Asthma in Pregnancy

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Disclosures

- No relevant disclosures
Learning Objectives

- Explain the pathophysiology of asthma in pregnancy, including the pulmonary, hormonal and immunological changes that contribute to changes in asthma symptoms throughout pregnancy
- Describe maternal and fetal outcomes related to asthma in pregnancy
- Describe important components of the management of asthma in pregnancy
Asthma

- Asthma is a heterogeneous disease characterized by airflow inflammation (GINA 2014)
- The inflammation can vary over time leading to variable airflow limitation
- It involves the presence of respiratory symptoms including
  - Dyspnea/shortness of breath
  - Wheeze
  - Cough
Airflow obstruction

- Airway narrowing can be caused by
  - Airway edema
  - Smooth muscle contraction
  - Airway thickening and fibrosis
  - Mucous production
Epidemiology

- Occurs in about 3-8% of pregnant women, one of the most common chronic diseases in pregnancy
- Increase in prevalence since the 1990s
- “Rule of 1/3”: Approximately one-third of patients with asthma in pregnancy improve, one-third clinically worsen and one-third remain the same
- Women with more severe asthma at baseline are more likely to worsen
Epidemiology

- Exacerbations can occur at any time during the pregnancy, but most often between 17 and 34 weeks.
- 26-30% of women will experience an asthma exacerbation during pregnancy.
  - ~10% will require hospitalization.
  - <1% will require intensive care/intubation.
- Subsequent pregnancies often with similar effects of asthma.
Maternal Risks

- Pre-eclampsia
- Hyperemesis gravidarum
- Placenta previa
- Uterine hemorrhage, post partum bleeding
- Gestational hypertension
- Gestational diabetes

- Risks factors for exacerbation:
  - Viral illness, stress, GERD, allergic rhinitis
  - Discontinuation of medications
  - Smokers
Fetal effects

- Low birth weight, SGA or IUGR
- Preterm birth
- Neonatal hypoxia

- If asthma is poorly controlled, associated with 15-20% increase in both maternal and fetal risks
<table>
<thead>
<tr>
<th>Study</th>
<th>Asthma n/N</th>
<th>Control n/N</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exacerbation during pregnancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gordon et al, 1970</td>
<td>2/10</td>
<td>3518/30861</td>
<td>1.75 (0.51, 6.06)</td>
</tr>
<tr>
<td>Jana et al, 1995</td>
<td>8/15</td>
<td>76/370</td>
<td>2.60 (1.55, 4.34)</td>
</tr>
<tr>
<td>Schatz et al, 1995</td>
<td>4/54</td>
<td>1/54</td>
<td>4.00 (0.46, 34.64)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.54 (1.52, 4.25)</td>
</tr>
<tr>
<td>No exacerbation during pregnancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gordon et al, 1970</td>
<td>38/255</td>
<td>3518/30861</td>
<td>1.31 (0.97, 1.76)</td>
</tr>
<tr>
<td>Jana et al, 1995</td>
<td>28/169</td>
<td>76/370</td>
<td>0.81 (0.54, 1.20)</td>
</tr>
<tr>
<td>Schatz et al, 1995</td>
<td>16/431</td>
<td>11/431</td>
<td>1.45 (0.68, 3.10)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.12 (0.89, 1.40)</td>
</tr>
</tbody>
</table>

Relative risk of low birth weight compared to women without asthma (95% confidence interval)
Respiratory Mechanics in Pregnancy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory Rate</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Vital Capacity</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Tidal Volume</td>
<td>Increased</td>
</tr>
<tr>
<td>Minute Ventilations</td>
<td>Increased</td>
</tr>
<tr>
<td>Minute Oxygen Uptake</td>
<td>Increased</td>
</tr>
<tr>
<td>Functional Residual Capacity</td>
<td>Decreased</td>
</tr>
<tr>
<td>Residual Volume of Air</td>
<td>Decreased</td>
</tr>
<tr>
<td>Airway Conductance</td>
<td>Increased</td>
</tr>
<tr>
<td>Total Pulmonary Resistance</td>
<td>Reduced</td>
</tr>
</tbody>
</table>
Pulmonary changes

- Tidal volume increases due to increased ventilatory drive
- Even as early as the first trimester, minute ventilation increases due to increased respiratory drive
- Elevation of the diaphragm as the uterus expands decreases the functional residual capacity
Hormonal changes

- Increased serum progesterone acts as a direct respiratory stimulant and can increase minute ventilation up to 50%, can increase gastroesophageal reflux symptoms as well
- Progesterone may also help with smooth muscle relaxation
- Increasing cortisol may be protective due to anti-inflammatory properties
- Increase in symptoms with female fetus perhaps due to hormonal variations? (i.e. estrogen may increase mucous production)
Immunologic changes

- Normal response in pregnancy to increase regulatory T cells and shift to a Th2 predominance from Th1
- Pregnant patients with asthma may induce less regulatory T cells with decreased surveillance and increased inflammation
  - Th2 response is exaggerated and asthma can worsen
  - If asthma is well controlled, the Th2 response does not seem to be as pronounced
AN IMMUNOLOGICAL “CLOCK” OF PREGNANCY

POSTPARTUM
(Poorly understood, but suspected to include the following)
- Immunological recovery/resolution
- Maternal tolerance to fetal cell implants

EARLY
- Mobilization of specialized uterine natural killer cells
- Entrapment of antigen presenting cells
- Dampened antigen presenting cell responses

MID TO LATE
- Progressive enhancement of pathogen responses via:
  - Increased neutrophil numbers
  - Enhanced neutrophil and natural killer cell responses to viral and bacterial pathogens
- Progressive expansion of peripheral regulatory T cell pool

Aghaeepour et al., Science Immunology (2017)
Goals of Management

- Prevention of daytime and nocturnal symptoms
- Maintain normal activity
- Prevention of exacerbations
- Maintain fetal oxygenation

- Team approach with OB to ensure monitoring of asthma status
Monitoring

- Baseline spirometry
- Monthly evaluation of asthma history and pulmonary function (peak expiratory flow and spirometry if indicated)
- Consideration for serial ultrasounds at 32 weeks in patients with suboptimal control
Education

- Preconception education
- During pregnancy
  - Ensure appropriate inhaler technique and medication adherence
  - Assess environmental factors
    - Allergens and irritants
  - Asthma action plan
  - Management of co-morbid conditions
    - Rhinitis, sinusitis and gastroesophageal reflux
  - Importance of immunizations
    - Influenza vaccination annually
    - Pneumococcal vaccination prior to pregnancy
# Classification of Severity

<table>
<thead>
<tr>
<th>Components of Severity</th>
<th>Intermittent</th>
<th>Mild Persistent</th>
<th>Moderate Persistent</th>
<th>Severe Persistent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impairment Symptoms</td>
<td>&lt;2 days/wk or less</td>
<td>&gt;2 days/wk, not daily</td>
<td>Daily</td>
<td>Throughout the day</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>&lt;2 Xs/mth or less</td>
<td>&gt;2 Xs per month</td>
<td>More than once a week</td>
<td>Four times per week or more</td>
</tr>
<tr>
<td>SABA prn</td>
<td>&lt;2 days/wk</td>
<td>&gt;2 days/wk, not daily, not &gt;1 X/day</td>
<td>Daily</td>
<td>Several xs/day</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>None</td>
<td>Minor limitation</td>
<td>Some limitation</td>
<td>Extremely limited</td>
</tr>
<tr>
<td>Lung function</td>
<td>Normal FEV₁ between exacerbations FEV₁&gt;80% FEV₁/FVC normal</td>
<td>FEV₁&gt;80% FEV₁/FVC normal</td>
<td>FEV₁&gt;60%, but &lt;80% FEV₁/FVC reduced 5%</td>
<td>FEV₁ &lt;60% FEV₁/FVC reduced &gt;5%</td>
</tr>
<tr>
<td>Risk</td>
<td>Exacerbations requiring oral steroids</td>
<td>0-1/yr</td>
<td>&gt;2/yr</td>
<td></td>
</tr>
<tr>
<td>Recommended Step for Initiating Treatment</td>
<td>Step 1</td>
<td>Step 2</td>
<td>Step 3</td>
<td>Step 4 or 5</td>
</tr>
</tbody>
</table>

Adapted from the NAEPP expert panel report
Management of Acute Exacerbation

- Similar to standard treatment guidelines
- Initial assessment: O2 supplementation, inhaled albuterol every 20 minutes up to three times in the first hour
- Severe symptoms: Add ipratropium 500 mcg (inhaled) or terbutaline (subcutaneous or IV)
- Add corticosteroids (oral or IV) if poor response to bronchodilators or patient had been receiving steroids prior to presentation
Management of Acute Exacerbation

- If patient responds to acute treatment within 4-6 hours, patient may be discharged with short course of oral prednisone 40-80 mg/day

- Hospitalization
  - Unable to maintain oxygenation >95% saturation on room air after medications given
  - FEV₁ or PEF remain persistently low (<70%)
  - Evidence of fetal distress
  - Evidence of significant hypercapnia, respiratory acidosis, maternal respiratory fatigue ---→ critical care setting/intubation
Management of Acute Exacerbation

- Pregnant women with asthma are more likely to be undertreated
  - Concern regarding appropriate medication management
  - Patient non-adherence to medications
  - Lack of knowledge surrounding the maternal and fetal outcomes
- Poor monitoring
  - Regardless of baseline severity
  - Spirometry or peak flow
  - Validated control assessment
Bronchodilators

- Short acting bronchodilators/ short acting inhaled beta_2_- agonists
  - Should be used per guidelines just as in non-pregnant individuals
  - Reassuring safety data, especially for albuterol
Bronchodilators

- Long acting bronchodilators
  - Limited data
  - Consensus: should be used if asthma control cannot be achieved using medium dose ICS and SABAs


- Examined whether exposure to LABA in addition to ICS increases risk of hypertensive disorders of pregnancy or preeclampsia/eclampsia as compared with non-exposure in pregnant patients with asthma
- Results: rates were similar in women exposed or not exposed to LABAs
- Safety of LABAs for treatment of asthma in pregnancy in terms of risks of hypertensive disorders of pregnancy and preeclampsia/eclampsia
Inhaled corticosteroids

- Reassuring evidence review on the safety of ICS
  - No studies which relate ICS use with increase in congenital malformations or adverse perinatal outcomes
- Risk of asthma exacerbations in pregnant patients are reduced and FEV₁ improved with ICS
- Budesonide is pregnancy category B; likely due to the fact it was specifically studied
- Consensus: ICS use decreases risk of maternal asthma exacerbations and does not increase risk to mother or fetus. Use as guidelines recommend.
- No apparent difference between specific ICS
Systemic corticosteroids

- Use only if patient unable to achieve control with other medications; short course for acute exacerbations
- Data is conflicting
  - First trimester use of oral corticosteroids associated with increased risk for isolated cleft lip with or without cleft palate
  - Length of course and dose was not well described in these studies
Leukotriene Modifiers

- Montelukast and Zafirlukast as well as 5-LO pathway inhibitors (Zileuton)
- Reassuring animal studies for LTRAs
- Minimal data
- Weigh risks and benefits
  - Likely safe, if choosing one, montelukast preferred due to more evidence
  - Pregnancy category B
Theophylline

- Not commonly used
- Animal studies demonstrated adverse pregnancy outcomes with high dose
- Human studies confirm safety of theophylline at recommended doses (serum concentration 5-12 mcg/mL) during pregnancy
- In one RCT, no differences in asthma exacerbations or maternal or perinatal outcomes in theophylline vs. beclomethasone groups; but higher rate of reported side effects and medication non-adherence in theophylline group as well are more women with FEV1 less than 80%
- Pregnancy category C
Cromolyn

- 2 human studies, 318 patients on cromolyn
- Appears to be safe
Omalizumab

- For patients with moderate to severe asthma not controlled by medium to high dose ICS/LABA
- Category B
### Table 2. Steps of Asthma Therapy during Pregnancy.∗

<table>
<thead>
<tr>
<th>Step</th>
<th>Preferred Controller Medication</th>
<th>Alternative Controller Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>Low-dose inhaled corticosteroid</td>
<td>LTRA, theophylline, or cromolyn</td>
</tr>
<tr>
<td>3</td>
<td>Medium-dose inhaled corticosteroid</td>
<td>Low-dose inhaled corticosteroid plus LABA, LTRA, or theophylline</td>
</tr>
<tr>
<td>4</td>
<td>Medium-dose inhaled corticosteroid plus LABA</td>
<td>Medium-dose inhaled corticosteroid plus either LTRA or theophylline</td>
</tr>
<tr>
<td>5</td>
<td>High-dose inhaled corticosteroid plus LABA</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>High-dose inhaled corticosteroid plus LABA plus oral prednisone</td>
<td>—</td>
</tr>
</tbody>
</table>

* Data are from the National Asthma Education and Prevention Program.24,25 We have modified step 3 to reflect the choice of a medium-dose inhaled corticosteroid over a low-dose inhaled corticosteroid plus a long-acting β-agonist (LABA) because of the lack of safety data on the use of LABA during pregnancy. LTRA denotes leukotriene-receptor antagonist.
Interventions for improving asthma management during pregnancy

- Few randomized controlled trials which look at interventions for asthma management during pregnancy, one Cochrane review with no detectable differences from current practice
- Recent study- Managing Asthma in Pregnancy (MAP) trial looked at an inflammation based management strategy to reduce exacerbations by measuring exhaled nitric oxide fraction of the airway in addition to ACQ score
- There was a 50% reduction in exacerbations in the exhaled nitric oxide group compared to control (ACQ only)
- Infants were followed at 12 months and those from exhaled nitric oxide group had less reported recurrent bronchiolitis or croup
Goals of therapy

- Maintain control of asthma for maternal well being and fetal growth
- Asthma control
  - Minimal or no chronic daytime or nocturnal symptoms
  - Minimal or no exacerbations
  - No activity limitation
  - Maintain normal pulmonary function
  - Minimal use of short acting Beta$_2$- agonist
  - Minimal or no adverse medication effects
### Table 1. Assessment of Asthma Control in Pregnant Women.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Well-Controlled Asthma</th>
<th>Asthma Not Well Controlled</th>
<th>Very Poorly Controlled Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of symptoms</td>
<td>≤2 days/wk</td>
<td>&gt;2 days/wk</td>
<td>Throughout the day</td>
</tr>
<tr>
<td>Frequency of nighttime awakening</td>
<td>≤2 times/mo</td>
<td>1–3 times/wk</td>
<td>≥4 times/wk</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>None</td>
<td>Some</td>
<td>Extreme</td>
</tr>
<tr>
<td>Use of short-acting β-agonist for symptom control</td>
<td>≤2 days/wk</td>
<td>&gt;2 days/wk</td>
<td>Several times/day</td>
</tr>
<tr>
<td>FEV(_1) or peak flow (% of the predicted or personal best value)</td>
<td>&gt;80</td>
<td>60–80</td>
<td>&lt;60</td>
</tr>
<tr>
<td>Exacerbations requiring use of systemic corticosteroid (no.)</td>
<td>0–1 in past 12 mo</td>
<td>≥2 in past 12 mo</td>
<td></td>
</tr>
</tbody>
</table>

* Data are from the National Asthma Education and Prevention Program.\(^{24}\) The level of control is based on the most severe category. The frequency and effect of symptoms should be assessed according to the patient’s recall of the previous 2 to 4 weeks. FEV\(_1\) denotes forced expiratory volume in 1 second.
Conclusions

- Asthma during pregnancy continues to be an important health concern for the mother and fetus
- Guidelines recommend active monitoring and management
- A multidisciplinary approach is important to ensure the best outcomes for mother and fetus


