregnant state. In approaching gestational rhinitis and/or sinusitis, 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 of quality of life and may exacerbate coexisting asthma which could adversely affect the pregnancy outcome (115). Particular attention should be placed on the diagnosis and treatment of sinusitis, which may have a unique tendency for occurrence during pregnancy and may be difficult to distinguish from other causes of rhinitis. Subtleties in clinical symptomatology and reluctance to

use radiographs make gestational sinusitis a particularly elusive diagnosis. Specialty consultation with otolaryngology and/or allergy may, at times, be necessary in the symptomatic pregnant woman before an accurate diagnosis and successful therapeutic recommendations can be made.

The medical-legal atmosphere in the United States today unfortunately poses problems in making clinical statements about the absolute safety of medicinal intervention during pregnancy. For those physicians choosing to take up this therapeutic challenge, there are suitable pharmacologic agents available to manage the pregnant patient with rhinitis and/or rhinosinusitis to achieve the desired therapeutic outcome. Some guidelines have been presented to assist the physician in choosing the "safest" form of therapy during pregnancy (Table 1). In the individual clinical situation, management decisions must be made only after establishing an exact clinical diagnosis and giving full consideration to the therapeutic risks, benefits, and alternatives and documenting this in the patients 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. It should be emphasized that a significant number of pregnant women suffering from rhinitis of pregnancy are allergic. Under these circumstances, the best first-line approach is avoidance of allergens, which can significantly reduce symptoms. Often, what is first chosen is either a medication or simply allowing the pregnant patient to suffer the symptoms, which can, as discussed, adversely affect the pregnancy outcome. Limited allergy consultation can be very useful under these circumstances to identify pertinent allergens and effectively direct avoidance. If avoidance is unsuccessful, then, with the informed consent of the patient and documentation in the chart, medicinal intervention can begin as shown in Table 1. Although many

women and caregivers may choose to not intervene with medications based on fear of teratogenicity, such notions are clearly contradicted by a significant amount of medical evidence to the contrary. This is especially true of drug intervention for rhinitis and rhinosinusitis after the first trimester.

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