Asthma in Pregnancy

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Introduction

- Asthma is the most common potentially serious medical problem to complicate pregnancy
- Asthma may worsen during pregnancy
- Maternal asthma increases the risk for perinatal complications
- Better asthma control during pregnancy is associated with improved perinatal outcomes
Goals of Asthma Management During Pregnancy

- Control maternal asthma
- Optimize health of the fetus
  - Asthma control
  - Optimal asthma medication choices

Outline of Presentation

- Background
  - Effect of asthma on pregnancy
  - Safety of asthma medications during pregnancy
- Management Recommendations
  - Components of management
  - Assessment
  - Pharmacological management
  - Overcoming barriers
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Increased Risks Defined in Meta-analyses

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of Studies</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preeclampsia</td>
<td>15</td>
<td>1.54 (1.32-1.81)</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>18</td>
<td>1.41 (1.23-1.62)</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>13</td>
<td>1.46 (1.22-1.75)</td>
</tr>
<tr>
<td>SGA</td>
<td>11</td>
<td>1.22 (1.14-1.31)</td>
</tr>
<tr>
<td>Neonatal death</td>
<td>6</td>
<td>1.49 (1.11-2.00)</td>
</tr>
<tr>
<td>Malformations</td>
<td>12</td>
<td>1.11 (1.02-1.21)</td>
</tr>
</tbody>
</table>

Murphy, et al. BJOG 2011; 118:1314 and BJOG 2013; 120:812
**Adverse Perinatal Outcomes in Asthmatic Women:**

**Potential Mechanisms**

- Common pathogenesis
- Confounding
- Poor asthma control
  - Hypoxia
  - Reduced uteroplacental blood flow
  - Placental dysfunction
- Asthma medications

**Common Pathogenesis**

- Factors (e.g. immunologic, inflammatory, other pathophysiologic) affect both asthma and reproductive functions
- Difficult to provide empiric data to evaluate
Confounding

- Smoking
- Race/ethnicity
- Obesity
- Depression

Asthma Control

- Better control (based on symptoms, pulmonary function, exacerbations) associated with improved perinatal outcomes
  - Spontaneous abortion
  - LBW
  - Preterm birth
  - SGA
  - Congenital malformations
- Relationship can’t be proven by RCTs (random assignment to controlled versus not controlled)
Adverse Perinatal Outcomes in Asthmatic Women: Potential Mechanisms

• Common pathogenesis
• Confounding
• Poor asthma control
  – Hypoxia
  – Reduced uteroplacental blood flow
  – Placental dysfunction
• Asthma medications

Short-Acting Beta Agonists

• Substantial reassuring data from large retrospective and prospective cohorts
• Some reports of increased specific malformations in case-control studies, but potential confounding by asthma control/exacerbations
• One report of increased risk of autism in case-control study, but potential confounding by asthma severity/control (Gidaya, et al. Pediatrics 2016; 137:e20151316)
• Benefits outweigh possible risks
• Albuterol most studied
Inhaled Corticosteroids (ICS)

- Substantial safety data for low and medium dose ICS
- Possible associations with high dose ICS from retrospective database studies may be confounding by severity
- Budesonide most studied but
  - No data suggest other inhaled corticosteroids are unsafe
  - Recent reassuring data for Fluticasone

Fluticasone versus Budesonide

- Number of pregnancies
  - Fluticasone: 3190
  - Budesonide: 608
- Low birth weight
  - OR 1.08 (CI 0.76-1.52)
- Preterm birth
  - OR 1.07 (0.78-1.49)
- Small for gestational age
  - OR 1.10 (0.85-1.44)

## Fluticasone versus Other ICS: Any Major Congenital Malformation (MCM)

<table>
<thead>
<tr>
<th>Treatment Intensity</th>
<th>ICS</th>
<th>Number of Pregnancies</th>
<th>Absolute Risk of MCM</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>Fluticasone</td>
<td>328</td>
<td>2.4%</td>
<td>1.1 (0.5-2.3)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>2598</td>
<td>2.3%</td>
<td>(ref)</td>
</tr>
<tr>
<td>Severe</td>
<td>Fluticasone</td>
<td>1274</td>
<td>2.7%</td>
<td>1.2 (0.7-2.0)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>1080</td>
<td>2.3%</td>
<td>(ref)</td>
</tr>
</tbody>
</table>


## Long-Acting Beta Agonists

- Less data than for ICS or SABA
- Recent reassuring data (low birth weight, preterm birth, SGA) from retrospective cohort studies for both salmeterol and formoterol (1,2)
- Reports of increased risk of specific malformations from case-control studies may reflect confounding by severity

Large Cohort Linkage Study
• 519,242 pregnancies in Norway, Wales and Denmark
• Evaluated any anomalies and 36 specific anomalies
• Drug classes evaluated (259 total comparisons)
  – Any asthma medication
  – Inhaled beta-2 agonists
  – Short-acting beta-2 agonists
  – Long-acting beta-2 agonists
  – Inhaled corticosteroids
  – ICS/LABA
  – Systemic corticosteroids

Garne, et al. BJOG 2016; 123:1609

Large Cohort Linkage Study
• Elevated odds ratios (95 % CI)
  – Any asthma medication and any major anomaly: 1.21 (1.09-1.34)
  – ICS and anal atresia: 3.40 (1.15-10.04)
  – ICS/LABA and severe heart defects: 1.97 (1.12-3.49)
  – SABA and renal dysplasia: 2.37 (1.20-4.67)
• Conclusions
  – Support the overall safety of asthma medications during pregnancy
  – Increased risks identified may be chance (multiple comparisons) and/or residual/unmeasured confounding
**Leukotriene Receptor Antagonists**

- Less data than for ICS
- Most data for montelukast
- Reassuring data from small cohort studies
- Reassuring data regarding montelukast and congenital malformations from large retrospective database study (1,535 exposed infants)


**Omalizumab**

- EXPECT is a single arm observational study to evaluate pregnancy outcomes in women exposed to omalizumab
- Report of 188 pregnant women exposed to omalizumab during their first trimester since 2012
- No increased risk of major congenital malformations
- Insufficient power to address specific malformations
- Rate of preterm birth and small for gestational age similar to rates reported in other studies for pregnant women with severe asthma

More Recently Approved Medications for Asthma

• Tiotropium
  – Animal studies showed no malformations at 800 times the maximum human daily dose
  – No human data

• Mepolizumab
  – No evidence of fetal harm in monkeys treated with IV administration of up to 30 times the maximum human dose
  – No human data
  – Pregnancy exposure registry

More Recently Approved Medications for Asthma

• Reslizumab
  – No teratogenic or embryofetal effects in mice and rabbits given 6 and 17 times, respectively, the maximum human dose
  – No human data

• Benralizumab
  – No evidence of fetal harm in monkeys at doses approximately 310 times the human dose
  – No human data
**Oral Corticosteroids**

- Associated in some studies with preeclampsia, prematurity, and oral clefts
- Potential confounding by disease severity
- Benefits outweigh risks when needed

**Outline of Presentation**

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  - Overcoming barriers
Management of Asthma During Pregnancy

Four Components of Therapy

- Assessment and Monitoring
- Reduction of triggers
- Patient education
- Pharmacologic therapy

NAEPP. *J Allergy Clin Immunol* 2005; 115:36

Multidisciplinary Approach to Management of Maternal Asthma (MAMMA)

- Pharmacist led intervention
- Asthma education
- Trigger avoidance
- Smoking cessation support (when needed)
- Monthly monitoring (ACQ, FEV₁, exacerbations, medications)
- Action plans
- Interaction with family physician (e.g. action plan, step up therapy)

Lim, et al. *Chest* 2014; 145:1046
### MAMMA: Mean ± SD ACQ Results

<table>
<thead>
<tr>
<th>Time</th>
<th>Intervention (n = 29)</th>
<th>Control (n = 29)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>1.43 ± 0.93</td>
<td>1.28 ± 0.95</td>
<td>0.56</td>
</tr>
<tr>
<td>6 months</td>
<td>0.54 ± 0.32</td>
<td>1.10 ± 0.67</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Baseline to 6 months</td>
<td>-0.89 ± 0.98</td>
<td>-0.18 ± 0.73</td>
<td>0.003</td>
</tr>
</tbody>
</table>

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Asthma Control Domains (NAEPP)

- Impairment
- Risk

Assessment of Asthma Control: Impairment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Well-controlled</th>
<th>Not well-controlled</th>
<th>Very poorly controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sx frequency</td>
<td>≤ 2 days/week</td>
<td>&gt; 2 days/week</td>
<td>Throughout the day</td>
</tr>
<tr>
<td>Nocturnal Sx</td>
<td>≤ 2 times/month</td>
<td>1-3 times/week</td>
<td>≥ 4 times/week</td>
</tr>
<tr>
<td>β agonist use</td>
<td>≤ 2 days/week</td>
<td>&gt; 2 days/week</td>
<td>Several times/day</td>
</tr>
<tr>
<td>Activity interference</td>
<td>None</td>
<td>Some</td>
<td>Extreme</td>
</tr>
<tr>
<td>FEV₁/PEF</td>
<td>&gt; 80 %</td>
<td>60-80 %</td>
<td>&lt; 60 %</td>
</tr>
</tbody>
</table>

Schatz and Dombrowski, NEJM 2009; 360:1862
Impairment: Asthma Control Test

- Validated for use during pregnancy
- Correlated with NAEPP and GINA measures of asthma impairment
- Correlated with spirometry


Asthma Control: Risk

- Number of exacerbations requiring oral corticosteroids in the prior year
- Two or more represents uncontrolled asthma
Asthma Control: Fractional Exhaled Nitric Oxide (FENO)

- Exhaled breath measurement
- Measures nitric oxide that is produced by the human lung
- Elevated levels reflect eosinophilic airway inflammation
- Elevated levels suggest likely response to inhaled corticosteroids

Managing Asthma in Pregnancy (MAP) Study

- Double blind parallel group RCT
- 220 pregnant asthmatic women
- Algorithm based on ACQ and FENO
  - Inhaled corticosteroids increased with inadequate control and high FENO
  - Formoterol increased with inadequate control and low FENO
  - Inhaled corticosteroids decreased with adequate control and low FENO

Incidence of Exacerbations Over Time

Control group: rate = 0.615
FENO group: rate = 0.288
IRR = 0.499
SE = 0.107
p = 0.001

Comparison of Treatment Profiles

Control
FENO

% ICS LABA
**Comparison of ICS Doses**

![Graph showing comparison of ICS doses between Control group and FENO group across visits.](image)

**FENO Study Conclusions**

- FENO may allow more targeted, more effective, and safer management of asthma during pregnancy
- This will require confirmation in further studies in other settings
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Asthma Step Therapy During Pregnancy

• Consider adherence, inhaler technique, or trigger reduction as target for therapy

Schatz and Dombrowski. *NEJM* 2009; 360:1862
**Preferred Controller Step Therapy for Asthma During Pregnancy**

- Based on benefit-risk considerations
- Controller Step Therapy
  - Step 1: None
  - Step 2: Low dose ICS
  - Step 3: Medium dose ICS or Low dose ICS + LABA
  - Step 4: Medium dose ICS + LABA
  - Step 5: High dose ICS + LABA
  - Step 6: High dose ICS + LABA + prednisone

Schatz and Dombrowski. *NEJM* 2009; 360:1862

**Asthma Step Therapy During Pregnancy**

- Step up one step for women with not well-controlled asthma
- Step up two steps, oral prednisone, or both for women with very poorly controlled asthma

Schatz and Dombrowski. *NEJM* 2009; 360:1862
2004 NAEPP Recommendations for Specific Medications During Pregnancy

- Short-acting beta agonist: albuterol
- Inhaled corticosteroid: budesonide
- Long acting beta agonist: salmeterol

Current Specific Medication Recommendations

- Budesonide or Fluticasone for women starting ICS in pregnancy
- Continue other ICS if providing control
- Decision regarding salmeterol versus formoterol can be based on non-pregnancy considerations
Other Medications

- **Montelukast**: alternative for mild persistent asthma or alternative add-on therapy to ICS, especially for patients who have shown a favorable response before pregnancy
- **Tiotropium**: consider for patients with uncontrolled asthma on medium or high dose ICS/LABA

Other Medications

- **Omalizumab**: continue in patients with a good response before pregnancy
- **Other biologics**: continue in patients with severe asthma and a definite response before pregnancy
- Encourage your patients to participate in registries
  - omalizumab (http://www.xolairpregnancyregistry.com)
  - mepolizumab (www.mothertobaby.org/asthma)
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Barriers to Asthma Control

• Smoking
  – Associated with increased exacerbations
• Clinician under-treatment
  – Documented in ED
• Adherence
  – Substantial proportion of women reduce medications
  – Common cause of exacerbations
• Viral infections
  – Most common cause of exacerbations
• Obesity
Potential Barrier: Rhinitis

- Commonly associated with asthma during pregnancy
- Change in course often concordant with change in asthma course during pregnancy
- Associated with poorer asthma control and quality of life
- May interfere with sleep and reduce quality of life during pregnancy in its own right


Oral Antihistamines

- Reassuring prospective cohort human data for loratadine and cetirizine
- No association with specific birth defects in large case control study (1)
  - Diphenhydramine
  - Loratadine
  - Chlorpheniramine
  - Doxylamine

**Intranasal Antihistamines**

- **Azelastine** – no human data but animal studies reassuring at oral doses 15 times maximum human dose
- **Olapatadine** – no human data, but oral doses of 100 times maximum human dose associated with reduction in number of live fetuses and reduction in birth weight

**Decongestants**

- All available oral decongestants have been associated with specific birth defects in some studies
- Reassuring specific malformation data for pseudoephedrine (1283 exposures) in recent large case control study (1)
- Association in that study of specific birth defects with phenylephrine, phenylpropanolamine, and possibly oxymetazoline/xylometazoline

Intranasal Corticosteroids

- Presumed safe due to *inhaled* corticosteroid data
- Recent large prospective cohort study
  - No increased risk of spontaneous abortion or small for gestational age infants
  - Association of triamcinolone with infant respiratory defects, but may be due to chance
  - No association of fluticasone (n = 912) or mometasone (n = 1127) with specific birth defects, in spite of more frequent exposure than triamcinolone (n = 318)


Rhinitis Management Conclusions

- Loratadine or cetirizine would be antihistamines of choice
- Avoid intranasal antihistamines unless essential for severe symptoms
- Avoid decongestants in first trimester, but pseudoephedrine would be decongestant of choice if essential
- Budesonide, Fluticasone or Mometasone if starting intranasal steroids during pregnancy; others may be continued if effective
Immunotherapy

• Reassuring data from two small and old studies of SCIT
  – 121 pregnancies in 90 women (1978)
  – 109 pregnancies in 81 women (1993)
• Reassuring data from one more recent small study of SLIT
  – 185 pregnancies in 155 women (2012)
• Anaphylaxis is a particular risk during pregnancy

Use of Immunotherapy (IT) for Asthma or Rhinitis During Pregnancy

• Continue IT in women
  – Already receiving IT
  – Who are deriving benefit
  – Who have not been prone to systemic reactions
  – At maintenance or effective dose
  – Consider prophylactic dose reduction
Use of Immunotherapy (IT) for Asthma or Rhinitis During Pregnancy

• Generally do not start IT
  – Uncertain propensity for systemic reactions
  – Increased likelihood of systemic reactions during SCIT initiation
  – Latency of effect
  – Uncertainty of benefit, especially for asthma

Asthma and Pregnancy
Conclusions

• Uncontrolled maternal asthma may increase the risk of adverse perinatal outcomes
• Recommended asthma medications have reassuring safety data during pregnancy
• Optimal guideline-based management of asthma during pregnancy should minimize the risks and optimize the health of both the mother and the baby
• Barriers to asthma control must be addressed for optimal outcomes