Thai Journal of Obstetrics and Gynaecology
April 2011, Vol. 19, pp. 40-44

SPECIAL ARTICLE

Laryngopharyngeal Reflux in Pregnancy

Worapong Vejvechaneyom MD.

Otolaryngologist-Head&Neck Surgeon, Samitivej Sukhumvit Hospital, Bangkok, Thailand

Introduction

Laryngopharyngeal reflux (LPR) is the retrograde movement of gastric contents (acid and enzymes such as pepsin) in to the upper aerodigestive tract especially the laryngopharynx leading to symptoms referable to inflammatory diseases of larynx/ hypopharynx/throat/ nose & paranasal sinuses/mouth/middle ears. Typical symptoms of LPR include hoarseness, globus pharyngeus (sensation of lump in the throat), cough, excessive mucus in the throat with throat clearing, and mild dysphagia. Sometime, the LPR patients including the pregnant women with LPR also have the excessive saliva and may occasionally complain of a sudden filling of the throat with bitter or salty saliva (water brash).

LPR is related to gastroesophageal reflux disease (GERD), but is not identical to it. Patients with GERD may have no LPR, and conversely, patients with LPR may have no GERD. Most patients are relatively unaware of LPR with only 30 percent reporting heartburn.[1] There are no certain criteria that reliably demonstrate a causal link between acid reflux and LPR symptoms. In fact, the validity of reflux as a cause of LPR symptoms, in the absence of symptoms of GERD, has been called into question. Thus, it is likely that some patients are mistakenly diagnosed with LPR, and investigation of other causes of upper airway symptoms (such as allergy, sinus, or other causes of cough, etc) should be considered for patients who fail to respond to LPR management.

Heartburn, the cardinal symptoms of GERD, is a normal consequence of pregnancy. The predominant etiology is the decrease in lower esophageal sphincter pressure (LESP) caused by female sex hormones, especially progesterone. Thus, GERD and LPR may be ones of normal consequence of pregnancy. Most patients begin to note their symptoms late in the first trimester or second trimester of pregnancy with symptoms becoming more frequent and severe in the latter months of gestation.

Epidemiology

There are relatively limited data on the prevalence of LPR. It is difficult to determine the prevalence of LPR in the population because there is no clear diagnostic gold standard criteria to diagnose LPR. There are no studies of the prevalence of LPR in pregnancy.

Pathophysiology

LPR can cause upper airway symptoms directly or indirectly. The direct mechanism involves irritation of upper aerodigestive mucosa by refluxate through the action of caustic materials (ie, acid, pepsin etc.) on the tissues. The indirect mechanism involves irritation of distal esophagus by refluxate that does not reach the upper aerodigestive mucosa, this irritation evokes the vagally-mediated reflexes that cause laryngeal and bronchial reflexes (laryngospasm, apnea, cough, asthma-like symptoms through bronchoconstriction

etc.). Regardless of the pathway, factors such as the resting tone of the upper and lower esophageal sphincters (UES and LES) and the duration and magnitude of increases in intraabdominal pressure are important to the creation of the refluxate bolus.

In the first trimester of pregnancy, basal (resting) lower esophageal sphincter pressure (LESP) may not change, but is less responsive to physiological stimuli (i.e. pentagastrin, edrophonium chloride, methacholine or a protein meal) that usually increase LESP[2,3]. In the later two trimesters, LESP gradually falls approximately 33-50% of basal values reaching a nadir at 36 weeks of gestation and rebounds to prepregnancy values 1-4 weeks postpartum[4]. Animal and human studies reported that the increased circulating levels of progesterone during pregnancy mediate the LES relaxation (decreased LESP), but estrogen is a necessary primer[2]. The role of increased intraabdominal pressure because of the enlarging gravid uterus is more controversial. All studies agreed with the increasing intraabdominal pressure with the increasing gestational age during pregnancy. It is unknown whether the normal compensatory increasing response of the LESP to these changes is impaired during pregnancy[2]. Others have suggested that abnormal gastric emptying or delayed small bowel transit might contribute to reflux in pregnancy. A limited number of studies have examined the role of the LES, esophageal motility, gastric emptying, and increased intraabdominal pressure from the enlarged gravid uterus in promoting reflux during pregnancy.

Although gastric acid is common to both LPR and GERD, there are many differences making LPR a distinct clinical entity. The majority of GERD patients have signs of esophagitis on biopsy, while only 25 percents of LPR patients do[5]. GERD is felt to be a problem of the LES and mainly occurs in a supine position. In contrast, LPR is seen as primarily an UES problem that mainly occurs in the upright position during periods of physical exertion (eg, bending over, Valsalva, exercise)[5]. There appears to be a lower incidence of esophageal dysmotility in LPR versus GERD.

CLINICAL MANIFESTATIONS

LPR is ubiquitous and associated with many upper airway symptoms and diagnoses. In some cases, the symptoms are the diagnosis, for example, LPR can cause sore throat, chronic cough, globus pharyngeus, and laryngospasm. Alternately, LPR can be associated with specific histopathologic lesions, for example, vocal process granulomas. LPR can be the sole cause or an etiologic cofactor in the development of many disorders of the upper airway.

The common LPR symptoms are dysphonia or hoarseness, cough, globus pharyngeus, excessive mucus in the throat/throat clearing, and mild dysphagia. Even though the symptoms and finding of LPR have been described, the clinical diagnosis is sometimes elusive. Symptoms can occur in the absence of conclusive physical findings, and they can be nonspecific symptoms. There are many factors possible contributing the symptoms similar to LPR, such as postnasal drip, allergic rhinitis, upper respiratory infections, habitual throat clearing, tobacco or alcohol use, excessive voice use, temperature or climate change, emotional issues, environmental irritants, etc.

In addition to typical LPR symptoms, reflux-induced respiratory symptoms are also common. The association between LPR and asthma has been well documented. Asthma can predispose a patient to have reflux. Also, LPR can exacerbate asthma. Microaspiration of gastric refluxate and resultant bronchiectasis can also occur. Some investigators have found strong associations between LPR and airway stenosis, sleep apnea, laryngospasm, and nasal congestion[5]. Although the etiology of these disorders is multifactorial, LPR as a sole cause or as a cofactor should be routinely considered in the differential diagnosis of subglottic stenosis, asthma, laryngospasm, bronchiectasis , chronic rhinitis, and sleep-disordered breathing.

Diagonosis in The Pregnant Patients

There is significant controversy over the appropriate way to diagnose LPR and there is no test that is both easy to perform and highly reliable. Most patients are diagnosed clinically based on symptoms associated with LPR. In patients who are seeing an

otolaryngologist, the clinical history is generally augmented with a laryngoscopic examination. However, the lake of standardized criteria for the diagnosis of LPR and the relatively poor correlation between symptoms and endoscopic findings of LPR have been cited as a rationale against the use of endoscopic techniques to diagnose LPR[6,7].

The initial diagnosis of LPR in pregnancy can reliably be made based on symptoms alone. Any radiographs are not necessary and should be avoided because of radiation exposure to the fetus. Esophageal manometry and pH monitoring studies, as in the non-pregnant patient, are rarely necessary during pregnancy but can be performed safely. Endoscopic examination (laryngoscopy or transnasal esophagoscopy) is the procedure of choice to evaluate intractable LPR symptoms.

Treatment of LPR During Pregnancy

The challenge of treatment during pregnancy is the potential teratogenicity of common antireflux medications. Diets and lifestyle modification is the key for treating mild symptoms. Smaller meals, not eating late at night, elevation of the head of the bed and sleep by the left side, and avoiding foods and medications causing reflux usually relieve the mild symptoms seen in early pregnancy. Chewing gum stimulates the salivary gland can help neutralize acid by salivary bicarbonate. Abstinence from alcohol and tobacco are encouraged to reduce reflux symptoms and to avoid fetal exposure to these harmful substances.

For more troubling reflux symptoms, the doctor must discuss with the patient about benefits versus the risk of drug therapy. Informed consent is appropriate. Nearly all medications are not tested in randomized-controlled studies in pregnant women because of ethical and medicolegal concerns. Most recommendations on drug safety arise from case reports and cohort studies by doctors, pharmaceutical companies or the FDA. Voluntary reporting by the manufacturers suffers from unknown duration of follow-up, absence of appropriate controls and possible reporting bias[8].

The incidence of major fetal malformations in the general population ranges between 1% and 3%. The US FDA divides the safety of drugs during pregnancy into five categories (A, B, C, D and X) based on systemic absorption and reports of congenital defects in animals or humans (Table 1)

Table 1. US FDA Classification of Drugs for Pregnancy[2]

FDA classification	Definition
Category A	Well controlled studies in humans show no fetal risk
Category B	Animal studies show no risks, but human studies inadequate or animal studies show some risk not supported by human studies
Category C	Animal studies show risk but human studies are inadequate or lacking or no studies in humans or animals
Category D	Definite fetal abnormalities in human studies but potential benefits may outweigh the risks
Category X	Contraindicated in pregnancy, fetal abnormalities in animals or humans. Risks outweigh benefits

Table 2. summarizes the drugs used for reflux diseases in pregnancy.

Table 2. FDA Classification of Drugs Used for Reflux Diseases in Pregnancy (modified from Ref.2)

Drugs	FDA class	Comments
Antacids		
Aluminium-, calcium- or magnesium-containing antacids	None	Most are safe for use during pregnancy and for aspiration prophylaxis during labour because of minimal absorption
Magnesium trisilicates	None	Avoid long-term, high-dose therapy in pregnancy
Sodium bicarbonate	None	Not safe for use in pregnancy as causes fluid overload and metabolic alkalosis
Mucosal protectant		
Sucralfate	B	No teratogenicity in animals. Generally regarded as acceptable for human use because of minimal absorption
Histamine$_2$-receptor antagonist (H_2RA)		
Ranitidine	B	Ranitidine is the only H_2RA whose efficacy during pregnancy has been established
Promotility agents		
Metoclopramide	B	No teratogeneic effects in animals or humans reported
Proton-pump inhibitors		
Omeprazole	C	Embryotoxic and fetotoxic in animals. Case reports in human suggest similar concerns. Acceptable for use for aspiration prophylaxis in labour
Lansoprazole	B	No fetal teratogenicity or harm. Limited human pregnancy data. Use is acceptable for aspiration prophylaxis during pregnancy
Rabeprazole	B	No fetal teratogenicity or harm. Limited human pregnancy data. Use is acceptable for aspiration prophylaxis during pregnancy
Pantoprazole	B	No fetal teratogenicity or harm. Limited human pregnancy data. Use is acceptable for aspiration prophylaxis during pregnancy
Esomeprazole	B	No fetal teratogenicity or harm. Limited human pregnancy data. Use is acceptable for aspiration prophylaxis during pregnancy

Alginates (Gaviscon) from a strong, non-systemic barrier in the stomach, preventing reflux of stomach's contents (acid, pepsin, and foods) in to the esophagus (acts as the "antirefluxant").

The H2RAs are the most commonly used and safest medications for the pregnant woman with reflux not responding to lifestyle modification and non-absorbable medication. The H2RAs are category B drugs for pregnancy. Ranitidine has no antiandrogenic activity in animal[10]. Neither H2RA has reports of human sexual defects in infants.

Proton-pump inhibitors (PPIs) are the most effective drug therapy for symptom control and healing of reflux esophagitis. The PPIs have not been as extensively used in pregnancy as the H2RAs, or is their efficacy proven in pregnancy, and the data about total safety are more limited. However, unlike the non-pregnant patients, PPIs should only be used during pregnancy in women with well-defined complicated reflux diseases, not responding to lifestyle modification, antacid, mucosal protectants, promotility drugs, and H2RAs.

Unlike the non-pregnant patient, step-up therapy is preferred (diets and lifestyle modification à antacids à mucosal protectants à alginate compoundsà promotility drugs à H2RAs à PPIs) in pregnant patients.

CONCLUSION

There are no studies of the prevalence of LPR in pregnancy, but LPR may be one of normal consequence of pregnancy. The predominant cause is a decrease in LESP caused by female sex hormones, especially progesterone. Serious reflux complications during pregnancy are uncommon; therefore upper endoscopy and other diagnostic tests are usually not needed. Symptomatic pregnant patient should be managed with a step-up algorithm beginning with diets and lifestyle modification. Antacids or sucralfate are considered the first-line medical therapy. If symptoms persist, alginate compounds or promotility drugs or any of the H2RAs can be used. PPIs are reserved for women with intractable symptoms or complicated reflux disease. Most drugs are excreted in breast milk. Of the systemic absorbed agents, only ranitidine is safe to use during lactation.

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