

Asthma and pregnancy

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Introduction

- Asthma is a chronic inflammatory disease of the airways that is characterized by increased responsiveness of the tracheobronchial tree to multiple stimuli
- Prevalence: 3-8% of pregnant woman
- Pregnancy affect course of asthma and asthma can affect the pregnancy outcome

Respiratory system change during pregnancy

- Lung volume
 - FRC $\downarrow$ 20% (RV + ERV $\downarrow$ 20%)
 - TV $\uparrow$ 40% , RR $\uparrow$ 16% (MV $\uparrow$ 50%)
 - Total respiratory compliance $\downarrow$ 30%
- increase oxygen consumption 20% by 36 week
- Hyperventilation - compensatory respiratory alkalosis
Ph 7.4 $\rightarrow$ 7.44 Pco₂ 40 $\rightarrow$ 30 mmHG
PO₂ 95 $\rightarrow$ 106 mmHg, BE 0 $\rightarrow$ -1.5 , HCO₃ 26 $\rightarrow$ 21-23
- ODC shift to right ($\uparrow$ 2,3 DPG) to facilitate oxygen unloading

Respiratory system change during pregnancy

- Airway mechanics do not change significantly during pregnancy. Thus, forced expiratory volume in one second (FEV₁), FEV₁/FVC ratio, or peak expiratory flow rate → still useful predictor of asthma control testing
- Methacholine test to demonstrate reversible airway obstruction is not recommended during pregnancy, therapeutic trials of asthma therapy should generally be used during pregnancy in patients with possible but unconfirmed asthma.



Fetal oxygenation

- Poorly controlled asthma adversely affect fetal oxygenation in a number of ways:
 - maternal hypoxemia directly reduces oxygen supply to the fetus.
 - Hypercapnia results in fetal acidosis.
 - Reduction in uterine blood flow (potentially due to exogenous or endogenous vasoconstrictors, dehydration, hypotension, aortocaval compression or significant maternal alkalosis) may compromise fetal oxygenation.



Effect of asthma on pregnancy

Studies show non conclusive association between poorly controlled asthma and adverse perinatal and maternal outcome:

- Premature labour
- Intrauterine growth restriction
- Low birth weight (direct correlation between maternal FEV₁ and infant birth weight)
- Congenital malformation
- Neonatal hypoglycemia, seizures, tachypnea, and neonatal intensive care unit (ICU) admission
- Preeclampsia



Effect of asthma on pregnancy

Possible explanations:

- Fetal hypoxia and respiratory acidosis from poorly controlled asthma
- Modest increased risk (OR 1.48, 95 % CI 1.04-2.09) of congenital malformations in the infants of asthmatic women experiencing an exacerbation during the first trimester of pregnancy
- Polymorphisms of the beta-2 adrenergic receptor, leading to bronchial hyperreactivity, uterine muscle hyperreactivity (preterm birth) and vascular hyperreactivity (preeclampsia). However, the clinical significance of these associations is also unclear.



Effect of pregnancy on asthma

- Effect of pregnancy on course of asthma is unpredictable
- Reported to worsen (35%), improved (28%), unchanged (33%) during pregnancy
- Some evidence suggest worsening is related to baseline asthma severity
- Acute exacebation is more likely to occur during the second and third trimester, with significantly fewer attacks occuring in last 4 weeks and during labour.



Effect of pregnancy on asthma

- Course of asthma in successive pregnancies found to be similar to experience in previous pregnancies.
- Exact reason for uneven distribution is unclear
- Postulated due to decrease or stop taking their asthma medication shortly after becoming aware of the pregnancy
- In particular, inadequate use of inhaled corticosteroids may increase the risk of an asthma exacerbation. In one of the prospective studies, only 4 percent of women taking inhaled corticosteroids from the start of pregnancy developed an acute attack, compared with 17 percent of women who were not.



Management of chronic asthma

- The two primary goals of asthma therapy during pregnancy are the prevention of acute exacerbations and optimization of ongoing pulmonary function.
- The four important components of effective asthma therapy during pregnancy are :
 - Objective monitoring of maternal lung function and fetal well-being as a guide to therapy
 - Proper control of environmental and other triggers for asthma (eg, cigarette smoking, animal allergen exposure)
 - Patient education
 - Pharmacologic therapy

Monitoring

- Mother:
 - Symptoms and signs:
 - episodic cough (esp nocturnal), wheezing, or dyspnea provoked by typical triggers
 - Tachypnea, audible wheeze, hyperinflated chest, reduced airway entry, diffuse polyphonic wheeze
 - Severe: unable to speak complete sentence, RR >25/min, Pulse >110bpm
 - Life threatening attack: silent chest, cyanosis, bradycardia, exhaustion

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- Demonstrate variable expiratory airway obstruction:
 - >20% variability in peak expiratory flow rate
 - Severe: PEF 33-50% predicted, life threatening < 33% expected
 - Spirometry: may demonstrate obstructive pattern, with reversible reduction in FEV₁ or FEV₁/FVC
 - ABG -Normally compensated respiratory alkalosis pattern.
 - PaCO₂>35 mmHg or PaO₂<70 mmHg represent more severe compromise during pregnancy
 - Respiratory alkalosis -> fetal hypoxia
 - Respiratory acidosis -> fetal acidosis from hypercapnia

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- CXR:
 - with a shielded maternal abdomen expose the fetus to approximately 0.00005 rad.
 - Indicated when coexisting conditions are present:
Pneumothorax, Superimposed chest infection
 - Fetus: regular monitor fetal movement, fetal growth +/- CTG during acute admission

Asthmatic medications in pregnancy

- Are there potential adverse effects of the medication on the developing fetus?
 - Miscarriage /Fetal death/Congenital malformation (especially first trimester exposure)/Reduced fetal growth/Impaired function of developing organs,/ Reduced uteroplacental blood flow/ Increased risk of preterm delivery/Drug related side effects in the newborn

Asthmatic medications in pregnancy

- Relatively few drugs have been proven harmful in pregnancy and less than 1 percent of congenital malformations can be attributed to drugs; however, statistical and ethical considerations make it unlikely that any drug will ever be "proven safe"
- Although unnecessary use of medication during pregnancy should be avoided, the risks of untreated disease must be considered in parallel. Fortunately, a relatively large body of evidence supports the use of several important therapies for asthma during pregnancy



FDA categories

- The United States Food and Drug Administration established five categories to describe a drug's potential for causing adverse effects during pregnancy
- The categories are based on the results of animal studies, human data, and consideration of whether the benefit of the drug's use during pregnancy outweighs the risk.

FDA classification

- **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 possibility 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 (e.g., 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.

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- No asthma or allergy medication labeled to date meets the requirements for category A
 - Most drugs used in the treatment of asthma fall into categories B or C.
 - Category D provides a strong relative contraindication to use in pregnancy
 - Category X drugs should not be used.

FDA use-in-pregnancy ratings for specific asthma medications

Drug class	Specific drug	FDA category
Beta adrenergic agonists	Terbutaline	B
	Albuterol	C
	Epinephrine	C
	Metaproterenol	C
	Pirbuterol	C
	Salmeterol	C
	Bitolterol	C
Methylxanthines	Theophylline	C
Anticholinergic drug	Ipratropium	B
Glucocorticoids	Prednisone (systemic)	B
	Methyl prednisone (systemic)	C
	Budesonide (inhaled)	B
	Fluticasone (inhaled)	C
	Beclomethasone (inhaled)	C
Cromoglycates	Cromolyn sodium	B

FDA use-in-pregnancy ratings for specific asthma medications

Drug class	Specific drug	FDA category
Agents affecting leukotrienes	Nedocromil	B
	Zafirlukast	B
	Montelukast	B
	Zileuton	C
Antihistamines	Astemizole	C
	Loratadine	B
	Fexofenadine	C
	Cetirizine	B
Decongestants	Chlorpheniramine	B
	Pseudoephedrine	C



Chronic asthma

- Pharmacologic therapy for asthma during pregnancy are similar to those in nonpregnant patients and involve a step-wise approach, as recommended by the "The National Asthma Education and Prevention Program

Preferred pharmacologic step therapy of asthma during pregnancy: NAEPP update 2004

Category	Step therapy
Mild intermittent	Inhaled short-acting beta2 agonist* as needed (for all categories)
Mild persistent	Low dose inhaled glucocorticoid*
Moderate persistent	Medium dose inhaled glucocorticoid*
	OR
	Low dose inhaled glucocorticoid* plus long-acting beta agonist ^Δ
	OR
	Medium dose inhaled glucocorticoid* plus long-acting beta agonist ^Δ , if needed
Severe persistent	High dose inhaled glucocorticoid* plus long-acting beta agonist ^Δ
	Prednisone if needed

* Albuterol is preferred inhaled short acting beta2 agonist during pregnancy.

• Budesonide is preferred inhaled corticosteroid during pregnancy.

Δ Salmeterol is preferred long-acting beta agonist during pregnancy.

Based on data from: Quick Reference. NAEPP Expert Panel Report Managing Asthma During Pregnancy: Recommendations for Pharmacologic Treatment-Update 2004. US Dept of Health and Human Services, Bethesda, MD. NIH Publication No. 04-5246, March, 2004.



Acute asthma

- does not differ substantially from the management in non-pregnant patients
- Intensive monitoring of both mother and fetus is essential
- Multidisciplinary approach involving intensivist, physician, obstetrician and paediatrician



a) Supportive care

- Supplemental oxygen (initially 3 to 4 L/min by nasal cannula to maintain an arterial oxygen tension (PaO_2) of at least 70 mmHg and/or oxygen saturation by pulse oximetry of 95 percent or greater
- Intravenous fluids (containing glucose if the patient is not hyperglycemic) are administered to ensure adequate hydration.
- Avoidance of aortocaval compression: rest in a seated or left lateral position
- Continuous fetal heart rate monitoring as well as maternal monitoring is essential



b) Pharmacological therapy

- Options: inhaled beta agonists, inhaled anticholinergic agents, oral or intravenous glucocorticoids, intravenous magnesium sulphate, intravenous/ subcutaneous beta 2 agonist
- Dosages of systemic glucocorticoids for acute asthma exacerbations in pregnancy are not different than those recommended for non-pregnant patients
- Intravenous aminophylline/theophylline is NOT generally recommended because it has been demonstrated that there is no additional benefit to optimal inhaled beta agonist and intravenous glucocorticoid therapy . In addition, when used in combination with intensive inhaled beta-agonist therapy, intravenous aminophylline causes increased adverse side effects



Pharmacological therapy

- Intravenous magnesium sulphate may be beneficial in acute severe asthma as an adjunct to inhaled beta agonists and intravenous glucocorticoids, especially in patients with coexistent hypertension or preterm uterine contractions.
- Magnesium sulfate is among the most extensively studied medications in pregnancy. It is routinely given to prevent eclamptic seizures in the mother and appears to have neuroprotective effects for the neonate if administered prior to preterm birth.
- Subcutaneous or intravenous terbutaline should also be considered if refractory to conventional treatment
- Systemic adrenaline should be **AVOIDED** (if possible) due to its vasoconstrictive effect on uteroplacental vasculature.

Pharmacologic management of acute asthma during pregnancy

1. Beta₂-agonist bronchodilator (nebulized or metered-dose inhaler)	
Albuterol by MDI 4 to 8 puffs every 20 minutes up to 4 hours, then every 1 to 4 hours, as needed	
Albuterol by nebulizer 0.083 percent (2.5 mg/3 mL), 2.5 to 5 mg every 20 minutes for 3 doses and then 2.5 to 5 mg every 1 to 4 hours, as needed	
Albuterol by continuous nebulization, administering 10 to 15 mg per hour	
2. Ipratropium	
By nebulizer, 500 mcg every 20 minutes for 3 doses, then as needed. Can be given simultaneously with beta ₂ -agonist.	
By MDI, 4 to 8 inhalations every 20 minutes for 3 doses, then as needed	
3. Systemic glucocorticoids (for those with a poor response to treatment after one hour, or with initial therapy for patients on chronic oral glucocorticoids)	
For patients who can be managed at home: prednisone 40 to 60 mg per day in a single or divided dose	
For patients who require hospitalization: prednisone 40 to 80 mg daily in a single or divided dose (or the equivalent dose of methylprednisolone* intravenously) until peak flow reaches 70 percent of predicted or personal best, and then taper as patient improves	
For patients who have a life-threatening exacerbation, a higher initial dose of methylprednisolone*, 60 to 80 mg every 6 to 12 hours, may be given intravenously, and then tapered as the patient improves, as above	
4. For patients not responding to above therapies, consider adjunct therapies	
Intravenous magnesium sulfate 2 g infused over 20 minutes, in absence of renal insufficiency*	
Subcutaneous terbutaline 0.25 mg every 20 minutes for up to 3 doses	

MDI: metered dose inhaler

* A conversion calculator is available in UpToDate. See Calculator:

Corticosteroid Medication Dosing Conversions (glucocorticoid effect).

- For patients with renal insufficiency, a baseline serum magnesium level is assessed. The decision to use intravenous magnesium requires consideration of the potential benefit in terms of asthma and the anticipated risk of hypermagnesemia based on the degree of renal insufficiency and baseline serum magnesium level.

Adapted from: National Asthma Education and Prevention Program: Expert panel report III: Guidelines for the diagnosis and management of asthma. Bethesda, MD: National Heart, Lung, and Blood Institute, 2007. (NIH publication no. 08-4051) www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm (Accessed on May 12,

c) Mechanical ventilation

- Indications:
 - Maternal exhaustion, altered consciousness
 - Respiratory failure $\text{PaCO}_2 > 40-45$ or progressive worsening $\text{PaCO}_2 > 35\text{mmHg}$, regardless of maintained oxygenation
 - Fetal distress
- early intervention to avoid maternal and fetal hypoxemia and fetal acidosis from hypercapnia



c) Mechanical ventilation

- Bronchospasm, airway inflammation, airway edema, and mucus plugging dramatically increase airflow obstruction.
- When the expiratory time is insufficient to completely exhale, inadequate emptying between breaths causes dynamic hyperinflation.
- Dynamic hyperinflation creates intrinsic PEEP and elevates the plateau pressure (P_{plat}), which can lead to cardiovascular collapse and barotrauma, as well as increase the work of breathing.

c) Mechanical ventilation

- The goal of mechanical ventilation should be minimizing intrinsic PEEP $<10-15\text{mmHg}$ and $P_{\text{plat}} <30\text{mmHg}$
 - Increasing the inspiratory flow ($100-120\text{L/min}$) will shorten the inspiratory time, increase the expiratory time, and allow the patient more time to exhale.
 - Decreasing the tidal volume ($6-8\text{ml/hr}$) causes less lung inflation and gives the patient a smaller volume to exhale before the next breath.
 - Decreasing the respiratory rate ($8-12\text{breath/min}$) increases the expiratory time and allows the patient more time to exhale.



c) Mechanical ventilation

- Minimize asynchrony by sedation and paralysis
- The risk and benefit of permissive hypercapnia in pregnant patient are more complex as transfer of CO₂ across the placenta is dependent on PaCO₂ difference of approximately 10mmHg between the maternal and fetal circulation.
- Maternal hypercapnia results in fetal acidosis
- Yet, minute ventilation should be adjusted to avoid hyperventilation as respiratory alkalosis will lead to reduce uterine blood flow and increase dynamic hyperinflation and barotrauma.

d) Adjuncts

- Few case reports show favourable outcome with helium oxygen mixture and bronchoalveolar lavage using saline.
- Uncontrollable life threatening refractory to intensive treatment and mechanical ventilation should liaise with obstetrician and paediatrician to consider early delivery
 - reduce oxygen consumption by 20-30%, improve oxygen reserve from removal of diaphragmatic splinting, improve oxygen delivery (removal of placental shunt)
 - Allow permissive hypercapnia



e) Peripartum care

- Oxytocin is the drug of choice for induction of labor and control of postpartum hemorrhage [
- Analogs of prostaglandin F₂-alpha can cause bronchoconstriction and should not be used for termination of pregnancy, cervical ripening, induction of labor, or control of uterine hemorrhage.
- Prostaglandin E₂ (in gel or suppository form) and prostaglandin E₁ have not been reported to cause bronchoconstriction and are safer analogs if prostaglandin treatment is required.
- For peripartum pain control, morphine, pethidine should be avoided since they can induce histamine release. However, evidence of acute bronchoconstriction caused by these agents is lacking. Fentanyl may be appropriate alternatives



e) Peripartum care

- Epidural anesthesia is preferred for the asthmatic patient who opts for pain control during labor because it reduces oxygen consumption and minute ventilation in the first and second stage of labor and usually can provide adequate anesthesia if cesarean delivery becomes necessary.
- If general anesthesia is required, ketamine and halogenated anesthetics are preferred, because they may have a bronchodilatory effect.
- Use of ergot derivatives for postpartum bleeding or headache should be avoided because of their potential to cause bronchoconstriction.



Summary

- Management of asthma during pregnancy requires a multidisciplinary team approach (obstetrician, paediatrician, intensivist) with the consideration of maternal well being, as well as fetal well being.
- Key to success for managing asthma during pregnancy includes early identification, treatment, close monitoring of mother and fetus, stabilizing the haemodynamic and oxydynamics of patient.
- Most drugs used in the treatment of asthma fall into categories B or C.



Summary

- The general principles of pharmacologic therapy for asthma during pregnancy are similar to those in nonpregnant patients and involve a step-wise approach, as recommended by the "The National Asthma Education and Prevention Program (NAEPP)
- Acute asthma should be promptly treated with bronchodilator therapy, systemic corticosteroid and oxygen therapy



Summary

- Intravenous magnesium sulphate may be beneficial in acute severe asthma as an adjunct to inhaled beta agonists and intravenous glucocorticoids
- Systemic adrenaline should be **AVOIDED** (if possible) due to its vasoconstrictive effect on uteroplacental vasculature
- Intravenous aminophylline/theophylline is NOT generally recommended
- Mechanical ventilation should be initiated early in life threatening situation with careful ventilator management strategy.
- Early caesarian section may be lifesaving .



Reference

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