Disclosures

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Learning Objectives

1. Identify knowledge gaps regarding the safety of asthma and allergy medications during pregnancy

2. Optimize use of the information provided by the new FDA pregnancy labeling system for providing counseling to pregnant patients

3. Explain the role of VAMPSS in providing new information for the pregnancy label and filling in knowledge gaps regarding the safety of asthma and allergy medications during pregnancy
The safety of asthma and allergy medications during pregnancy: Knowledge Gaps

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CSHP October 28, 2016
Importance of Understanding Asthma During Pregnancy

• Most common potentially serious medical problem to complicate pregnancy
• May increase the risk of perinatal complications
• Optimal management improves maternal and fetal outcomes
Gaps in Knowledge

- Number of controlled trials addressing efficacy and safety of medication used for asthma during pregnancy is extremely limited.
- Attempts to separate the effects of asthma alone from the effects of asthma medications on pregnancy outcomes has been difficult.
## Effect of Asthma on Pregnancy

<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

• Poor asthma control
  – Hypoxia
  – Reduced uteroplacental blood flow
  – Placental dysfunction

• Asthma medications
Commonly used asthma and allergy medications

- Fluticasone, albuterol, salmeterol and montelukast are the most commonly prescribed asthma medications
- Diphenhydramine, loratadine, pseudoephedrine, and cetirizine are the most commonly used allergy medications
Safety of short acting beta agonists (SABA)

- Substantial reassuring data – from larger retrospective and prospective cohorts which assessed asthma severity and control
- Conflicting results from small case control studies where disease severity was assessed only based on medication use.

**CONCLUSION:**
- SABA appear to be safe but there still may be specific risks.
- Challenge is to design a study that will be large enough and consider asthma severity/control as well as other medications used.
Safety of long acting beta agonists (LABA)

• May carry an increased risk of congenital malformations – bias by indication?
• Outcomes (LBW, preterm, SGA) similar between
  – Salmeterol versus Formoterol
• Risk of major malformations similar with a LABA plus ICS combination and ICS monotherapy at higher doses.
• Conclusion:
  – Further investigation is required.
  – LABA are prescribed for more severe asthma symptoms. As a result, asthma severity may be an important confounder
Safety of inhaled corticosteroids

• Concerns raised regarding the use of high dose inhaled corticosteroids during pregnancy and risk of perinatal mortality, congenital malformations, preterm birth, LBW, SGA

• In the majority of studies, the effects of asthma versus the effects of asthma medication were not addressed

• No data suggest ICS other than Budesonide are unsafe

• No reason to switch ICS in patients controlled on an ICS other than Budesonide

• Conclusion:
  – Substantial reassuring data – especially budesonide, and most recently, fluticasone propionate, for low to medium dose inhaled corticosteroid therapy.
  – Safety of high dose inhaled corticosteroids needs further investigation.
  – The risks associated with non-adherence to inhaled corticosteroids pose a much greater risk
Safety of oral corticosteroids

- OCS are frequently used during asthma exacerbation 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.
- Several case control studies have shown that OCS was associated with cleft lip +/- palate.
- Conclusion:
  - Difficult to separate the effects of asthma exacerbation or OCS use (or other medication use) and outcomes.
  - The benefits outweigh the risk.
Safety of Leukotriene receptor antagonists (LTRA)

• Small prospective study of 96 women who used montelukast showed increased rate of congenital malformations in LTRA group - but no consistent pattern

• Multicenter, prospective, comparative study of 180 montelukast exposed pregnancies vs ICS- No increased risk of congenital malformations

• Retrospective insurance claims cohort analysis of more than 50,000 pregnancies - malformations were reported at rates similar to ICS and that of the general population

• Conclusion:
  – Less data but reassuring.
  – Consider if a patient demonstrates a clinical response prior to pregnancy
Safety of Omalizumab (Xolair)

- EXPECT is a single arm observational study to evaluate pregnancy outcomes in women exposed to omalizumab
- 188 pregnant women exposed to omalizumab during their first trimester
- No increased risk of major congenital malformations
- Insufficient power to address specific malformations
- External comparator group

**Conclusion:**
- Rate of preterm birth and small for gestational age similar to those reported for pregnant severe asthmatics.
Safety of Newer asthma medications

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

• Mepolizumab
  – Prenatal and postnatal development study in animals – no fetal harm with IV administration of 30 times the exposure of maximum human doses
  – No human data
  – Pregnancy exposure registry – Mother to Baby
Safety of Decongestants –

- Available in topical nasal sprays and oral preparation

- **Pseudoephedrine** – association with gastroschisis, limb reduction defects, hemifacial microsmia and small intestinal atresia in some case control studies

- **Phenylpropanolamine** – increase in total and specific congenital malformations in one study; ear defect - case control

- **Phenylephrine** – associated with club foot, eye and ear malformations; endocardial cushion defects - case control

- A prospective study of over 2000 women, no increased risks of teratogenic effects in the group using oral decongestants, which included pseudoephedrine

- **Oxymetazoline** - some reassuring human data but possible uteroplacental insufficiency at higher doses

- **Conclusion**: Pseudoephedrine is the agent of choice in the second and third trimesters in women without hypertension.
Safety of oral antihistamines

• Sloane Epidemiology Center Birth Defects Study

• Diphenhydramine, Hydroxyzine, chlorpheniramine
  – no increase in congenital malformation

• Fexofenadine – active metabolite of terfenadine has been associated with dose related weight gain in animal studies

• Conclusion:
  – Most appropriately treated with a second generation agent, because these drugs are less sedating and have fewer cholinergic side effects compared with first generation agents.
  – Reassuring prospective cohort human data for loratadine and cetirizine
Safety of Intranasal corticosteroids -

- Data is largely extrapolated from inhaled corticosteroids therefore budesonide is Category B
- No important differences in efficacy or safety appear to exist between the various intranasal glucocorticoid preparations
Safety of Intranasal Corticosteroids – Recent Update

- Population based prospective cohort study
- Intranasal triamcinolone exposed vs other intranasal CS exposed vs nonexposed
- Intranasal triamcinolone use associated with an increased risk of respiratory defects (OR, 2.71; 95% CI, 1.11-6.64)
- Intranasal fluticasone and mometasone were not associated with any adverse outcomes
Safety of Intranasal Corticosteroids – Recent Update

• Limitations
  – Confounding factors

• Strengths –
  – Large pregnancy cohort
  – Well validated database
  – Confounding by indication limited
  – Size
Safety of Intranasal antihistamines

• **Azelastine** – animal studies reassuring at oral doses, 15 times maximum human dose.

• **Olapatadine** – at oral doses of 100 times maximum human dose – reduction in number of live fetuses, and reduction in birth weight in animal studies.

• **Conclusion**: Inadequate safety data in humans.
Bridging the Gap

- Database studies
- Adverse event reports
- Pregnancy registries
- VAMPPS
Conclusion

- Asthma during pregnancy has been associated with risk of adverse perinatal outcomes
- Poor asthma control and severe asthma has been associated with adverse perinatal outcomes
- The available data for most asthma medications is generally reassuring
- Medication non adherence should be regularly assessed to avoid worsening control of asthma during pregnancy
- More data are needed for all classes of asthma medications to answer remaining questions and assure safety