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Review

Asthma and pregnancy: Coexisting and Comorbid Conditions

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Asthma is the most prevalent chronic disorder to complicate pregnancy. Epidemiologically the females are 10% more likely than males to be diagnosed as having asthma in their lifetime. Asthma has been reported to affect 3.7 to 8.4 percent of pregnant women, and higher than 12% in women between 18-24 years. Asthma is considered the most common serious medical problem that could complicate pregnancy. During pregnancy the severity of asthma often changes, hence the patients need close follow up and monitoring exacerbations. The focus of asthma treatment in pregnant women is achieved the control of symptoms and maintenance of normal lung function. Poorly controlled of asthma can have an adverse effect on the fetus, resulting in increased perinatal mortality, increased prematurity and low birth weight. Acute exacerbations should be treatment aggressively in order to avoid fetal hypoxia. Treatment should include supplement oxygen, β-2 agonist and systemic corticosteroids. The evidence suggests that the risks of uncontrolled asthma are greater than any known risks from medication. The overall perinatal prognosis for children born to women with asthma that is well-controlled during pregnancy is comparable to that for children born to women without asthma.

Keywords: asthma, pregnancy, pregnant medication, delivery, fetal growth, fetal risk.

INTRODUCTION

Asthma and allergic diseases are major chronic respiratory diseases (Bousquet et al., 2007; Bousquet and Khaltaev, 2007). Epidemiologically the females are 10% more likely than males to be diagnosed as having asthma in their lifetime (American Lung Association, 2005; Ostrom N, 2006). Studies have demonstrated more self-reported asthma symptoms, greater morbid-mortality, greater asthma medication use and reduced quality of life in women compared with men (Langhammer et al., 2000; Cydulka et al., 2001; Ford et al., 2003). Asthma has been reported to affect 3.7 to 8.4 percent of pregnant women, and higher than 12% in women between 18-24 years

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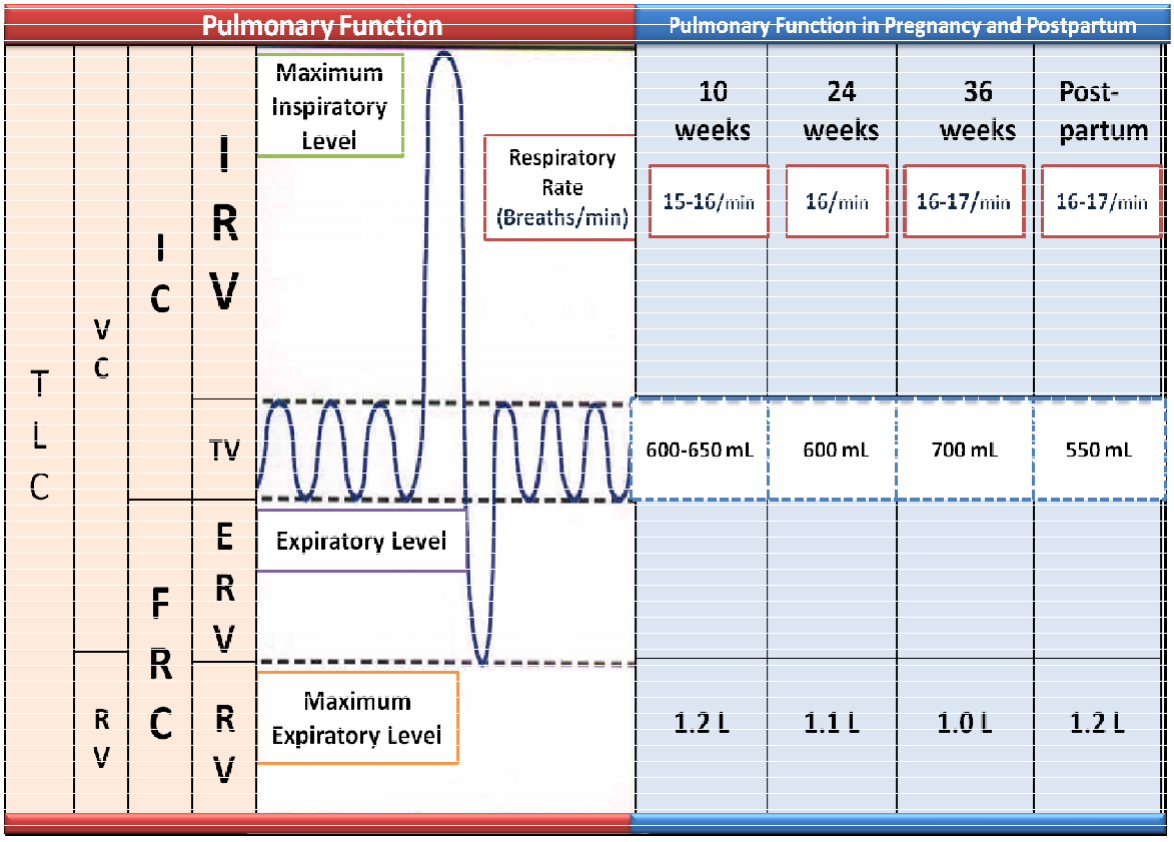


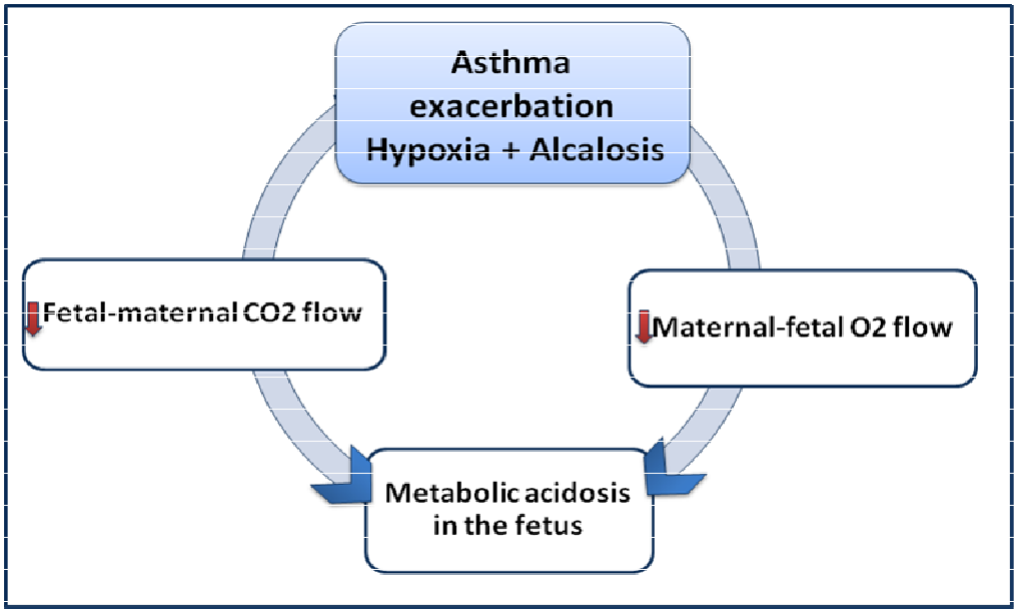
Graph 1. Pulmonary physiological changes in pregnancy and postpartum.
Abbreviations: TLC, Total Lung Capacity; VC, Vital Capacity; RV, Residual Volume; IC, Inspiratory Capacity; FRC, Functional Residual Capacity; IVR; Inspiratory Reserve Volume; TV, Tidal Volume; ERV, Expiratory Reserve Volume.

(Kwon et al., 2003). Furthermore, population data suggest that these rates may be increasing. Asthma is considered the most common serious medical problem that could complicate pregnancy (Kwon et al., 2003). Higher rates of asthma were observed among women who were younger, white, obese, and less well educated, had lower income, and smoked during pregnancy (Louik et al., 2010; Blais and Forget, 2008). Recent studies suggest that uncontrolled maternal asthma increases the risk of perinatal mortality, preeclampsia, preterm birth, and low birth weight infants (Langhammer et al., 2000; Cydulka et al., 2001; Bateman et al., 2009).

Clinical Features

Physiological changes during pregnancy

There are several physiological changes that might modify asthma in the expectant mother. As part of anatomical changes during pregnancy, diaphragm is raised 4 cm, the diameter of the rib cage increases 2 cm, and the circumference is increased 6 cm (Kelsen, 2003). While increasing gestational age, the uterine enlargement restricts diaphragmatic excursion, reducing residual volume and functional residual capacity (Graphic 1). Forced expiratory volume at 1 second (FEV1) and peak expiratory flow (PEF), are not be affected as part of physiological changes (Gluck, 2006). Metabolism also increase 15% and O_2 consumption increase of 21-35% during pregnancy (Gluck, 2006). Changing levels of the female hormones may be a factor in both the improvement and worsening of asthma symptoms during pregnancy. Estrogen and/or progesterone may alter pulmonary function and asthma, some asthmatic patients experience improved pulmonary function and reduced asthma medication requirement during pregnancy while others women can experience decreases in pulmonary function and increases in asthma exacerbations and hospitalizations during pregnancy (Haggerty et al., 2003). This variability is related to progesterone effect on smooth muscle, while in bronquial smooth muscle has a relaxation effect that may contribute to diminished asthma symptoms in patients who might be particularly sensitive to these hormone. The simultaneous relaxation effects of progesterone on the smooth muscle of the lower esophageal sphincter, may lead to increased gastric acid in the esophagus, cause heartburn and



Graphic 2. Maternal-fetal risk in asthma exacerbation.

increase nocturnal symptoms in pregnancy women (Ostrom N, 2006; Haggerty et al., 2003).

Effects of asthma during pregnancy and perinatal outcome

Maternal asthma is associated with an increased risk of pregnancy complications that may lead to reduced infant birth size, preeclampsia/eclampsia, pregnancy-induced hypertension, and vaginal hemorrhage (Tan and Thomson, 2000; Bakhireva et al., 2005; Breton et al., 2010). The National Asthma Education Program Working Group on Asthma and Pregnancy (NAEPP) defined asthma severity as mild, moderate, or severe on the basis of symptoms and spirometry (Breton et al., 2010). This initial asthma classification was significantly related to subsequent asthma morbidity during pregnancy (hospitalizations, unscheduled visits, corticosteroid requirements, and asthma symptoms during labor and delivery). A commonly quoted generalization based on previous data from several small and select study populations is that the course of asthma worsens in one-third of pregnant women, improves in one-third, and remains unchanged in one-third (Schatz et al, 1988; Schatz, 1999; Demissie et al., 1998; Lao and Huengsburg, 1990). Schatz et al, reported in a prospective cohort study with 1,739 pregnant asthmatic patients that thirty percent of initially mild patients were reclassified as moderate-severe during pregnancy, and 23% of the initially moderate-severe patients were reclassified as mild later in pregnancy (Schatz et al., 2003). The exacerbation rate among pregnant women with asthma also is higher. Exacerbations occurred in 12.6% of patients initially classified as mild, 25.7% of patients classified as moderate, and 51.9% of patients classified as severe (Schatz et al., 2003). Pregnant women with asthma have been, reported a higher rate of exacerbation at a mean gestational age of 25.1 +/- 0.9 (range 9-39) weeks of gestation (Murphy et al., 2005). In a cohort of 8,149 pregnant asthmatic women, the use of short β2-agonist was a good indicator of change in asthma control during pregnancy (Valet et al., 2009). Pregnant women had an initial decrease in short acting β2-agonist used in the first trimester before experiencing peak use in the third trimester; therefore, the asthma control improves during the first half of pregnancy and then worsens. The rebound in albuterol use early in the third trimester may be attributable to previously stopping use of controller medications or may be partly attributable to the physiologic effects of pregnancy on asthma control (Valet et al., 2009).

The cause of asthma is not well controlled during pregnancy and can be attributed to multiple factors. Murphy et al. reported that forty-three percent of severe exacerbations occurred in winter, 34% were associated with self-reported viral infection, and 29% with non adherence to inhaled corticosteroid medication (Murphy et al., 2005). Low maternal pulmonary function in pregnant women with asthma plus decreased fetal blood oxygen, could result in abnormal growth and development of the fetus (Graphic 2) (Bakhireva et al., 2005). Among women who had severe exacerbations, a significantly increased rate of low birth weight and lower maternal pregnancy weight gain was documented. The birth weights among infants of women with asthma were,

on average, 38 g lower; and among infants of women with exacerbated asthma they were, on average, 56 g lower (Enriquez et al., 2007). Uncontrolled maternal asthma with severe exacerbation during the first trimester of pregnancy, which is recognized as the most critical period, has been hypothesized as more risk of having a baby with a congenital malformation. Blais et al, found in a Canadian cohort of 4, 344 pregnancies of asthmatic women, a crude prevalence of malformations of 12.8% and 8.9%, respectively, for women who had and those who did not have an exacerbation during the first trimester of pregnancy (Blais and Forget, 2008). Women who had an asthma exacerbation but who did not fill a prescription for oral corticosteroids were 2 times more likely to have a baby with a major congenital malformation than women who did not have an exacerbation. Other features associated with an increased risk of congenital malformations were lower level of education, multiple pregnancies, and maternal epilepsy (Blais and Forget, 2008). Of all malformations, the most frequently observed were musculoskeletal, followed by cardiac defects (Blais and Forget, 2008). Studies in asthmatic pregnancy women are focus on the risk of stillbirth, neonatal mortality, and/or perinatal mortality. Breton et al, studied a cohort of 13, 100 asthmatic women and 28, 048 nonasthmatic women who had at least 1 pregnancy between 1990 and 2002, they found a significantly increased crude risk of perinatal mortality of 34% among asthmatic women compared with nonasthmatic women, but this risk did not remain significant after adjustment for placental abruption and cigarette smoking (Breton et al., 2010). Cigarette smoking is considered an important potential confounder in the association between maternal asthma and the risk of perinatal mortality. However, higher smoking rates among asthmatic patients compared with nonasthmatic patients have been reported by others, suggesting that this may be an important factor for further research and intervention (Louik et al., 2010).

A significantly increasing trend of perinatal mortality was found with an increased number of antiasthmatic drugs used during pregnancy and/or by the severity of asthma, because asthmatic women who used 3 or more antiasthmatic drugs had probably more severe asthma; whereas no significant increased risk was found among infants whose mothers used 1 or 2 antiasthmatic medications (Breton et al., 2010).

Co morbid, co-existing and/or differential diagnoses

Rhinitis, sinusitis, and gastroesophageal reflux are conditions that are often associated with asthma, are frequently more troublesome during pregnancy, and may exacerbate coexisting asthma. If these conditions are present, appropriate treatment is an integral part of asthma management (NAEPP, 2005). Based on safety and effectiveness, inhaled corticosteroid and second generation anti-histamines (loratadine or cetirizine) are recommended for the management of allergic rhinitis. If is necessary some descongestants, the recommendations is a short-term of topical oxymetazoline, through a relationship between use of oral decongestants in early pregnancy and a gastroschisis (NAEPP, 2005).

Gastroesophageal reflux disease (GERD) occurs in up to 50% of pregnant women (Bateman et al., 2009). The two major factors that promote gastroesophageal reflux in pregnant women are changes in hormones and the growing fetus. This co morbidity could be an additional factor to contributing to the symptoms and poor asthma control during pregnancy. In addition to general measures to diminish acid reflux (elevation of the head of the bed; lying on one's left side at night; avoiding caffeine, chocolate and peppermints; and eating frequent, small meals) in selected cases is recommender the use of H2 blockers medications (e.g. ranitidine), which have not revealed any adverse effects on the developing fetus. Moreover, Proton pump inhibitors (e.g. omeprazole) should be used only in severe cases that are not responsive to H2 blockers. While they are felt to be safe, there is no long-term studies available confirming this (British Guideline on the Management of Asthma, 2009).

Asthma is a risk factor of severity in an anaphylactic reaction (Simons et al., 2011). Anaphylaxis in asthmatic pregnant women can be catastrophic for the mother and, especially, the infant. Anaphylactic reaction may be during pregnancy, labour and delivery. Symptoms and signs can include intense vulvar and vaginal itching, low back pain, uterine cramps, fetal distress, and preterm labor. Although, during first trimester the etiologies are similar to those in nonpregnant women, during labour and delivery we should suspect of β-lactam antibiotics, neuromuscular blockers, local anesthetics, oxytocin, transfusion of blood or blood products, natural rubber latex, and other agents used in medical and perioperative settings (Simons and Schatz, 2012). Important caveats in management include epinephrine (adrenaline) promptly injected intramuscularly in the mid-outer thigh using a first aid dose of 0.3 mg (0.3 mL) of a 1 mg/mL (1:1000) solution; this dose can be repeated every 5 to 15 minutes, depending on the clinical response. High-flow humidified supplemental oxygen (up to 100%) should be administered promptly through a close-fitting face mask or oropharyngeal airway (Simons et al., 2011). In addition, remember positioning the mother on her left side to improve venous return to the heart, maintaining a minimum maternal systolic blood pressure of 90 mm Hg to ensure adequate placental perfusion, and continuous electronic monitoring (Simons and Schatz, 2012). Cardiopulmonary resuscitation and emergency cesarean delivery should be performed when indicated. In medical setting should follow clinical criteria for the diagnosis of anaphylaxis considering that in late pregnancy, respiratory rate increases by 10% and heart rate

increases by 15%. Systolic blood pressure does not change but diastolic blood pressure decreases by 15% (Simons and Schatz, 2012).

Differential diagnosis including: Pulmonary embolism (thrombotic, amniotic fluid embolism) and pulmonary edema, cardiomyopathy, other cardiac conditions (acquired and congenital), hypotension caused by spinal block, local anesthetic, or hemorrhage, for example, secondary to abruptio placentae or uterine rupture; cerebrovascular accident, preeclampsia/eclampsia-associated symptoms, such as laryngopathia gravidarum and seizures (Simons and Schatz, 2012).

Allergy/immunology specialists can play an important role in the prevention of anaphylaxis in pregnancy through pre pregnancy risk assessment and risk reduction strategies in all women of child-bearing age. In pregnant women the skin test and initiation of immunotherapy should be deferred until after parturition.

Lifestyle/ behavior modification strategies

The control measures for environmental factors are important to ensure a control of symptoms during pregnancy in women with asthma and can lead to improved maternal well-being with less need for medications. It is recommender to reduce or eliminate de exposure: (1) indoor and outdoor allergens (animal dander, house-dust mite, cockroaches, molds, pollens),

(2) tabacco smoke (if a member of family smoke, they should stop smoking or smoke out of house), (3) Indoor and outdoor pollutants (burning smoke, gas, unvented stoves, cleaning agents, etc) (NAEPP, 2005). The treatment of viral infections, agents that exacerbate asthma symptoms, should follow the same principles of management in nonpregnant patients. The higher prevalence of smoking among asthmatic patients with poorly controlled disease (35%) was disturbing, given that the 2000 Joint Position Statement of the American College of Obstetrics and Gynecology, the American College of Asthma, Allergy, and Immunology, and the American Academy of Asthma, Allergy, and Immunology specifically identifies cigarettes as one of the asthma triggers to be avoided during pregnancy (American College of Obstetricians and Gynecologists (ACOG) and American College of Allergy, Asthma and Immunology (ACAAI), 2000). Despite national guidelines that recommend continuation of maintenance asthma medications, use of inhaled corticosteroids and rescue medications decreases overall during pregnancy. Recent study in pregnant women show that there are a significant number of pregnant women with asthma who are not use appropriate drug therapy (Louik et al., 2010). Of patients with uncontrolled asthma, 63% do not use asthma medications during pregnancy, 60% of women with asthma used inhaled β-agonists, less than 25% used inhaled corticosteroids, and only 3.4% used leukotriene modifiers (Enriquez et al., 2007). However, reported use of inhaled corticosteroids by pregnant women has been even lower in other studies (4% to 15%), possibly because of safety concerns for the baby (Bakhireva et al., 2007). Nowadays, there is an unmet need of understand the risks and safety of asthma medications during pregnancy. National guidelines recommend the continued use of appropriate asthma medications because adverse maternal and neonatal outcomes have been described among women with more severe asthma (NAEPP, 2005; Enriquez et al., 2007).

Effects of asthma control drugs during pregnancy and perinatal outcomes

Common anti-asthma medications include inhaled corticosteroids (ICSs), long-acting beta agonists (LABAs), ICS/LABA combinations, and short-acting beta-agonists (SABAs) (Guo et al., 2011). Even today, there are many questions regarding the safe use of these drugs during pregnancy and the possible adverse effects on both, mother and baby.

Bronchodilatadors.

The inhaled β2-agonists are the most frequently medication used in >50% of pregnancy asthmatic women (Louik et al., 2010). In a group of studies included 6, 667 pregnant women, of whom 1,929 had asthma and β2-agonists had used drugs in 1,599 patients; the used of short acting β2-agonists (SABAs) was safety during pregnancy, but in regard to used long acting β2-agonists (LABAs) the results are limited (NAEPP, 2005). The 2007 National Asthma Education and Prevention Program (NAEPP) Asthma Guidelines recommended the use of LABA therapy as a supplemental treatment to SABAs and ICSs to achieve favorable long-term asthma control in adults with moderate to severe persistent asthma (National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program. Guidelines for the diagnosis and management of asthma (Expert Panel Review-3), 2007). Since their introduction, the LABA drugs have been plagued by safety concerns (Currie et al., 2006; Castle et al., 1993; Nelson et al., 2006). A number of other studies, including several additional large meta-analyses, did not come to the same conclusion regarding safety, especially for patients taking an LABA and ICS concomitantly (Castle et al., 1993; Nelson et al., 2006). In post-marketing study formoterol appears to have been well tolerated by the majority of patients, including pregnancy women (Wilton and Shakir, 2002). Guo et al, examined the association between LABAs and severe asthma exacerbations (SAEs) in 940,449 patients (age <40) with asthma. In this study LABAs used was found to be positively associated with

hospitalizations and intubations, with higher risk of SAEs in African American, alcohol/substance used disorder, pregnancy, and obesity (Guo et al., 2011). On the other hand, possible protective association of inhaled SABAs with pregnancy-induced hypertension (PIH) has been observed in previous studies. Martel et al, determined the effect of inhaled SABA used during pregnancy on the risk of PIH (gestational hypertension, preeclampsia, or eclampsia) in a cohort of 3, 505 asthmatic women. Compared with nonuse, inhaled SABA use during pregnancy was significantly associated with a reduced risk of PIH (adjusted rate ratios: >0-3 doses/week, 0.62 (95% CI, 0.44- 0.87); > 3-10 doses/week, 0.51 (95% CI, 0.34-0.79); and >10 doses/week, 0.48 (95% CI, 0.30-0.75)). These results increase the evidence about the safety of inhaled SABAs during pregnancy (Wilton and Shakir, 2002). Theophylline has demonstrated clinical effectiveness in some studies and has been used for years in pregnant women with asthma (NAEPP, 2005). Studies in human and clinical experience confirm the safety of theophylline at recommended doses (to serum concentration of 5–12 mcg/mL) during pregnancy (NAEPP, 2005). It also, has the potential for serious toxicity resulting from excessive dosing and/or select drug–drug interactions (e.g., with erythromycin). The side effects are commonly reported and also discontinuation of this medication (NAEPP, 2005).

Corticosteroids.

Since 1997, inhaled corticosteroids have been recommended as first-line therapy in pregnancy (Louik et al., 2010). However, observed no substantial increase in inhaled corticosteroid use from 1997–1999 of 19.0% to 23.3% in 2003–2005. It is possible that women might discontinue their use of inhaled steroids on learning that they are pregnant because of concerns for the fetus, and discontinued used of these medications in early pregnancy has been reported (Louik et al., 2010; Enriquez et al., 2006). Because oral glucocorticoids inhibit both growth hormone and insulin-like growth factor 1 and also negatively affect collagen synthesis, concern has been raised regarding the potential of inhaled corticosteroids (ICSs) to impede fetal growth. Blais et al, investigate the association between doses of ICS during the first trimester of pregnancy and the risk of congenital malformations among cohort study of 13,280 women with asthma. Observed that women who used >1000 g/d ICS (beclomethasone dipropionate chlorofluorocarbone equivalent) were significantly more likely (63%) to have a baby with a malformation than women who used >0 to 1000 g/d. On the other hand, women who used >0 to 1000 g/d were not found to be more at risk than women who did not use ICSs during the first trimester.[44] This study adds evidence on the safety of low-to moderate doses of ICS taken during the first trimester but raises concerns about high doses. Bakhireva et al, examined the effect of inhaled corticosteroids, systemic corticosteroids, and β2-agonists on fetal growth in 654 infants born to women with asthma compared with 303 infants born to controls without asthma. The mean birth weight of full-term infants born to mothers who used systemic corticosteroids (3373 g) was lower than in the β2-agonist group (3552 g) and controls without asthma (3540 g; $P < 0.05$) after adjustment for other risk factors. However, no differences in the incidence of small for gestational age for weight were observed among groups (Bakhireva et al., 2005). Adjusted mean birth length was slightly shorter in the systemic steroid group compared with controls. Asthma management with β2-agonists and/or inhaled corticosteroids during pregnancy does not impair fetal growth, whereas systemic corticosteroids have a minimal effect which should be weighed against the necessity to control severe asthma (Bakhireva et al., 2005). In a prospective study of 873 pregnancy women with history of asthma, preterm delivery was associated with use of oral steroids and theophylline, independent of severity and symptoms of asthma (Bracken et al., 2003). Gestation was reduced by 2.22 weeks in women using oral steroids daily and 1.11 weeks after theophylline (Bracken et al., 2003). Intrauterine growth restriction was associated with asthma severity, which possibly reflects a hypoxic fetal effect (Bracken et al., 2003). In other research oral corticosteroids have been found to be associated with an increased risk of congenital malformations, more specifically, cleft lip, cleft palate, or both (the risk in the general population was 0.1 percent; the risk in women on oral corticosteroids was 0.3 percent) (NAEPP, 2005). Oral corticosteroid use during pregnancy in patients who have asthma is associated with an increased incidence of preeclampsia and the delivery of both preterm and low birth weight infants. However, we cannot rule out the possibility of residual confounding by severity or uncontrolled asthma, which has been associated with maternal and/or fetal mortality.

Leukotriene modifier

LTRAs improve asthma symptoms antagonizing the contractile and inflammatory activities of leukotrienes C4, D4, and E4 in airway smooth muscles. LTRAs demonstrated no teratogenic effect in studies in experimental animals, but needed adequate studies in pregnant women (NAEPP, 2005). In the absence of published safety data in human beings, the National Asthma Education and Prevention Program expert panel does not recommend LTRAs as preferred therapy during pregnancy (NAEPP, 2005). This add-on controller medication were used by only 3.4% of asthmatic women during pregnancy (Louik et al., 2010) In the Organization of Teratology Information Specialists Asthma Medications in Pregnancy Study, perinatal outcomes among 96

women who were medicated LTRAs (montelukast or zafirlukast) were compared with women who exclusively used short-acting β2-agonists (n= 122) and women without asthma (n=346). The majority of subjects had a first trimester exposure (89.6%) in combination with other controller and/or rescue medications (99% of subjects in the LTRA group used short-acting β2-agonists, 40% used oral corticosteroids, and 39% used inhaled corticosteroids sometime in pregnancy). Use of LTRAs was not associated with an increased risk of pregnancy loss, gestational diabetes, preeclampsia, low maternal weight gain, preterm delivery, low Apgar scores, or reduced measures of birth length and head circumference in infants (Bakhireva et al., 2007). Slightly decreased birth weight in infants born to LTRA users could be attributed to maternal asthma severity/control. The birth prevalence of major structural defects in the LTRA group (5.95%) was significantly higher compared with 3.9% among exclusive β2-agonists users, and 0.3% among controls without asthma, whereas no significant difference was observed between LTRAs and exclusive β2-agonists users. Furthermore, the defects observed in the LTRA group did not represented a consistent pattern (Bakhireva et al., 2007).

Mast cell stabilizer

There are a few studies in humans regarding cromolyn use in pregnancy. In 4, 110 pregnant women, of whom 1.917 had asthma and 318 had been medicated with cromolyn. The safety of using cromolyn during pregnancy is supported by the current review of evidence (NAEPP, 2005).

Omalizumab

This humanized murine monoclonal antibody decreases free serum IgE and drecreases expression of FcεRI on mast cells, basophils, dendritic cells and monocytes (Ledford, 2009). There are some reassuring animal studies in teratogenicity and was classed as category B of Food and Drug Administration (FDA). There are as yet no clinical data of omalizumab for moderate-severe asthma in pregnancy (British Guideline on the Management of Asthma, 2009; Ledford, 2009).

Management of asthma during pregnancy

Assessment and monitoring of asthma

Severe asthma or poorly controlled maternal asthma has also been linked directly with intrauterine growth restriction (IUGR), prematurity, and congenital anomalies that may in turn lead to compromised fetal growth (Bakhireva et al., 2005). Asthmatic pregnancy women should be monitored to achieving and maintaining asthma control, an hence, maintain lung function and blood oxygenation that ensures oxygen supply to the fetus (NAEPP, 2005). In the management of asthma during pregnancy, it is recommended the participation of a multidisciplinary team, including allergist, pulmonologist, obstetrician and perinatologist. Monthly assessment of asthma control and lung function evaluation (spirometry at the time of initial assessment and peak expiratory flow (PEF) as follow) recommended in each visit. In severe asthma or partially controlled asthma and even after an exacerbation should be recognize uterine activity and is recommended a serial ultrasound after 32 weeks of pregnancy to ensure asthma control and fetal wellbeing (NAEPP, 2005).

In addition, reinforce patient education are measures to be implemented at each visit: (González-Díaz, 2005)

Identifying and avoid asthma triggers (allergens, viral infections, irritants, cigarette smoke, etc.)

Self-monitoring of asthma
Written action plan

Peak flow meter daily
Correct use of inhalers
Plan long-term treatment

Early identification and management of exacerbations

Learning to differentiate between breathing changes due to pregnancy and asthma symptoms, especially in the last trimester of pregnancy, is part of a good education (Gluck, 2006).

Pharmacologic treatment

The goals of asthma therapy in pregnant women consist: (1) None or minimal symptoms during the day or night, (2) Minimal or no exacerbations (which would cause a decrease in oxygen supply to the fetus), (3) No limitations in activities, (4) Maintain normal lung function or close to normal, (5) Minimal use of β-2 agonists inhaled short-acting and (6) Minimal or no adverse effects of medication in both, mother and fetus (NAEPP, 2005).

The Food and Drug Administration (FDA) classified asthma medications for use in pregnancy women based in categories (Table 1). Pregnancy category “A” medications are medications in which there are good studies in pregnant women showing the safety of the medication to the baby in the first trimester. There are very few medications in this category, and no asthma medications (American College of Obstetricians and Gynecologists (ACOG) and American College of Allergy, Asthma and Immunology (ACAAI), 2000; National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program. Guidelines for the diagnosis and management of asthma (Expert Panel Review-3), 2007). Category “B” medications show good safety

Table 1. Asthma medications for use in pregnancy based in FDA categories.

FDA Category	Drug Group	Active	Dosage (most used)
Pregnancy Category B	ICS	Budesonide	DPI: 200 mcg/inhalation
	Mast cell stabilizer	Cromolyn	MDI: 1mg/puff
		Nedocromyl	MDI: 2mg/puff
	Leukotriene modifier	Montelukast	4mg granules; 5, 10mg tablets
		Zafirlukast	10, 20mg tablets
	Anticholinergic agents	Ipratropium	MDI: 18mcg/puff
	Anti IgE monoclonan antibody	Omalizumab	150mg/vial
Pregnancy Category C	ICS	Beclomethasone	HFA: 40 or 80 mcg/puff
		Mometasone	
		Fluticasone	DPI:50, 100, 250mcg/inhalation
		Triamcinolone	100mcg/puff
	Leikotriene modifier	Zileuton	600mg tablets
	Methylxanthines	Theophylline	100, 200, 300, 400 mg capsules extended release 125mg, 250mg tablets
	Short-acting β2- adrenergic agonist	Albuterol	MDI: 90mcg/puff
	Long-acting β2- adrenergic agonist	Formoterol	DPI: 9mcg/inhalation; 12mcg capsules
		Salmeterol	MDI: 21mcg/puff; DPI: 50mcg/blister
	Combination products	Fluticasona/ Salmeterol	DPI: 100/50, 250/50, 500/50 mcg/blister

Abbreviation: FDA, Food and Drug Administration; ICS, Inhaled Corticosteroids; DPI, Dry Powder Inhaler; MDI, Metered Dose Inhaler; HFA, Hydrofluoroalkane; mg, milligrams; mcg, micrograms.

studies in pregnant animals but there are no human studies available. Pregnancy category "C" medications may result in adverse effects on the fetus when studied in pregnant animals, but the benefits of these drugs may out weight the potential risks in humans. Category "D" medications show clear risk to the fetus, but there may be instances in which the benefits outweigh the risks in humans (NAEPP, 2005; American College of Obstetricians and Gynecologists (ACOG) and American College of Allergy, Asthma and Immunology (ACAAI), 2000). And finally, category "X" medications show clear evidence of birth defects in animals and/or human studies and should not be used in pregnancy (Bakhireva et al., 2005). While rescue medications used for the immediate relief of asthma symptoms, include inhaled bronchodilators (e.g. albuterol), is category "C", there are no evidence of adverse effects on the fetus (NAEPP, 2005). Despite the diversity of drugs for asthma management, inhaled corticosteroids (ICSs) continued being recognized as the first-line controller therapy, and the same doses are recommended during pregnancy and under other circumstances (NAEPP, 2005; Blais et al., 2009). The preferred inhaled steroids include budesonide, the only category "B" inhaled steroid (Bakhireva et al., 2005; NAEPP, 2005; American College of Obstetricians and Gynecologists (ACOG) and American College of Allergy, Asthma and Immunology (ACAAI), 2000). Other controller medications such as theophylline (category "C") and cromolyn, nedrocromil and montelukast (all category "B") are reasonable to continue during pregnancy if the mother has had good benefit from the medications prior to pregnancy (NAEPP, 2005). However, none of these medications would be considered a "first choice" to start during pregnancy. Omalizumab, is an injectable medication used for the treatment of asthma as a controller therapy. It does have a category "B" status. However, it should be used with caution in pregnant asthmatics (NAEPP, 2005; Ledford, 2009).

Pharmacotherapy is essential for asthma management and is based on stepwise treatment for different levels of asthma severity: intermittent, mild persistent, moderate persistent, and severe persistent (National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program. Guidelines for the diagnosis and management of asthma (Expert Panel Review-3), 2007).

Table 2. Stepwise treatment of asthma during pregnancy based on asthma severity and control.

Asthma Severity	Mild Intermitent Asthma	Mild Persistent Asthma	Moderate Persistent Asthma	Severe Persistent Asthma	Exacerbated asthma during pregnancy
Symptoms /Day Symptoms /Night Interference with normal activity PEF o FEV1 PEF Variability	≤ 2 days/week ≤ 2 nighst/month None ≥ 80% < 20%	> 2 days/week but < daily > 2 nights/month Minor limitation ≥ 80% 20-30%	Daily > 1night/week Some limitation >60% - <80% >30%	Continual Frequent Extremely limited ≤ 60% >30%	•Oxygen flow to maintain O2 Saturation ≥ 95% •Inhaled short acting β2-agonist every 20 min in firts hour • Systemic (oral or IV) CS •Add albuterol plus inhaled ipratropium in moderate-severe exacerbation •Maintain continuous mathernal-fetal monitoring until patient stabilized •Re evaluate, categorized and act •Discharge home giving patient education and written action plan •Continue course of oral systemic corticosteroid, and start ICS* or increase dose for patients on ICS*
Steps of Recomendation	**Step 1**	**Step 2**	**Step 3**	**Step 4**	
Drugs options recommended	Short acting inhaled β2-agonist as needed	Prefered: Low-doses ICS* Alternative treatment: cromolyn, Leukotriene receptor antagonist or sustained-release theophyline§	Prefered treatment: Either Low-doses ICS* and Long-acting inhaled β2- agonist OR Medium doses ICS* OR Medium doses ICS* and Long-acting inhaled β2- agonist Alternative treatment: Low-doses ICS* and either Theophyline§ or Leukotriene receptor antagonist OR Medium-doses ICS* and either Theophyline§ or Leukotriene receptor antagonist	Prefered treatment: High doses ICS* and Long-acting inhaled β2- agonist and if needed Oral corticosteroid Alternative treatment: High doses ICS and sustained release Theophyline§	
Patient education and enviromental control in all steps of treatment					
Levels of Asthma Control§	**Controlled**	**Partly controled**		**Very poorly controlled**	
Gradual stepwise reduction up to maintain the smallest step that achieves symptoms control		If control is not maintained, consider step up			
Quick Reliefe (All patients)	Short-acting bronchodilatador: 2-4 puff short-acting inhaled β2-agonist, up to 3 treatment at 20-minutes intervals. Course of systemic corticosteroid may be needed. Increasing use of short-acting inhaled β2-agonist may indicate the need to initiate (increase) Long-term control therapy.				Maintain contac with clinician for follow up intructions

Abbreviations: PEF, Pick Expiratory Flow; FEV1, Forced Expiratory Volume in the 1 second; IV, intravenous; ICS, Inhaled corticosteroid.
* There are more date on using budesonida during pregnancy than others inhaled corticosteroids.

Note: Classify severity, clinical features before treatment or adequate control. Assign patient the most severe step in which any feature occur and choose the drug options recommended. Gain control as quickly as possible, maintain under control and then step down to the least medication necessary to maintain asthma control.

The dose and number of medications and the frequency of administration are increased as necessary, based on the severity and control of the patient's asthma, and are decreased when possible (Table 2).

Step 1: Mild Intermittent Asthma. Short-acting bronchodilators, albuterol, are recommended as quick-relief medication for treating symptoms as needed in patients with intermittent asthma. It has an excellent safety profile during pregnancy. No evidence has been found either of fetal injury from the use of short-acting inhaled β2-agonists or of contraindication during lactation (NAEPP, 2005; British Guideline on the Management of Asthma, 2009).

Step 2: Mild Persistent Asthma. The preferred treatment for long-term-control medication is daily low-dose inhaled corticosteroid. This preference is based on the strong effectiveness data in nonpregnant women, as well as effectiveness and safety data in pregnant women that show no increased risk of adverse perinatal outcomes. More data are available on using budesonide in pregnant women. Therefore, inhaled corticosteroids other than budesonide may be continued in patients who were well controlled by these agents prior to pregnancy. Cromolyn, leukotriene receptor antagonists, and theophylline are alternative but not preferred therapies (NAEPP, 2005; British Guideline on the Management of Asthma, 2009).

Step 3: Moderate Persistent Asthma. In this step, is preferred a combination of low-dose inhaled corticosteroid and a long-acting inhaled β2-agonist, or increasing the dose of inhaled corticosteroid to the medium dose range. Limited data describe the effectiveness and/or safety of using combination therapy during pregnancy, but strong evidence from randomized

controlled trials in nonpregnant adults shows that adding long-acting inhaled β2-agonist to a low dose of inhaled corticosteroid provides greater asthma control than only increasing the dose of corticosteroid (NAEPP, 2005; British Guideline on the Management of Asthma, 2009; Jaeschke et al., 2008; Rodrigo et al., 2009).

Step 4: Severe Persistent Asthma. Inhaled corticosteroid dose should be increased within the high-dose range to achieve symptom control. If this is insufficient to manage asthma symptoms, then the addition of systemic corticosteroid is warranted (NAEPP, 2005). According to the evidence, the risks of uncontrolled asthma are greater than any known risks from medication (Louik et al., 2010; NAEPP, 2005; Murphy et al., 2005). Omalizumab could be an option used with caution in pregnant asthmatics (NAEPP, 2005; British Guideline on the Management of Asthma, 2009).

Management of acute exacerbations

Uncontrolled asthma and exacerbations are potentially dangerous to the mother and fetus. In acute asthma, maternal hypoxia combined with respiratory alkalosis can decrease the placental blood flow decreasing fetal blood oxygen that could result in abnormal growth and development of the fetus (Graph 2) (Blais and Forget, 2008; SteniusAarniala et al., 1996, Cousins, 1999; Guy et al., 2004). Women with asthma symptoms but no diagnosis were at particular risk of exacerbations, that has the potential to lead to severe problems for the fetus (Bracken et al., 2003). Therefore, asthma exacerbations during pregnancy is an emergency and should be managed aggressively in hospital (NAEPP, 2005; British Guideline on the Management of Asthma, 2009). Initial assessment include clinic history and physical examination (consciousness, degree of cough, breathlessness, wheeze, chest tightness, and FEV1 or PEF; accessory muscle use and suprasternal retractions suggest severe exacerbation), monitoring respiratory rate, oxygen saturation, hearth rate, temperature, blood pressure. The fetal assessments include search for fetal activity, maintain continuous fetal monitoring and carry out a biophysical profile in fetus (NAEPP, 2005; British Guideline on the Management of Asthma, 2009). The British Guideline on the Management of Asthma recommended give drug therapy for acute asthma as for non-pregnant patient including systemic steroids and magnesium sulphate (British Guideline on the Management of Asthma, 2009). Deliver high flow oxygen immediately to maintain saturation 95-98%. For women with poorly controlled asthma during pregnancy there should be close liaison between the respiratory physician and obstetrician with early referral to critical care physicians for women with acute severe asthma (British Guideline on the Management of Asthma, 2009). In respiratory arrest (FEV1 or PEF <50%, PCO2 >42mmHg, severe symptoms, drowsiness, confusion) admit to hospital intensive care unit (ICU), maintain orotracheal intubation and mechanical ventilation with O_2 100%, dispense inhaled short-acting β2-agonists hourly or continuously plus inhaled ipratropium bromide, and intravenous corticosteroid; continue fetal assessment until patient stabilized. In mild-moderate asthma exacerbation (FEV1 or PEF is $\geq$50%- $\leq$80%) initially dispense inhaled short acting β2-agonist MDI or nebulized every 20 minutes in first hour, oral corticosteroid, and maintain oxygen saturation $\geq$95%. Maintain continuous management with inhaled short action β2-agonist for 1-3 hours. After the first intervention is necessary re evaluate, categorize and act. In incomplete response (FEV1 or PEF ≥ 50% but < 70%, persist wheeze and shortness of breath) admit to hospital ward, add high doses of inhaled short β2-agonist plus inhaled ipratropium bromide every 20 minutes or continuously for 1 hour, systemic (oral or intravenous) corticosteroids, oxygen, monitor FEV1 or PEF, O_2 saturation, pulse and continue fetal assessment until patient stabilized. If the response is favorable (FEV1 or PEF≥ 70%, response sustained 60 minutes after last treatment, no respiratory distress, physical exam normal and reassuring fetal status), discharge home giving patient education and written action plan, continue course of oral systemic corticosteroid, and start ICS or increase dose for patients on inhaled corticosteroid. Maintain contact with clinician for follow up instructions (NAEPP, 2005; British Guideline on the Management of Asthma, 2009).

Management of asthma in labour

Fortunately, an exacerbation of asthma is rare in labour. Nevertheless, is important advise women to continue their usual asthma medications in labour. Women received steroid tablets at a dose exceeding prednisolone 7.5mg per day for more than two weeks prior to delivery should receive parenteral hydrocortisone 100 mg 6-8 hourly during labour (British Guideline on the Management of Asthma, 2009). If anesthesia is required, regional blockade is preferable to general anesthesia in women with asthma (British Guideline on the Management of Asthma, 2009). Epidural analgesia reduces O2 consumption and cardiac output decreases, whereas the use of halogenated compounds increases the risk of uterine atony. Carefully with indomethacin use, may induced bronchospasm, especially in aspirin-sensitive asthma. Prostaglandin F2α also should be used with extreme caution in women with asthma because of the risk of inducing bronchoconstriction (British Guideline on the Management of Asthma, 2009). Oxytocin and prostaglandin E_2 are safe to induce labor. In the absence of acute severe asthma, cesarean section should be reserved for the usual obstetric indications (British

Guideline on the Management of Asthma, 2009). The British Guideline on the Management of Asthma also recommended encourage women with asthma to breastfeed and use asthma medications as normal during lactation (British Guideline on the Management of Asthma, 2009).

Unmet/ future research needs

- Physicians (obstetrician, pulmonologist, and allergist) should be aware of the significant burden of asthma during pregnancy.
- The low rates of use of controller medications, underscore the need to better understand the risks and safety of asthma medications during pregnancy.
- Further research is needed with cohorts of long-term monitoring, to determine the role of LABAs and ICS/ LABA combination during pregnancy.
- To evaluate the effect of omalizumab during pregnancy in patients with severe asthma and the risk to the baby, nowadays more studies are needed.
- Global efforts are required for the generation of prevention programs in allergy and asthma during pregnancy.

CONCLUSIONS

Asthma is a risk factor for several common adverse outcomes of pregnancy, and poorly controlled asthma during pregnancy increases the fetal risk and therefore perinatal outcome. Health professionals should encourage pregnant women to continue their treatment at recommended doses once they know that they are pregnant, with the aim of keeping asthma under control and avoid asthma exacerbations during pregnancy. The evidence suggests that the risks of uncontrolled asthma are greater than any known risks from medication. Acute exacerbations should be treatment aggressively in order to avoid fetal hypoxia. Integrated management of asthma during pregnancy includes education, trigger avoidance measures, self-management of asthma, knowledge of controller medications and rescue, also maintain a close physician-patient communication. Multidisciplinary management is necessary to achieve better asthma control in pregnancy.

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