Asthma in Pregnancy

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Disclosures

- No relevant disclosures

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

- Asthma is a heterogeneous disease characterized by airflow inflammation (GINA 2014)
- The inflammation can vary over time leading to variable airflow limitation
- It involves the presence of respiratory symptoms including
  - Dyspnea/shortness of breath
  - Wheeze
  - Cough

Airflow obstruction

- Airway narrowing can be caused by
  - Airway edema
  - Smooth muscle contraction
  - Airway thickening and fibrosis
  - Mucous production

Epidemiology

- Occurs in about 3-8% of pregnant women, one of the most common chronic diseases in pregnancy
- Increase in prevalence since the 1990s
- "Rule of 1/3": Approximately one-third of patients with asthma in pregnancy improve, one-third clinically worsen and one-third remain the same
- Women with more severe asthma at baseline are more likely to worsen

Epidemiology

- Exacerbations can occur at any time during the pregnancy, but most often between 17 and 34 weeks
- 26-30% of women will experience an asthma exacerbation during pregnancy
  - ~10% will require hospitalization
  - <1% will require intensive care/intubation
- Subsequent pregnancies often with similar effects of asthma

Maternal Risks

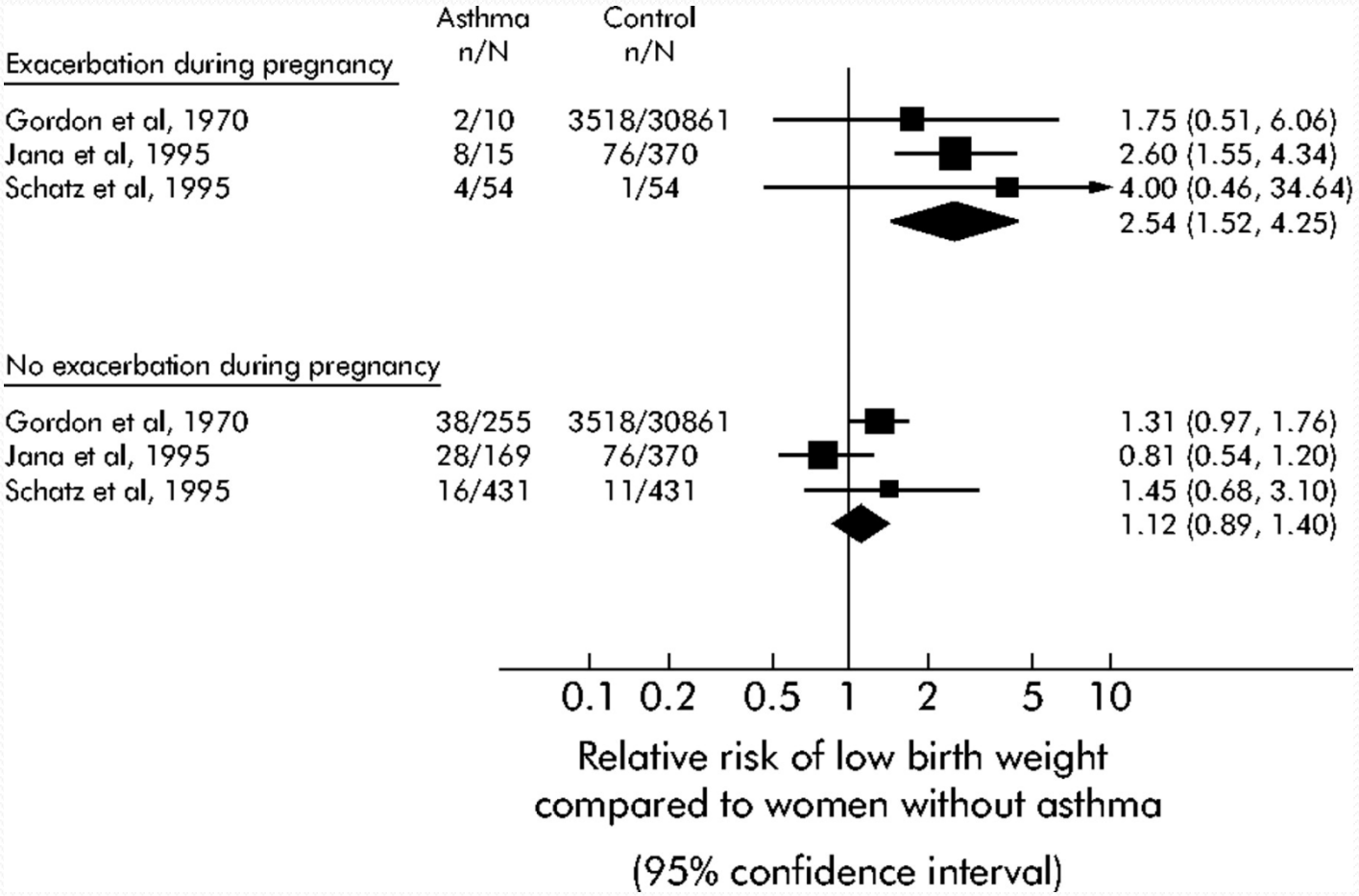
- Pre-eclampsia
- Hyperemesis gravidarum
- Placenta previa
- Uterine hemorrhage, post partum bleeding
- Gestational hypertension
- Gestational diabetes

- Risks factors for exacerbation:
  - Viral illness, stress, GERD, allergic rhinitis
  - Discontinuation of medications
  - Smokers

Fetal effects

- Low birth weight, SGA or IUGR
- Preterm birth
- Neonatal hypoxia

- If asthma is poorly controlled, associated with 15-20% increase in both maternal and fetal risks

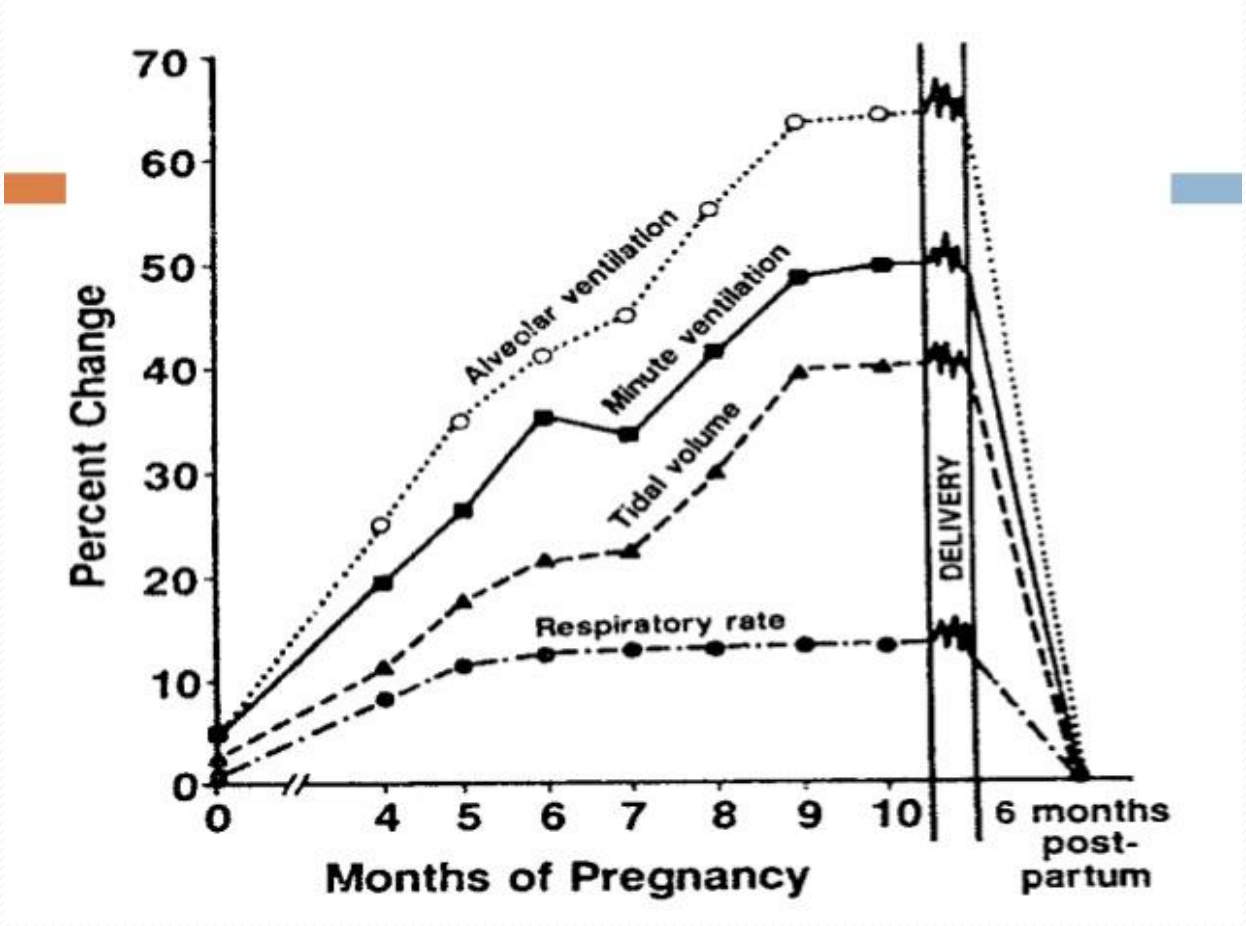

Asthma n/N
Control n/N
Exacerbation during pregnancy
Gordon et al, 1970 2/10 3518/30861 1.75 (0.51, 6.06)
Jana et al, 1995 8/15 76/370 2.60 (1.55, 4.34)
Schatz et al, 1995 4/54 1/54 4.00 (0.46, 34.64)
2.54 (1.52, 4.25)
No exacerbation during pregnancy
Gordon et al, 1970 38/255 3518/30861 1.31 (0.97, 1.76)
Jana et al, 1995 28/169 76/370 0.81 (0.54, 1.20)
Schatz et al, 1995 16/431 11/431 1.45 (0.68, 3.10)
1.12 (0.89, 1.40)
0.1 0.2 0.5 1 2 5 10
Relative risk of low birth weight compared to women without asthma
(95% confidence interval)

Respiratory Mechanics in Pregnancy

Respiratory Rate Vital Capacity	Unchanged Unchanged
Tidal Volume	Increased
Minute Ventilations	Increased
Minute Oxygen Uptake	Increased
Functional Residual Capacity	Decreased
Residual Volume of Air	Decreased
Airway Conductance	Increased
Total Pulmonary Resistance	Reduced

Pulmonary changes

- Tidal volume increases due to increased ventilatory drive
- Even as early as the first trimester, minute ventilation increases due to increased respiratory drive
- Elevation of the diaphragm as the uterus expands decreases the functional residual capacity

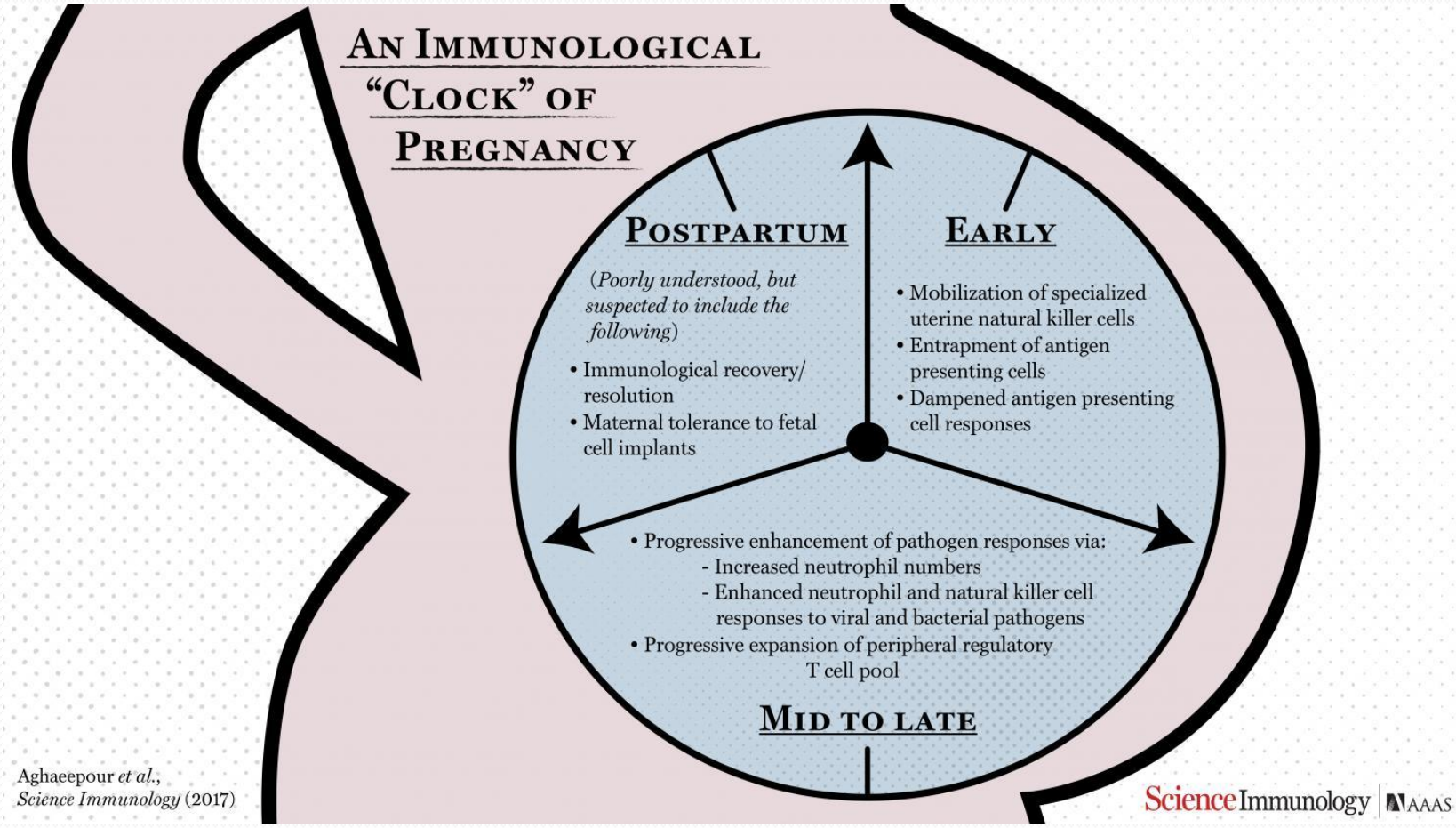

Percent Change
70
60
50
40
30
20
10
0
Alveolar ventilation
Minute ventilation
Tidal volume
Respiratory rate
DELIVERY
0
4
5
6
7
8
9
10
6 months post-partum
Months of Pregnancy

Hormonal changes

- Increased serum progesterone acts as a direct respiratory stimulant and can increase minute ventilation up to 50%, can increase gastroesophageal reflux symptoms as well
- Progesterone may also help with smooth muscle relaxation
- Increasing cortisol may be protective due to anti-inflammatory properties
- Increase in symptoms with female fetus perhaps due to hormonal variations? (i.e. estrogen may increase mucous production)

Immunologic changes

- Normal response in pregnancy to increase regulatory T cells and shift to a Th2 predominance from Th1
- Pregnant patients with asthma may induce less regulatory T cells with decreased surveillance and increased inflammation
  - Th2 response is exaggerated and asthma can worsen
  - If asthma is well controlled, the Th2 response does not seem to be as pronounced


AN IMMUNOLOGICAL "CLOCK" OF PREGNANCY
POSTPARTUM
(Poorly understood, but suspected to include the following)
• Immunological recovery/ resolution
• Maternal tolerance to fetal cell implants
EARLY
• Mobilization of specialized uterine natural killer cells
• Entrapment of antigen presenting cells
• Dampened antigen presenting cell responses
• Progressive enhancement of pathogen responses via:
- Increased neutrophil numbers
- Enhanced neutrophil and natural killer cell responses to viral and bacterial pathogens
• Progressive expansion of peripheral regulatory T cell pool
MID TO LATE
Aghaeepour et al., Science Immunology (2017)
Science Immunology | AAAS

Goals of Management

- Prevention of daytime and nocturnal symptoms
- Maintain normal activity
- Prevention of exacerbations
- Maintain fetal oxygenation

- Team approach with OB to ensure monitoring of asthma status

Monitoring

- Baseline spirometry
- Monthly evaluation of asthma history and pulmonary function (peak expiratory flow and spirometry if indicated)
- Consideration for serial ultrasounds at 32 weeks in patients with suboptimal control

Education

- Preconception education
- During pregnancy
  - Ensure appropriate inhaler technique and medication adherence
  - Assess environmental factors
    - Allergens and irritants
  - Asthma action plan
  - Management of co-morbid conditions
    - Rhinitis, sinusitis and gastroesophageal reflux
  - Importance of immunizations
    - Influenza vaccination annually
    - Pneumococcal vaccination prior to pregnancy

Classification of Severity

Components of Severity		Intermittent	Mild Persistent	Moderate Persistent	Severe Persistent
Impairment	Symptoms	<2 days/wk or less	>2 days/wk, not daily	Daily	Throughout the day
	Nighttime awakenings	<2 Xs/mth or less	>2 Xs per month	More than once a week	Four times per week or more
	SABA prn	<2 days/wk	>2 days/wk, not daily, not >1 X/day	Daily	Several xs/day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	Normal FEV_1 between exacerbations FEV_1>80% FEV_1/FVC normal	FEV_1>80% FEV_1/FVC normal	FEV_1>60%, but <80% FEV_1/FVC reduced 5%	FEV_1 <60% FEV_1/FVC reduced >5%
Risk	Exacerbations requiring oral steroids	0-1/yr	>2/yr		
Recommended Step for Initiating Treatment		Step 1	Step 2	Step 3	Step 4 or 5

Adapted from the NAEPP expert panel report

Management of Acute Exacerbation

- Similar to standard treatment guidelines
- Initial assessment: O2 supplementation, inhaled albuterol every 20 minutes up to three times in the first hour
- Severe symptoms: Add ipratropium 500 mcg (inhaled) or terbutaline (subcutaneous or IV)
- Add corticosteroids (oral or IV) if poor response to bronchodilators or patient had been receiving steroids prior to presentation

Management of Acute Exacerbation

- If patient responds to acute treatment within 4-6 hours, patient may be discharged with short course of oral prednisone 40-80 mg/day
- Hospitalization
  - Unable to maintain oxygenation >95% saturation on room air after medications given
  - FEV_1 or PEF remain persistently low (<70%)
  - Evidence of fetal distress
  - Evidence of significant hypercapnia, respiratory acidosis, maternal respiratory fatigue ---→ critical care setting/intubation

Management of Acute Exacerbation

- Pregnant women with asthma are more likely to be undertreated
  - Concern regarding appropriate medication management
  - Patient non-adherence to medications
  - Lack of knowledge surrounding the maternal and fetal outcomes
  - Poor monitoring
    - Regardless of baseline severity
    - Spirometry or peak flow
    - Validated control assessment

Bronchodilators

- Short acting bronchodilators/ short acting inhaled $beta_2$- agonists
  - Should be used per guidelines just as in non-pregnant individuals
  - Reassuring safety data, especially for albuterol

Bronchodilators

- Long acting bronchodilators
  - Limited data
  - Consensus: should be used if asthma control cannot be achieved using medium dose ICS and SABAs
  - Blais et. al J Allerg Clin Immunol Pract 2018;6:555-61
    - Examined whether exposure to LABA in addition to ICS increases risk of hypertensive disorders of pregnancy or preeclampsia/eclampsia as compared with non-exposure in pregnant patients with asthma
    - Results: rates were similar in women exposed or not exposed to LABAs
    - Safety of LABAs for treatment of asthma in pregnancy in terms or risks of hypertensive disorders of pregnancy and preeclampsia/eclampsia

Inhaled corticosteroids

- Reassuring evidence review on the safety of ICS
  - No studies which relate ICS use with increase in congenital malformations or adverse perinatal outcomes
- Risk of asthma exacerbations in pregnant patients are reduced and FEV1 improved with ICS
- Budesonide is pregnancy category B; likely due to the fact it was specifically studied
- Consensus: ICS use decreases risk of maternal asthma exacerbations and does not increase risk to mother or fetus. Use as guidelines recommend.
- No apparent difference between specific ICS

Systemic corticosteroids

- Use only if patient unable to achieve control with other medications; short course for acute exacerbations
- Data is conflicting
  - First trimester use of oral corticosteroids associated with increased risk for isolated cleft lip with our without cleft palate
  - Length of course and dose was not well described in these studies

Leukotriene Modifiers

- Montelukast and Zafirlukast as well as 5-LO pathway inhibitors (Zileuton)
- Reassuring animal studies for LTRAs
- Minimal data
- Weigh risks and benefits
  - Likely safe, if choosing one, montelukast preferred due to more evidence
  - Pregnancy category B

Theophylline

- Not commonly used
- Animal studies demonstrated adverse pregnancy outcomes with high dose
- Human studies confirm safety of theophylline at recommended doses (serum concentration 5-12 mcg/mL) during pregnancy
- In one RCT, no differences in asthma exacerbations or maternal or perinatal outcomes in theophylline vs. beclomethasone groups; but higher rate of reported side effects and medication non-adherence in theophylline group as well are more women with FEV1 less than 80%
- Pregnancy category C

Cromolyn

- 2 human studies, 318 patients on cromolyn
- Appears to be safe

Omalizumab

- For patients with moderate to severe asthma not controlled by medium to high dose ICS/LABA
- Category B

Schatz M, Dombrowski M. N Engl J Med 2009;360:1862-1869

Table 2. Steps of Asthma Therapy during Pregnancy.*

Step	Preferred Controller Medication	Alternative Controller Medication
1	None	—
2	Low-dose inhaled corticosteroid	LTRA, theophylline, or cromolyn
3	Medium-dose inhaled corticosteroid	Low-dose inhaled corticosteroid plus LABA, LTRA, or theophylline
4	Medium-dose inhaled corticosteroid plus LABA	Medium-dose inhaled corticosteroid plus either LTRA or theophylline
5	High-dose inhaled corticosteroid plus LABA	—
6	High-dose inhaled corticosteroid plus LABA plus oral prednisone	—

* Data are from the National Asthma Education and Prevention Program.[24,25] We have modified step 3 to reflect the choice of a medium-dose inhaled corticosteroid over a low-dose inhaled corticosteroid plus a long-acting β-agonist (LABA) because of the lack of safety data on the use of LABA during pregnancy. LTRA denotes leukotriene-receptor antagonist.

The NEW ENGLAND JOURNAL of MEDICINE

Interventions for improving asthma management during pregnancy

- Few randomized controlled trials which look at interventions for asthma management during pregnancy, one Cochrane review with no detectable differences from current practice
- Recent study- Managing Asthma in Pregnancy (MAP) trial- looked at an inflammation based management strategy to reduce exacerbations by measuring exhaled nitric oxide fraction of the airway in addition to ACQ score
- There was a 50% reduction in exacerbations in the exhaled nitric oxide group compared to control (ACQ only)
- Infants were followed at 12 months and those from exhaled nitric oxide group had less reported recurrent bronchiolitis or croup

Goals of therapy

- Maintain control of asthma for maternal well being and fetal growth
- Asthma control
  - Minimal or no chronic daytime or nocturnal symptoms
  - Minimal or no exacerbations
  - No activity limitation
  - Maintain normal pulmonary function
  - Minimal use of short acting $Beta_2$- agonist
  - Minimal or no adverse medication effects

Table 1. Assessment of Asthma Control in Pregnant Women.*

Variable	Well-Controlled Asthma	Asthma Not Well Controlled	Very Poorly Controlled Asthma
Frequency of symptoms	≤2 days/wk	>2 days/wk	Throughout the day
Frequency of nighttime awakening	≤2 times/mo	1–3 times/wk	≥4 times/wk
Interference with normal activity	None	Some	Extreme
Use of short-acting β-agonist for symptom control	≤2 days/wk	>2 days/wk	Several times/day
FEV_1 or peak flow (% of the predicted or personal best value)	>80	60–80	<60
Exacerbations requiring use of systemic corticosteroid (no.)	0–1 in past 12 mo	≥2 in past 12 mo	

* Data are from the National Asthma Education and Prevention Program.[24] The level of control is based on the most severe category. The frequency and effect of symptoms should be assessed according to the patient's recall of the previous 2 to 4 weeks. FEV_1 denotes forced expiratory volume in 1 second.

Schatz M, Dombrowski M. N Engl J Med 2009;360:1862-1869

Conclusions

- Asthma during pregnancy continues to be an important health concern for the mother and fetus
- Guidelines recommend active monitoring and management
- A multidisciplinary approach is important to ensure the best outcomes for mother and fetus

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