Asthma and Pregnancy

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Reported Complications of Pregnancy due to Asthma

- Preterm labor
- Preterm delivery
- Small for gestational age
- Low birth weight
- Preeclampsia
- Gestational diabetes
- Congenital malformations
- Fetal or neonatal death

Reported Complications of Pregnancy due to Asthma in 8 Recent Prospective Studies (n = 4411)

- Preterm labor (if asthma severe or on OCS)
- Small for gestational age (Only with daily symptoms)
- Preeclampsia (only with daily symptoms)
- Gestational diabetes (only if asthma severe)
- Cesarean section (Moderate/severe asthma or elective)
- Congenital malformations (No)
- Fetal or neonatal death (No)

Dombrowski MP. Obstet Gynecol 2006;108:667-81
Effect of Maternal Moderate to Severe asthma on Perinatal Outcomes.

F Firoozi, et al. Respir Med 2010;104:1278-87

- From 3 Canadian databases information obtained on 1274 pregnancies in asthmatic women.
- Distribution of asthma severities and incidence of small for gestational age babies were:

<table>
<thead>
<tr>
<th>Severity</th>
<th>Prevalence</th>
<th>SGA</th>
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<tbody>
<tr>
<td>mild</td>
<td>82.6%</td>
<td>13.8%</td>
</tr>
<tr>
<td>moderate</td>
<td>12.4%</td>
<td>17.4% Sig</td>
</tr>
<tr>
<td>severe</td>
<td>5.0%</td>
<td>19.5% Sig</td>
</tr>
</tbody>
</table>
Pregnancy and Asthma

“The ultimate goal of asthma therapy during pregnancy is to maintain adequate oxygenation of the fetus by prevention of hypoxic episodes in the mother”

Dombrowski MP. Obstet Gynecol 2006;108:667-81
Pregnancy and Pulmonary Function

- The enlarging uterus elevates the diaphragm about 4 cm with reduction in FRC, but not in flows.
- Progesterone-mediated stimulation of the respiratory center produces a 50% increase in minute ventilation.
- Shortness of breath at rest or with mild exertion is common.

Dombrowski MP. Obstet Gynecol 2006;108:667-81
The Effect of Pregnancy on Asthma

- Conventional notion is that asthma in one-third gets better, in one third stays the same and in one-third gets worse.
- In a large prospective study 23% improved and 30% became worse.
- Asthma more likely to deteriorate in severe asthma (52-65%) than mild asthma (8-13%).

Schatz M et al. JACI 2003;112:283-8
Murphy V, et al Obstet Gynecol 2005;106:1045-4
The Asthma Exacerbations in Pregnancy

- A prospective observational study of asthma in pregnancy included 873 with mild asthma, 814 with moderate asthma, 52 with severe asthma and 881 non-asthmatic controls.

<table>
<thead>
<tr>
<th></th>
<th>Exacerbations</th>
<th>Hospitalizations</th>
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</thead>
<tbody>
<tr>
<td>Mild asthma</td>
<td>13%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Moderate</td>
<td>25%</td>
<td>6.9%</td>
</tr>
<tr>
<td>Severe</td>
<td>52%</td>
<td>26.9%</td>
</tr>
</tbody>
</table>

The Effect of Asthma Exacerbations in Pregnancy on the Fetus

- From 3 Canadian databases information obtained on 4,344 pregnancies of asthmatic women.
- Exacerbations in first trimester included oral corticosteroids, emergency department or hospital admission.
- With exacerbations OR for malformation in baby 1.48 (CI 1.04-2.09) for any and 1.32 (CI .86-2.04) for major.
- Exacerbation increases risk for low birth weight baby (OR 2.54)

Murphy VE Thorax 2006;61:169-76
MANAGEMENT OF ASTHMA DURING PREGNANCY

NATIONAL INSTITUTES OF HEALTH
National Heart, Lung, and Blood Institute
Pregnancy and the use of Inhaled Corticosteroids

- The NAEPP Working Group reviewed 10 studies including 6,113 patients who took inhaled corticosteroids during pregnancy.
- There was no evidence linking inhaled corticosteroid use and increases in:
  - Congenital malformations
  - Adverse perinatal outcomes

Dombrowski MP. Obstet Gynecol 2006;108:667-81
Pregnancy and the use of Inhaled Beta-Adrenergic Agonists

- The NAEPP Working Group reviewed 6 studies including 1,599 patients who took inhaled beta-agonists during pregnancy.
- Additional a prospective study examined beta-agonist use in 1,828 patients.
- There was no evidence of adverse pregnancy outcomes with inhaled beta-agonist use.

Dombrowski MP. Obstet Gynecol 2006;108:667-81
Pregnancy and the use of Oral Corticosteroids

- The NAEPP Working Group reviewed 8 studies of patients who took oral corticosteroids during pregnancy.
- OC use during the first trimester was associated with a 3-fold increased risk for isolated cleft lip.
- OC use in patients who have asthma was associated with increased risk for preeclampsia, preterm delivery and low birth weight, perhaps related to uncontrolled asthma.

Dombrowski MP. Obstet Gynecol 2006;108:667-81
Pregnancy and the use of Theophylline, LTRA, Cromolyn

- Cromolyn is considered without significant adverse reactions.
- Leukotriene receptor antagonists are Category B for pregnancy, but there is not extensive reported experience.
- Theophylline has frequent side effects, but was found safe in a review by the NAEPP of studies in 600 women.

Dombrowski MP. Obstet Gynecol 2006;108:667-81
Pregnancy and the Treatment of Rhinitis

- Intranasal corticosteroids are the most effective treatment.
- Oral or intranasal antihistamines are generally considered safe.
- Oral decongestants in the first trimester have been reported to be associated with gastroschisis. However, the Swedish Birth Register found no increased malformations (OR 0.96) with their use in >4,000 pregnancies.

Dombrowski MP. Obstet Gynecol 2006;108:667-81
Killien & Olausson AJOG 2006;194:480-5
Maternal Conditions as Risk Factors for Asthma in the Child

- **Dietary Factors:**
  - Low intake vitamin D & vitamin E
  - Intake of Mediterranean diet, oily fish and dairy products reported to be protective.
- Acetaminophen in 2nd and 3rd trimester a risk.
- Exposure to household cleaning products a risk
- Use of antibiotics in pregnancy a risk
- Cesarean section delivery a risk
- Maternal smoking a risk
- Farm exposure protective

Dombrowski MP. Obstet Gynecol 2006;108:667-81
Killien & Olausson AJOG 2006;194:480-5
Epigenetic Contributions to Asthma Phenotypes

- Early environmental exposures (particularly in utero) play a key role in activating or silencing genes by altering DNA and histone methylation, histone acetylation and chromatin structure.
- These changes are passed on to somatic daughter cells and are heritable across generations.

Martino and Prescott. Allergy 2010;65:7-5
Consequences of Low Vitamin D

- Vitamin D insufficient leads to dysfunctional T cell regulation with lack of down regulation of Th1 and Th2.
- Vitamin D participates in TLR signaling; deficiency may predispose to increased respiratory tract infections.

AA Litonjua & ST Weiss. JACI 2007;120:1031-5
Viral infections in infancy are a risk for school age asthma.

In two birth cohort studies low maternal vitamin D was associated with increased risk of wheezing at age 3 and 5 with population attributable risk of > 40%.

AA Litonjua & ST Weiss. JACI 2007;120:1031-5
Maternal Vitamin D intake During Pregnancy is Inversely Associated with Asthma and Allergic Rhinitis in 5-year-old Children.


- Finnish birth cohort (n = 1669).
  - Food frequency questionnaire during pregnancy
  - Children assessed at age 5-years.
- Maternal intake of vitamin D in food negatively associated with risk in offspring of:
  - Asthma (HR 0.80)
  - Allergic rhinitis (HR 0.85)
Objective: Assess the effects of maternal use of domestic chemicals during pregnancy on wheezing and lung function in children age up to 8.5 years.

Maternal composite household chemical exposure score (CHCE) derived during pregnancy.
Household Chemicals, Persistent Wheezing, and Lung Function: Effect Modification by Atopy?

- CHCE score was associated with:
  - Early (< 18 months) and Intermediate (18-36 months) persistent and Late (>30 month) wheezing in non-atopic children.
  - Decrements in FEV1 and FEF25-75%.

- Effects may result from prenatal development effects or post-natal irritant effects.

Odds Ratio for Wheezing Phenotypes by CHCE Z-Score

- **LOW**: Late-onset wheeze
- **IOP**: Intermediate onset persistent
- **IOT**: Intermediate onset transient
- **EOP**: Early onset persistent
- **EOT**: Early onset transient

**Never wheeze**

Risk of Asthma with Acetaminophen Use in Adulthood: Nurses’ Health Study
Barr et al. Am J Respir Crit Care Med 2004;169:836-41

- Prospective study (1990-6) of 48,028 nurses, mean age 57 years.
- > 14 days/month versus no use associated with OR 1.62 for development of physician diagnosed asthma.
Prenatal Acetaminophen Exposure and Risk of Wheeze at Age 5 years in an Urban, Low-Income Cohort

M Perzanowski, et al. thorax 2009

- Prenatal acetaminophen use predicted wheezing and atopy at age 5-years in a minority, New York cohort (n = 301)

<table>
<thead>
<tr>
<th>none</th>
<th>1d</th>
<th>2-4d</th>
<th>≥5d</th>
<th>p</th>
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<tbody>
<tr>
<td>wheezing 1.0</td>
<td>1.06</td>
<td>1.95</td>
<td>2.26</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Seroatopy 1.0</td>
<td>1.21</td>
<td>1.32</td>
<td>1.99</td>
<td>&lt;.001</td>
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</tbody>
</table>
The association of prenatal acetaminophen exposure and current wheezing (OR 2.08) & atopy (OR 1.96) at age 5 years was limited to children with GSTP1 AG or GG alleles.

- GSTT1 (present vs. null) associated with seroatopy (p < 0.001)
Association Between Acetaminophen Use, Wheezing age 5 years, and GSTP1 Polymorphisms

- GSTP1-01 AA (31%), Trend P = 0.65
- GSTP1-01 AG/GG (68%), Trend P < 0.001

Reported days prenatal acetaminophen exposure:

- None: 52
- 1 day: 143
- 2-4 days: 15
- 11 days: 22
- 25 days: 11
- 7 days: 2
- >5 days: 18

Prevalence of wheeze age 5 years:

- 0%

Perzanowski Thorax 2010

Reported days prenatal acetaminophen exposure

Prevalence of wheeze age 5 years
Asthma and Pregnancy

- Pregnancy has little effect on well-controlled asthma.
- Well-controlled asthma has little effect on the outcome of pregnancy.
- The drugs required to control asthma have no deleterious effect on the outcome of pregnancy.
- Many conditions during pregnancy can effect the likelihood of the offspring developing asthma and atopy.