
MANAGEMENT OF COMMON MINOR DISCOMFORTS IN PREGNANCY

Part I: Managing Upper Respiratory Infections in Pregnancy

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ABSTRACT

The minor discomforts of pregnancy present difficulties for the health care provider as well as for the pregnant woman herself. Management of the various symptoms requires astute observations and the ability to individualize therapy. Knowledge of a variety of treatment options, therefore, allows practitioners to collaborate with their patients in selecting the best therapeutic approach for the specific situation.

This three-part series reviews the common discomforts associated with upper respiratory infections, minor pain, and gastrointestinal problems as they are manifested during pregnancy. Both nonpharmaceutical and pharmaceutical therapies are discussed. Frequent references are made to the Food and Drug Administration (FDA) Risk Factors which categorize both over-the-counter and prescribed drugs according to their documented safety for ingestion during pregnancy.

Part I, "Managing Upper Respiratory Infections in Pregnancy," appears in this issue (JNM 32:6); Part II, "Managing Minor Pain in Pregnancy," will appear in JNM 33:1; and Part III, "Managing Gastrointestinal Problems in Pregnancy," will appear in JNM 33:2.

Certified nurse-midwives (CNMs) are well known for their use of non-invasive treatment modalities. CNMs' avoidance of routine medications preceded the current obstetrical cautions about drugs in pregnancy. However, pharmaceutical interventions have recently taken their place within the armamentarium of practicing CNMs.

This first part of a three-part series will review the common discomforts associated with upper respiratory infections as they are manifested during pregnancy. Both nonpharmaceutical and pharmaceutical therapies will be discussed. Frequent reference will be made to the FDA Risk Factors (Appendix A). This risk sum-

mary categorizes both over-the-counter and prescribed drugs for use in pregnancy. Unfortunately, it does not categorize drugs for use in lactation. The FDA class for specific drugs as well as information on their safety during breast-feeding can be found in other sources, however.^{1,2} Use of the FDA categories can aid a nurse-midwife in assessing available drugs in terms of their relative safety in pregnancy. Knowledge of a variety of treatment options allows practitioners to collaborate with their patients in selecting the best therapeutic approach for the specific situation.

UPPER RESPIRATORY INFECTIONS IN PREGNANCY

Although pregnancy is a normal physiologic event, it is not always an

uncomplicated condition. Until a germ-free environment is developed, the average pregnant woman will remain at risk for such minor health problems as upper respiratory infections (URIs). Upper respiratory infections are the most common types of adult infectious diseases, accounting for an estimated \$10 to \$15 billion annually and 150 million days lost from work. The average American experiences two to four such infections per year.^{3,4} The condition of pregnancy further complicates the treatment of URIs insofar as two patients are involved. Much of that which is written concentrates on URIs in the nonpregnant state. Thus, a review of the etiology, symptomatology, and application of treatment of URIs in pregnancy is warranted.

It has been well established that the "common cold" is a term of dubious distinction. Although it has al-

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most universal connotation, it actually names a collection of symptoms associated with a virus. Moreover, URIs are not caused by one single virus. More than 100 different strains of viruses have been implicated as causative agents.⁵ The major two types of viruses are rhinoviruses and coronaviruses. Although these usually are implicated as the cause, fully one-third of URIs are unable to be linked with a specific etiologic agent.⁶

Normally, an individual is exposed to such viruses without consequences. The healthy person has a variety of inherent protection including mechanical and anatomical barriers in the nose and throat, mucociliary clearance, coughing, phagocytosis, surfactant, and other factors.⁷ The issue of susceptibility to a cold virus has been well researched within the last decade. Although once dismissed as a myth, changes in weather and drafts are now recognized as part of multiple stresses which may decrease a host's resistance to a virus.⁸ Actual transmission of a cold virus has been proposed through infected droplets found on tissues, as well as self inoculation from mouth to finger. It is rare that an individual transmit a cold simply by sneezing or coughing.⁹ Regular handwashing has been found to be the single most preventative policy.^{10,11}

The pregnant woman is not innately at higher risk for more or worse URIs than her nonpregnant

counterpart.¹² However, other environmental factors may increase her risk. For example, if she has other children in preschool or day care, she is at greater risk for an URI.⁶ Moreover, an URI may be more inconvenient and uncomfortable during pregnancy, possibly compounding the vascular congestion of the sinuses associated with pregnancy, or interfering with breathing techniques in labor.

When a cold virus invades a woman's body, the target area is the epithelium of the nasopharynx and bronchii. The epithelium of these mucous membranes is normally protected by a thin mucoid film composed of immunoglobulins, glycoproteins, lysozymes, and other components. Minute cilia enable the mucous to be moved toward the nasopharynx while continually coating the epithelium of the mucous membranes.^{8,13}

Once an epithelial invasion has been established, usually after one to four days, various symptoms may occur. Prodromal symptoms include fatigue and malaise. One normal response to the epithelial invasion is the release of inflammatory mediators which increase the serum in nasal secretion resulting in rhinorrhea with increased vascular permeability and edema causing nasal stuffiness. The cold virus also causes cholinergic stimulation which not only increases mucoid production and rhinorrhea, but also can alter respiratory function by bronchial constriction. This bronchial constriction, associated with the rhinorrhea and cellular tissue damage of the nasal membranes and pharynx from the cold virus can be expressed as a cough or sore throat. Histamine is released in response to the cellular tissue damage, compounding the discomfort.⁸ A cold is a self-limiting entity, commonly lasting three to seven days. Such a condition is communicable for two to three days after onset.

The diagnosis of an URI is often

self made. Exposure and accompanying symptomatology are usually adequate diagnostic aids. Past history or length of symptoms will help to differentiate between a cold and seasonal allergies, the latter being of a recurrent nature and associated with allergens instead of a usual short-term episodic cold. Bacterial pharyngitis is another condition that can be confused with an URI. Bacterial pharyngitis is usually of a rapid onset, without the prodromal or the increasing intensity of symptoms found with a cold. Furthermore, it is most commonly associated with febrile episodes, where simple URIs are nonfebrile conditions, or evidencing a slight low-grade temperature elevation at best. Influenza may mimic the signs and symptoms of an URI but will also have associated fever and usually gastrointestinal symptomatology. Pneumonia is differentiated from a simple cold as its symptoms include severe cough, fever, chills, and such serious signs as respiratory distress.^{13,14}

Once an upper respiratory infection is diagnosed, or self-diagnosed, the question of therapy remains. No curative agent yet exists. Indeed, although vaccines were once heralded as the promise of the future, unlike influenza, the sheer numbers of viruses involved make the development of such extremely unlikely.^{6,15} Thus, all treatment for URIs are based on symptomatology. The approaches to treatment for URIs are basically two: nonpharmaceutical and pharmaceutical.

NONPHARMACEUTICAL TREATMENTS

The primary nonpharmaceutical treatments are rest, hydration, and humidification. Rest combats fatigue and assists in maximizing air exchange by minimizing the body's needs for such. Fluids may help with expectoration of respiratory secretions while still maintaining hydration, a point of particular importance in pregnancy. The issue of starving a

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cold not only has little relevance, but can be of danger in pregnancy where dehydration has been implicated in preterm labor. Humidified air decreases the viscosity of respiratory secretions. Such air is particularly comforting for the individual with a sore throat. Cool air vapor has been suggested as superior to hot steam because of safety reasons. However, such vaporizers quickly become contaminated. To prevent this, they should be frequently cleaned according to manufacturer's instructions.¹³

PHARMACOLOGIC TREATMENTS

The decision to initiate a drug as opposed to using a nonpharmaceutical approach is an individual one. Parameters to be considered include fatigue, weight loss, patient desire, insomnia due to cold symptoms, and inability to perform activities of daily living.

Pharmacologic approaches to the treatment of URIs in pregnancy pose a great challenge to the clinician. Although most patients are well aware of the dangers of medications in pregnancy, some will initiate self-medication without knowing of the pregnancy, or assuming that the drug's availability over the counter indicates safety. Others may use over-the-counter drugs at half dosage or less, assuming increased safety, but actually still experiencing drug exposure at subtherapeutic level of medication. In general, both pregnant women and practitioners should know that there are several categories of drugs that have not been implicated in teratogenic outcomes, and can be of assistance to the woman with a URI in pregnancy.

The major drugs used for cold relief are categorized as antihistamines, decongestants, antitussives, and expectorants. Many of these pharmaceutical agents are available as over-the-counter remedies. Antibiotics are not recommended for a simple URI as they are not effective against the

viruses implicated in the disease. Vitamin and mineral therapy is more controversial. Although large clinical studies have failed to demonstrate the efficacy of vitamin C, other studies are now investigating various other remedies such as zinc supplementation.⁹

Antihistamines

Histamine is released in the common URI when the epithelium is invaded, although to a lesser extent than during an allergic reaction. In either case, histamine acts as an irritant to the body causing itching and tear formation among other symptoms. Antihistamines compete with histamine at the receptor site. Although the histamine released with a cold is less than during seasonal allergies, antihistamines are common cold remedies, especially in conjunction with other agents.

Antihistamines should be administered with food or fluids to decrease gastric upset. The major side effect to antihistamines is drowsiness due to occupation of sites in the brain that are involved in the control of wakefulness.² This sedative quality is directly related to the antihistamine prescribed. In fact, some antihistamines are often prescribed for acute, short-lived insomnia due to this effect. Additionally, antihistamines have been prescribed for vertigo or nausea, although the precise mechanism of action is unknown. Most of the antihistamines are categorized as FDA Pregnancy Category B or Category C (Appendix B).

Small amounts of almost all of the antihistamines can be found in the breast milk of lactating women. Manufacturers generally warn against usage of such agents in lactation due to potential excitement or irritability of the infant as well as decrease in milk production. The exceptional antihistamine to this statement is terfenadine because little is known at all about its excretion in breast milk or the reaction of the infant.^{1,2}

Drug interactions do exist with antihistamines. Antihistamines interact with alcohol. The result is additive sedation. This is somewhat ironic as many over-the-counter combination syrups and elixirs contain both antihistamines and alcohol. Excessive central nervous system depression may also occur with antihistamines when used with magnesium sulfate.²

Of the antihistamines available, there appears to be little difference in efficacy between over-the-counter and prescribed agents. One possible exception is the relative new non-sedating antihistamine terfenadine, which appears to be more effective.⁸ Terfenadine further differs from the other antihistamines as its primary excretion is fecal, as opposed to renal. However, its relative newness means little information is available as to its use in pregnancy. Rats exposed to terfenadine in pregnancy have demonstrated decreased pup weight and survival. Excretion in breast milk and significance remain unreported for terfenadine. This lack of information may encourage the certified nurse-midwife to seek a more recognized antihistamine.

Doxylamine is an established antihistamine that has been in existence for some time. Although rarely used for URIs, it remains of significant historic interest and should be acknowledged as such. For many years, doxylamine was combined with pyridoxine and marketed as "Bendectin" to treat morning sickness. Although the FDA reported that there is no convincing evidence linking doxylamine and pyridoxine to teratogenic effects, the manufacturer removed the combined drug from the marketplace. Because doxylamine is still available as an antihistamine with marked sedative potential, the clinician has the ability to prescribe it in combination with over-the-counter pyridoxine. The advisability of doing this must be tempered with the recognition of the risk of dealing with "litogens" as opposed to teratogens in today's liti-

gious society.¹⁶ It also is important to note that the FDA continues to conduct investigation of the combination drug "Bendectin".²

Antihistamines used to treat URIs also demonstrate anticholinergic properties, including dry mouth and blurred vision. People intolerant of one oral antihistamine may also be intolerant of others. Furthermore, women who have routinely used one specific antihistamine for treatment of recurrent allergies may develop tolerance to it. Although commonly used for URIs, antihistamines have questionable effectiveness when used alone. Howard et al¹⁷ demonstrated that the relief obtained by antihistamines alone was minimal. The more common single agent for URIs are decongestants.

Decongestants

A variety of sympathomimetic amines have been used for decongestant purposes. These sympathomimetics work on the sympathetic nervous system causing vasoconstriction of mucous membranes. Decongestants are in oral or intranasal formulations. Oral decongestants are less effective, but have a longer duration of action. Unfortunately, many of the oral decongestants have potent side effects. For example, the most commonly used decongestants, phenylpropanolamine and ephedrine, often elevate blood pressure, making them poor medications for a patient at risk for pregnancy-induced hypertension. Epinephrine, ephedrine, and pseudoephedrine may increase serum glucose due to β -2 adrenergic receptor activity.

Phenylpropanolamine often adversely affects the appetite. In fact, it is a common ingredient in over-the-counter diet aids. Common oral decongestants are summarized in Appendix B. The dosages are those recommended by the United States Pharmacopeial Dispersing Information (USPDI). They may not be the same as on the over-the-counter

packaging. The over the counter packaging is occasionally at subtherapeutic levels. In fact, due to their potentially severe side effects, oral decongestants are not the first line of medications for colds in pregnancy; That distinction belongs to intranasal decongestants. (Appendix B)

Nasal, or topical decongestants can be administered by intranasal spray or drops. Such administration allows rapid effect and few side effects. The decongestant shrinks the mucous membranes and little is absorbed into the circulation if the medication is given appropriately. Appropriate administration means that the woman should have her head lowered when the spray or drops are given and should avoid swallowing the drug. One spray or drop should be administered and the nose blown. After three to five minutes, the rest of the dosage should be administered. The medication should be discarded if it is discolored. Because the tips can be colonized by the virus, each episode should be limited to one user, and one URI episode. Topical decongestants should not be used for more than two or three days.

The one side effect specific to nasal decongestants is rebound congestion (rhinitis medicamentosa). When a nasal decongestant is used for a prolonged period, the subsequent hypoxia of the mucous membranes is replaced with hyperemia, which encourages use of the decongestant agent again. Patients should be counseled about this danger of this vicious cycle, and particularly should be aware of the normalcy of minor nasal congestion in pregnancy.

When coughs accompany an URI, an antitussive may be indicated. Codeine is the gold standard for antitussives. For relief of coughs it has a low risk of addiction. Dextromethorphan is chemically related to codeine, but lacking addictive, analgesic, or respiratory side effects. Diphenhydramine, an antihistamine,

also has evidenced some antitussive effects by directly effecting the cough center in the medulla of the brain.² The common antitussives are summarized in Appendix B.

Expectorants are a traditional remedy for an URI, although their efficacy is questionable. They are advocated as some studies have implicated them in decreasing thickness of sputum and thus increasing patient comfort, although little data suggests they are more efficacious than increased oral fluids alone. Moreover, little documentation supports their use as antitussives. The common expectorants are summarized in Appendix B. Any expectorant should be taken with a full glass of water to minimize gastric upset.

Other medications suggested for URIs include topical anesthetics. The effectiveness of these have not been evaluated by the FDA for pharyngeal use.⁹ The most common agent currently used is Benzocaine. Clinical studies suggest Benzocaine is beneficial only in dosages of more than 5%; nevertheless, 5% is the usual over-the-counter formulation for lozenges or sprays.

Many over-the-counter preparations are combination therapies. Common ingredients include alcohol, caffeine, and analgesics. Sources have recommended combination therapy because of decreased cost. A myriad of formulations are available under generic and brand names. A few of those available are included in Appendix B. Moreover, such combination treatment does not reflect individual metabolism of certain drugs, or even recommended doses. Note the variations compared with recommended doses of the individual medication. In pregnancy, the fewer medications, the better. Therefore, combination therapy is best avoided. Instead, prescription of single decongestants, antihistamines, expectorants, or antitussives are recommended in an individual regime.

In summary, there is a variety of

relatively safe and effective treatments for an upper respiratory infection in pregnancy. Topical nasal decongestants can provide symptomatic relief when they are used judiciously. Antihistamines are also useful in the pharmaceutical armamentarium for some relief in URIs as well as for other indications such as allergies and insomnia. Combination treatment should be avoided. The use of an agent depends on many factors, not the least of which is an appreciation of the various options available.

The author would like to give special acknowledgement to the creators and other faculty of the ACNM *Maternal Fetal Pharmacology* course wherein the interest in this field was first generated. These individuals include Marilyn Frederickson, MD; Sandy Sasso, CNM; Nancy Reedy, CNM; and Carolyn Routledge, CNM.

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APPENDIX A

FDA Risk Factors

Category A: Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possi-

bility of fetal harm appears remote.

Category B: Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).

Category C: Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

Category D: There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (eg, if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Category X: Studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

Federal Register 44:37434-37467, 1980.

APPENDIX B

Common Antihistamines, Decongestants, Intranasal Drugs, Antitussives, Expectorants, and Examples of Over-The-Counter Preparations

General/ (brand name)	Mode of administration	Dosage	Duration	FDA class	Comments
Azatadine maleate (Optimine)	tab	1–2 mg/8–12 hr	6hr	B	mild drowsiness
Brompheniramine maleate (Brombay, Bromphen, Dimetane, Veltane, Oramenic)	elixir tab extended release parenteral	4mg/4–6 hr max 24mg/24hr same 8–12mg/8–12hr 10mg/8–12hr max 40mg/24hr	3–6hr	B	sedation
Carbinoxamine maleate (Clistin)	tab	4–8mg/6–8hr	3–6hr	C	sedation
Chlorpheniramine (Chlor-mal Chlor-trimeton Chlor-amine Repetabs)	syrup tabs/chew extended release parenteral	4mg/4–6hr max 24mg/24hr same 8–12hr/8–12hr 5–40mg max 40mg	4–12hr	B	mild sedation
Diphenhydramine HCl (Alledryl, Benadryl, Bendylate)	elixir syrup	25–50mg/4–6hr max 300/24hr 25mg/4–6hr max 100/24hr as elixir	3–6hr	C	sedation
Doxylamine succinate (Unisom)	capsule tab	12.5–25mg/4–6hr max 150mg/24hr	3–6hr	B	sedation (marketed as sedative)
Phenindamine Tartrate (Nolahist)	tab	25mg/4–6hr max 150mg/24hr		C	
Terfenadine (Seldane)	tab	60mg/8–12hr	>12hr	C	mild sedation
Triprolidine (Triafed)	syrup tab	2.5mg/6–8hr max 10mg/24hr as syrup	4–12hr	B	mild sedative

Common systemic decongestants

Generic/ (brand name)	Dosage	FDA class	Comments
Phenylpropanolamine (Propagesst, Sucrets cold decongestant)	25mg/4hr 150mg	C	transient BP elevation
Ephedrine	25–50mg/3–4hr	C	rarely used for URIs
Pseudoephedrine (Novafed, Sudafed, Afrinol)	60mg/6–8hr	C	

Common intranasal drugs

<i>Generic/(brand name)</i>	<i>Dosage</i>	<i>Duration</i>
Phenylephrine HCl (Neo-Synephrine, Coricidin)	^a 0.25%–1% Several gtt/ 3–4 hr	30min–4hr
Xylometazoline HCl (Neo-Synephrine II, Otrivin)	^a 0.1% 2–3gtt/spray 8–10hr	3–6 hr
Oxymetazoline HCl (Afrin, Dristan Neosynephrine 12 hour, Sinex long lasting)	^a 0.05% 2–4gtt/spray 12 hr	5 hr
Naphazoline HCl (Erivme)	^b 0.05% 2gtt/spray 3hr spray 4–6hr gtt	2–6 hr

^a No problems observed in humans, but no controlled human studies yet performed.

^b No studies yet done on humans or animals in pregnancy.

Common antitussives

<i>Generic/(brand name)</i>	<i>Dosage</i>	<i>FDA Class</i>
Codeine phosphate/ Sulfate	10–20mg/4–6hr max 120mg/24hr	C
Dextromethorphan Hydrobromide (Benlyn DM, Cremacoat, Delsym)	10–20mg/4hr or 30mg/6–8hr max 120mg/24hr	B
Diphenhydramine HCl (Benlyn)	25mg/4hr max 150mg/24hr	C

Common expectorants

<i>Generic/(brand name)</i>	<i>Dosage</i>	<i>FDA Class</i>	<i>Comments</i>
Guaifenesin, Glyceryl guaiacolate (Breonesin, Glycotuss, Robitussin, 2/g)	200–400mg/4hr max 2.4g/day	C	
Terpin hydrate elixir	200mg/4hr 1.2g/day	B	Alcohol 42.5%

Examples of over-the-counter preparations

<i>Brand name</i>	<i>Antihistamine/ other</i>	<i>Decongestant</i>	<i>Antitussive</i>	<i>Dosage</i>
Actified DM	Tripolidine HCl 1.25mg	Pseudoephedrine HCl 30 mg	Dextromethorphan 15mg/5ml	10ml/4–6hr
Coactifed	Tripolidine HCl 4mg	Pseudoephedrine HCl 60mg	Codeine 20mg	1tab/4–6hr
Comtrex	Chlorpheniramine maleate 1mg Acetaminophin 325mg	Phenylpropanolamine HCl 12.5mg	Dextromethorphan 10mg	2caps/4hr
Contact Severe Cold Formula	Chlorpheniramine maleate 2mg Acetaminophin 500mg	Pseudoephedrine HCl 30 mg	Dextromethorphan 15mg	2 caps/6hr
Dimetapp-DM	Brompheniramine 4mg	Phenylephrine HCl 5mg + Phenyl- propanolamine HCl 5 mg	Dextromethorphan 15mg	1 tab/6–8hr
Robitussin-CF		Phenylpropanolamine HCl 12.5mg	Dextromethorphan 20 mg	10ml/4hr
Triaminicin with Codeine	Guaifenesin 100mg Alcohol 4.75% Pheniramine 12.5mg + Pyrilamine maleate 12.5mg + Acetaminophen 325mg Caffeine 30mg	Phenylpropanolamine HCl 25mg	Codeine PO ₄ 8mg	1tab/4–6hr