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 in Pregnancy

- Asthma affects ~8% of pregnant women
- Variable course of asthma in pregnancy
  - One-third experience an improvement in symptoms
  - One-third experience worsened symptoms
  - One-third experience no changes
- Each individual may also experience variation in symptoms throughout the pregnancy
- Poor asthma control during pregnancy has been shown to contribute to increased rates of both fetal and maternal adverse effects

Asthma In Pregnancy

Hayley Blackburn, Pharm.D.
Why the variation?
• Complex changes during pregnancy can have a number of effects on asthma symptoms during pregnancy

1. Pulmonary changes
2. Hormonal changes
3. Immunological changes

Pulmonary Changes
• A number of physiological changes of pregnancy result in increases in dyspnea and may contribute to perception of changing symptoms during pregnancy
  - Elevation in diaphragm as uterus expands results in decreases in FRC
  - Minute-ventilation increases up to 50% as a result of elevations in progesterone

Hormonal Changes
• Changing levels of cortisol may lead to anti-inflammatory activity, improvement in asthma symptoms
• Elevations in estrogen may increase airway mucus
• Elevations in progesterone may result in smooth muscle relaxation
  - May help open airways
  - BUT... may also increase gastroesophageal reflux
• Interrelationship between hormonal changes and immunological changes
• Appears there may also be a difference in maternal symptoms based on fetal gender
  - Fewer symptoms with male fetus
  - Increase in symptoms with female fetus
Immunological Changes

- Immune responses are normally modified during pregnancy to allow for feto-maternal tolerance and normal gestation
- In healthy patients, changes include:
  - Increased regulatory T cells
  - Shift from a Th1-predominant to a Th2-predominant immune response
- In asthmatic patients, immune responses may differ when compared to healthy controls:
  - Decreased regulatory T cell responses, resulting in increased inflammation
  - Exaggerated Th2 responses, leading to worsening of asthma symptoms
- Evidence suggests that the degree of asthma control and immunological changes have a bidirectional relationship
  - Abnormal Th2 response is not observed in those with well-controlled asthma; similar response to healthy controls
  - Those with poorly controlled asthma have exaggerated immune response

Asthma in Pregnancy: Adverse Outcomes

- Large body of evidence consistently shows poorly controlled asthma associated with significantly increased risk of adverse outcomes
- Most evidence suggests non-significant differences between healthy controls and those with well-controlled asthma (both maternal and fetal outcomes)

- Maternal outcomes
  - Increased rates of preeclampsia, pregnancy-induced hypertension, gestational diabetes, premature labor/delivery, C-section and postpartum bleeding in those with poor asthma control
### Pregnancy-Associated Morbidity by Severity Classification

<table>
<thead>
<tr>
<th>Asthma Exacerbation</th>
<th>Schatz et al 2003 (n=873)</th>
<th>Murphy et al 2005 (n=43)</th>
<th>Schatz et al 2005 (n=52)</th>
<th>Murphy et al 2006 (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma exacerbated</td>
<td>110 (12.6%)</td>
<td>5 (9%)</td>
<td>209 (25.7%)</td>
<td>16 (47%)</td>
</tr>
<tr>
<td>Unscheduled</td>
<td>99 (11.3%)</td>
<td>4 (6.3%)</td>
<td>157 (19.3%)</td>
<td>14 (41%)</td>
</tr>
<tr>
<td>Oral corticosteroid</td>
<td>19 (2.2%)</td>
<td>0 (0%)</td>
<td>71 (8.7%)</td>
<td>4 (11.8%)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>20 (2.3%)</td>
<td>2 (3.2%)</td>
<td>55 (6.6%)</td>
<td>4 (11.8%)</td>
</tr>
</tbody>
</table>

Significance noted in comparison to preceding severity group (mild to moderate; severe to mild).

### Asthma in Pregnancy: Fetal Adverse Outcomes

- **Fetal outcomes**
  - Increased rate of preterm delivery (<37 weeks), low birth weight (<2.5 kg), intrapartum growth restriction, congenital malformations and fetal mortality

- **Biggest challenge:** separating impact of maternal asthma from effects of medications when looking at resultant fetal malformations
  - Low overall rate of congenital malformations in general population (<3%) requires very large studies (~12,000 women) to detect small differences in rates of major malformations
  - Quality of study design is variable—healthy controls? stratification by asthma severity, medication use? where to get data?

### Acute Asthma Exacerbations in Pregnancy

- 20-30% of women will experience an asthma exacerbation during their pregnancy
- ~10% will require hospitalization
- ~1% will require intensive care/unit admission
- Most exacerbations occur during the 25th-36th weeks of pregnancy, with lower risk during the peripartum period
Management of Acute Asthma Exacerbations in Pregnancy

- Follow standard treatment guidelines for emergency treatment:
  1. Initial treatment:
     - O2 supplementation
     - Inhaled albuterol every 20 minutes up to three times in the first hour
  2. Supplemental treatment:
     - If severe → ipratropium 500 mcg (inhaled) or terbutaline (subcutaneous or IV) may be used as a supplement to the above
     - Corticosteroids (oral or IV) may be used if:
       - Inadequate response to bronchodilators in ED
       - Patient has required multiple short-courses of steroids throughout pregnancy
       - OR if already receiving oral corticosteroids prior to presentation to ED
     - Systemic epinephrine should be avoided

- If adequate response within 4 hours, patient may be discharged
  - Short course (5-10 days) of oral prednisone 40-80 mg/day recommended

- Hospitalization is recommended if patient meets any of the following criteria:
  - Unable to maintain O2 sat >95% on room air after medication administration
  - FEV1 or PEF are persistently <70%
  - Fetal distress is evident

- If life threatening (significant hypoxemia, hypercapnia, respiratory acidosis, maternal respiratory fatigue, and/or fetal distress), intubation and mechanical ventilation may be required

Management of Asthma in Pregnancy

- Goals and principles of management in pregnancy are similar to those for non-pregnant women
- Importance of appropriate management is emphasized by the data regarding adverse fetal and maternal outcomes
- Despite this, pregnant women are more likely to be undertreated versus non-pregnant women with asthma for any given severity
- Reasons include:
  - Lack of education
  - Lack of monitoring
  - Hesitation to prescribe medications
  - Patient non-adherence
Monitoring

• Correlation between baseline asthma severity and risk of exacerbation
  - Study of 1739 pregnant women with asthma found at least one exacerbation during pregnancy in:
    • 13% of those with mild asthma at baseline
    • 16% of those with moderate asthma at baseline
    • 52% of those with severe asthma at baseline
  - BUT baseline severity is not entirely predictive
    - Findings from the same study:
      • 30% of those with mild to moderate asthma progressed to severe asthma
      • 23% of those with severe asthma improved to mild to moderate category
  - Important to closely monitor regardless of baseline asthma severity
    • Spirometry or peak flow
    • Validated questionnaire assessing control (ACT, ACQ)

Patient Education

• As with nonpregnant patients, education is an important component of asthma management
  - Proper use of medications/devices
  - Control of environmental factors
  - Management of comorbid conditions
  - Development of an asthma action plan
  - Education can also improve patient knowledge of risks, self-monitoring and medication compliance— all especially important in pregnancy
    - In one recent study, 70% of pregnant women were unaware of the risks of uncontrolled asthma in pregnancy and 32% discontinued medication use without consulting a healthcare provider

Immunizations and Comorbid Conditions

• Immunizations:
  - Annual influenza
  - Pneumococcal vaccine prior to pregnancy

• Comorbid conditions:
  - Smoking cessation
  - Treatment of rhinitis
  - Treatment of GERD
Medication Safety in Pregnancy

- Information regarding the safety of asthma medications in pregnancy can be difficult to interpret

1. Difficult to tease out effects of medications from effects of disease
   - Those with more severe asthma use more medications...BUT are the adverse effects observed due to asthma or medication use?
   - Studies use healthy non-asthmatic women as controls

2. Conflicting evidence or lack of evidence

3. Information is largely observational and retrospective, often relies on maternal reporting, pulling information from databases

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### Stepwise approach to asthma therapy in pregnant and nonpregnant patients

<table>
<thead>
<tr>
<th>Step</th>
<th>Preferred Therapy in Nonpregnant Patients</th>
<th>Preferred Therapy in Pregnant Patients</th>
<th>Alternative Therapy in Pregnant Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SABA, as needed*</td>
<td>SABA, as needed*</td>
<td>N/A</td>
</tr>
<tr>
<td>2</td>
<td>Low-dose ICS</td>
<td>Low-dose ICS</td>
<td>LTRA</td>
</tr>
<tr>
<td>3</td>
<td>Low-dose ICS + LABA</td>
<td>Medium-dose ICS</td>
<td>LTRA</td>
</tr>
<tr>
<td>4</td>
<td>Medium-dose ICS + LABA</td>
<td>Low-dose ICS + LABA</td>
<td>Medium-dose ICS + LABA, LTRA</td>
</tr>
<tr>
<td>5</td>
<td>High-dose ICS + LABA</td>
<td>Medium-dose ICS + LABA, or High-dose ICS + LABA, or High-dose ICS + LABA</td>
<td>LTRA + theophylline, Omalizumab</td>
</tr>
<tr>
<td>6</td>
<td>High-dose ICS + LABA + Oral corticosteroids</td>
<td>High-dose ICS + LABA + Oral corticosteroids</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*SABA should be included as quick acting bronchodilator at all steps of severity in all patients

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### Bronchodilators

- Short-acting bronchodilators (SABAs)
  - Lots of evidence
  - Most studies do not demonstrate any significant increase in adverse effects with their use in pregnancy and breastfeeding
  - Those studies that do demonstrate significant differences use healthy non-asthmatic women as controls
  - Consensus these medications are thought to be safe, and should be used per guidelines to treat intermittent shortness of breath
<table>
<thead>
<tr>
<th>Medication</th>
<th>US FDA Pregnancy Category</th>
<th>Australian Drug Evaluation Pregnancy Category</th>
<th>German Pregnancy Risk Category</th>
<th>Lactation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albuterol</td>
<td>C</td>
<td>A</td>
<td>--</td>
<td>Likely safe</td>
</tr>
<tr>
<td>Levalbuterol</td>
<td>C</td>
<td>A</td>
<td>--</td>
<td>Unknown</td>
</tr>
<tr>
<td>Terbutaline</td>
<td>C</td>
<td>A</td>
<td>--</td>
<td>Likely safe</td>
</tr>
</tbody>
</table>

**Bronchodilators**

- Long-acting bronchodilators (LABAs)
  - Data is very limited
  - Retrospective cohort study (Eltonsy et al): nonsignificant trend towards increased major congenital malformations as a whole with LABA use, but significantly increased risk for specific malformations:
    - Major cardiac malformations (aOR = 2.38, 95% CI: 1.13-5.0)
    - Genital organ malformations (aOR = 4.45, 95% CI: 1.54-12.10)
    - All other/unspecified malformations (aOR = 3.97, 95% CI: 1.29-12.20)
  - Other studies did not demonstrate significant increase in risk with LABA use, but small studies, lack of data
  - Consensus: LABAs should only be used if asthma control cannot be achieved using medium-dose inhaled corticosteroids and SABAs

<table>
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<tr>
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<th>German Pregnancy Risk Category</th>
<th>Lactation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formoterol</td>
<td>C</td>
<td>B3</td>
<td>Group 4</td>
<td>Unknown</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>C</td>
<td>B3</td>
<td>Group 5</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
Corticosteroids

- Inhaled corticosteroids (ICS)
  - Most studies support safety of ICS use in pregnancy
  - Lots of data, but comparative studies between ICS medications and/or doses are lacking
    - Budesonide = pregnancy category B: only due to the fact that this ICS was studied specifically in one study and found to be safe
    - In those studies that have tried to differentiate between specific ICS, no significant differences have been found
      - Studies looking at doses have found nonsignificant trends, but also very difficult to differentiate between disease severity and medication use
    - Low systemic absorption minimizes exposure to fetus (and via breastfeeding)
    - Consensus: ICS decrease the risk of maternal asthma exacerbations without increasing risk to mother or fetus should be used as guidelines recommend, no true preference between different ICS although budesonide looks to be “safer” if only considering pregnancy category

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<tr>
<th>Medication</th>
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<th>German Pregnancy Risk Category</th>
<th>Lactation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone</td>
<td>C</td>
<td>B3</td>
<td>Group 3</td>
<td>Unknown</td>
</tr>
<tr>
<td>Budesonide</td>
<td>B</td>
<td>A</td>
<td>Group 3</td>
<td>Unknown</td>
</tr>
<tr>
<td>Ciclesonide</td>
<td>C</td>
<td>B3</td>
<td>--</td>
<td>Unknown</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>C</td>
<td>B3</td>
<td>Group 5</td>
<td>Unknown</td>
</tr>
<tr>
<td>Mometasone</td>
<td>C</td>
<td>B3</td>
<td>Group 5</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Corticosteroids

- Systemic corticosteroids
  - Data demonstrates higher incidence of maternal adverse effects, including preeclampsia and gestational diabetes
  - Possible increase in risk of malformations
    - Again, must consider disease severity versus medication use
  - Consensus: avoid use if possible, use only if patient is unable to achieve control using other agents; short course if patient presents with acute exacerbation
**Medication** | **US FDA Pregnancy Category** | **Australian Drug Evaluation Committee Pregnancy Category** | **German Pregnancy Risk Category** | **Lactation™**
--- | --- | --- | --- | ---
**Systemic Corticosteroids**
Dexamethasone | C | A | -- | Likely safe
Methylprednisolone | C | A | Group 3 | Likely safe
Prednisone | C | A | Group 3 | Likely safe

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**Leukotriene Receptor Antagonists**

- **Leukotriene Receptor Antagonists (LTRAs)**
  - Limited data, further studies needed
  - One study: use of montelukast in first trimester was associated with increased rate of low birth weight, premature labor and fetal distress when compared to healthy non-asthmatic controls
  - RCT in those that continued montelukast beyond the first trimester and throughout the pregnancy, no increase in adverse effects was noted

Consensus: LTRAs are likely safe (or at least benefit > risk); if choosing a LTRA, montelukast preferred over zafirlukast due to more evidence of safety in pregnancy and lactation
Theophylline

- Rarely used, but may have place in therapy for select patients
- Studies have not demonstrated any significant difference in rates of adverse effects associated with theophylline use
- Consensus: likely safe, may be used if needed

Biological Treatments

- Omalizumab (monoclonal antibody)
  - Reserved only for those with moderate to severe asthma unable to be controlled by medium- to high-dose ICS plus LABA therapy
  - Evidence for safety of use is limited (new agent, very little use in pregnancy to date)
  - Current pregnancy registry: Xolair® Pregnancy Registry (EXPECT)
  - Of 128 births:
    - 16% premature
    - 7% low birth weight (<2.5 kg)
    - 4% major birth defects
  - Must consider that this agent is reserved for more severe asthma, and thus differentiating effects of disease versus drug is difficult
  - Currently FDA category B based upon animal studies

Stepwise approach to asthma therapy in pregnant and nonpregnant patients

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<th>Step</th>
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<th>Persistent Asthma</th>
</tr>
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</tr>
<tr>
<td>3</td>
<td>LABA, Medium-dose ICS</td>
<td>Medium-dose ICS</td>
</tr>
<tr>
<td>4</td>
<td>Medium-dose ICS + LABA</td>
<td>Low-dose ICS + LABA</td>
</tr>
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<td>Medium-dose ICS + LABA, or High-dose ICS + LABA</td>
</tr>
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<td>6</td>
<td>High-dose ICS + LABA + Oral corticosteroid</td>
<td>High-dose ICS + LABA + Oral corticosteroid</td>
</tr>
</tbody>
</table>

*SABA should be included as quick-acting rescue medication to be used as needed in all patients.
Conclusions

- Asthma is a common condition in pregnancy and can have serious implications for both maternal and fetal outcomes.
- Disease course is not always predictable; frequent monitoring and optimization of treatment regimen is very important.
- Education is key: patients should be educated on risks associated with poor control and appropriate self-management, nonpharmacologic interventions.
- Despite provider/patient hesitation to use medications, it appears that most asthma medications are relatively safe to use in pregnancy and that benefits associated with improved asthma control outweigh risks associated with medication use.

References