Managing Asthma and Allergy During Pregnancy

Michael Schatz, MD, MS
Department of Allergy
Kaiser Permanente Medical Center
San Diego, CA
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  – Merck
  – GlaxoSmithKline
  – AstraZeneca
Learning Objectives

• Examine the data available regarding the safety of asthma and allergy medications during pregnancy

• Provide optimal management for asthma and other allergic diseases during pregnancy
Conditions To Be Discussed

• Asthma
• Rhinitis
• Anaphylaxis
• Chronic Urticaria/Angioedema
• Hereditary Angioedema
• Atopic Dermatitis
For Each Condition

- Optimum avoidance therapy, education, and follow-up assumed
- Potential maternal and fetal consequences of uncontrolled condition during pregnancy
- Review of pregnancy safety data of relevant medications
- Practical medication recommendations
### Asthma: Increased Risks Defined in Meta-analyses

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of Studies</th>
<th>Result</th>
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</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>
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<tr>
<td>SGA</td>
<td>11</td>
<td>1.22 (1.14-1.31)</td>
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<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
Question 1

• Which of the following is true regarding asthma control during pregnancy?
  – A. Randomized controlled trials show that better asthma control is associated with fewer pregnancy complications
  – B. Observational data suggest that there is no relationship between pulmonary function in asthmatic women and pregnancy outcomes
  – C. The risk of congenital malformations does not appear to be related to asthma control
  – D. The risk of spontaneous abortion has been shown to be related to asthma control
  – E. Asthma exacerbations only increase the risk of preterm birth
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
- Two reports of increased risk of autism spectrum disorder and one report of increased risk of cerebral palsy in female offspring, but potential confounding by asthma severity/control
- 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>
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</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>Fluticasone</td>
<td>328</td>
<td>2.4 %</td>
<td>1.1 (0.5-2.3)</td>
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<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>
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<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

Cossette, et al. *Ann Allergy Asthma Immunol* 2014; 112:459
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
DOI: 10.1111/1471-0528.14026
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 residual and 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)

Oral Corticosteroids (OCS)

- OCS are frequently used during asthma exacerbations when patients are already taking other asthma medications.
- Cohort studies have reported associations between OCS and preeclampsia, preterm delivery, preterm birth, and low birth weight, but potential confounding by severity/control/exacerbations.
- Conflicting data regarding association with cleft lip/palate.
- Benefits outweigh potential risks when indicated.
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 those reported 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
More Recently Approved Medications for Asthma

- **Dupilumab**
  - No evidence of fetal harm in pregnant monkeys at doses up to 10 times the maximal human dose
  - No published human studies
  - “Available data from case reports and case series...have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes”
Asthma Management Conclusions

• Step therapy as per current guidelines
• Budesonide or Fluticasone for women starting ICS in pregnancy; continuation of others 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](http://www.xolairpregnancyregistry.com))
  - mepolizumab ([www.mothertobaby.org/asthma](www.mothertobaby.org/asthma))
Role of FENO: 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

ICS LABA

%
Comparison of ICS Doses

Mean ICS Dose (µg/day)

Control group

FENO group

Visit

p=0.043
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
Question 2

Which of the following have NOT been associated with worse asthma control or exacerbations specifically during pregnancy?

- A. Active maternal smoking
- B. Passive smoke exposure
- C. Viral infections
- D. Reducing asthma medications
- E. All of the above have been associated
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
Conditions To Be Discussed

• Asthma
• **Rhinitis**
• Anaphylaxis
• Chronic Urticaria/Angioedema
• Hereditary Angioedema
• Atopic Dermatitis
Rhinitis

- No direct effect of rhinitis on perinatal outcomes
- Snoring associated with increased risk of preeclampsia
- Interference with sleep and reduced quality of life not optimal during pregnancy
- Shown to be associated with poorer asthma control and quality of life during pregnancy (1)

Question 3

• Which of the following is true regarding the safety of rhinitis treatment during pregnancy?
  – A. Data regarding second generation antihistamines are inadequate to recommend their use during pregnancy
  – B. All oral decongestants are equally safe
  – C. Reassuring human data exist for intranasal antihistamines during pregnancy
  – D. The available data suggest that budesonide, fluticasone, or mometasone would be good choices if starting intranasal steroids during pregnancy
  – E. There are extensive gestational safety data available for both SCIT and SLIT
Oral Antihistamines

- Reassuring prospective cohort human data for loratadine and cetirizine
- No association with birth defects in large case control study
  - 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.

• 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 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**
  - Patient already receiving IT
  - Patient deriving benefit
  - Has 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 IT initiation
  - Latency of effect
  - Uncertainty of benefit, especially for asthma
Question 4

Which of the following is true regarding the management of other allergies during pregnancy?

- A. Ephedrine is a better choice than epinephrine to treat anaphylaxis during pregnancy due to an association of epinephrine with birth defects and decreased uteroplacental blood flow
- B. Based on studies in pregnant women, the management of chronic urticaria during pregnancy is the same as in non-pregnant patients
- C. Human plasma-derived C1 esterase inhibitor is the treatment of choice for HAE during pregnancy
- D. Fetal growth restriction has been reported with use of mild-moderate potency topical corticosteroids during pregnancy
- E. Human data are reassuring regarding the use of Dupilumab for atopic dermatitis during pregnancy
Conditions To Be Discussed

- Asthma
- Rhinitis
- **Anaphylaxis**
- Chronic Urticaria/Angioedema
- Hereditary Angioedema
- Atopic Dermatitis
Anaphylaxis

• Has been associated with maternal death, fetal death or both during pregnancy
• May be associated with infant neurologic abnormalities
• Expeditious treatment is essential to prevent adverse maternal or fetal outcomes
Epinephrine

- Associated with birth defects in some studies, but may be confounding by indication.
- Has the potential to reduce uteroplacental blood flow.
- Still the drug of choice since there is no equally effective substitute, and observations in pregnant women with anaphylaxis suggest benefits outweigh risks.
Other Aspects of Anaphylaxis Treatment During Pregnancy

- Position the patient on her left side to prevent compression of the aortocaval vessels by the gravid uterus
- Give high flow supplemental oxygen to support fetal oxygenation
- Maintain a minimum maternal systolic blood pressure of 90 mm Hg
- Fetal heart rate monitoring
- Diphenhydramine and corticosteroids may be used as in non-pregnant patients
Conditions To Be Discussed

- Asthma
- Rhinitis
- Anaphylaxis
- Chronic Urticaria/Angioedema
- Hereditary Angioedema
- Atopic Dermatitis
Chronic Urticaria/Angioedema

- No direct effect on perinatal outcomes
- Interference with sleep and reduced quality of life not optimal during pregnancy
- No studies on the use of antihistamines, montelukast, omalizumab, or oral corticosteroids specifically for urticarial/angioedema
- Recommendations based on previously presented data for these drugs
Chronic Urticaria/Angioedema

Treatment

• Start with loratadine or cetirizine (higher than usual doses not studied during pregnancy)
• Consider diphenhydramine or chlortrimeton at night
• Consider hydroxyzine if above fails
• Consider trial of montelukast
• Consider omalizumab for refractory symptoms
• Prednisone for severe symptoms
Conditions To Be Discussed

- Asthma
- Rhinitis
- Anaphylaxis
- Chronic Urticaria/Angioedema
- Hereditary Angioedema
- Atopic Dermatitis
Hereditary Angioedema (HAE)

- One study reported an increase in the rates of spontaneous abortions and premature labor in women with HAE compared to their healthy relatives (1)
- Course of HAE is variable during pregnancy
- HAE attacks are rare during labor and delivery but may increase in frequency post-partum and during breast-feeding

Hereditary Angioedema

- Reassuring data on the use of human plasma-derived C1 esterase inhibitor during pregnancy from retrospective cohort data (1) and case reports, but no controlled studies.
- Case reports of successful use of Icatibant during pregnancy.
- No human data on other specific treatments.

Hereditary Angioedema: Consensus Recommendations

- Human plasma-derived C1 esterase inhibitor is treatment of choice for
  - Long term prophylaxis
  - Short-term prophylaxis
  - Acute therapy

Conditions To Be Discussed

- Asthma
- Rhinitis
- Anaphylaxis
- Chronic Urticaria/Angioedema
- Hereditary Angioedema
- Atopic Dermatitis
Atopic Dermatitis

- No direct effect on perinatal outcomes
- Interference with sleep and reduced quality of life not optimal during pregnancy
- No studies on the use of antihistamines or oral corticosteroids specifically for urticarial/angioedema
- Recommendations based on previously presented data for these drugs
Topical Corticosteroids

- UK General Practice Research Database Study (n = 84,133 pregnant women)
  - A previously reported association with oral clefts was not confirmed
  - No increased risk of fetal death or preterm birth
  - Increased risk of fetal growth restriction in women receiving potent/very potent preparations
  - NO increased risk of fetal growth restriction in women receiving mild/moderate potency preparations

Other Common Atopic Dermatitis Treatments

- Antihistamines based on previously reviewed data
- Prednisone based on previously reviewed data
- Limited human data for topical calcineurin inhibitors
- Ultraviolet light B phototherapy considered safe
- Penicillins, cephalosporins, erythromycin considered safe based on human data
Dupilumab

- No evidence of fetal harm in pregnant monkeys at doses up to 10 times the maximal human dose
- No published human studies
- “Available data from case reports and case series...have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes”
Treatment of Atopic Dermatitis: First Line

- Emollients
- Mild-moderate potency topical corticosteroids
  - Betamethasone valerate 0.025%
  - Clobetasone butyrate 0.05%
  - Fluocinolone acetonide 0.00625%
  - Hydrocortisone 0.1-2.5%
Treatment of Atopic Dermatitis: Antihistamines

- Start with loratadine or cetirizine
- Consider diphenhydramine or chlortrimeton at night
- Hydroxyzine if above fails to control itching along with other therapy
Treatment of Atopic Dermatitis: Other

- Ultraviolet light B phototherapy
- Penicillin, cephalosporin or erythromycin for concomitant infection
- Higher potency topical corticosteroids administered to smallest necessary area for shortest necessary time
- Prednisone for severe flare
- Calcineurin inhibitors for localized recalcitrant area
- Consider Dupilumab for recalcitrant disease
Asthma and Allergy During Pregnancy

Conclusions

• Uncontrolled maternal asthma may increase the risk of adverse perinatal outcomes
• Anaphylaxis is a risk for both mother and baby
• Other allergic conditions may reduce quality of life during pregnancy
• Most recommended asthma and allergy medications have reassuring safety data during pregnancy
• Optimal guideline-based management of asthma and allergic diseases during pregnancy should minimize the risks and optimize the health of both the mother and the baby