Asthma and Pregnancy

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Literature review current through June 2023
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Educational Objectives:

1. Review the interactions between asthma and pregnancy
2. Discuss the pharmacologic management of asthma during pregnancy & lactation
3. Review pregnancy risk categories of common asthma medications
4. Review management principles of asthma exacerbation during pregnancy
5. Discuss the management of smoking cessation and allergic rhinitis in the pregnant patient

Scenario:
Ms. M is a 23-year-old woman with a history of asthma. She is 26 weeks pregnant with her second child and is referred to you by OB for managing her asthma. She complains of increasing fatigue and dyspnea on exertion with 2 flights of stairs. She has never been hospitalized or intubated for asthma but was admitted for a brief stay for pneumonia 1 year ago and was found to have influenza B at that time. She uses albuterol as needed, which she currently requires twice daily. She smokes about 7 cigarettes a day and is trying to cut down. She is taking prenatal vitamins. She has not seen a pulmonologist and has Medicaid insurance pending secondary to her pregnancy. On ROS, she also complains of rhinitis, heartburn, lower extremity swelling and weight gain. In the office she is comfortable appearing. Her resting sat on room air is 97%. Her other vitals are within normal limits and the pulmonary exam is unremarkable. She has a gravid abdomen and trace lower extremity edema.

Question 1: What are the effects of pregnancy on the natural history of asthma, and how does asthma impact pregnancy? Are PFTs and peak flows reliable?

Asthma is one of the most common chronic medical conditions seen in pregnant women, impacting 8-9% of all pregnancies.[1]

The traditional teaching pearl is that 1/3 of asthma patients will worsen during pregnancy, 1/3 will stay the same, and 1/3 will improve. A woman is at the highest risk for exacerbation in the 2nd trimester, with a common cause of exacerbation being maternal or health care provider concerns surrounding asthma medications leading to reduction or complete cessation of therapy.[2]

In women who improved, the improvement was gradual as the pregnancy progressed.

- When asthma worsened, the increase in symptoms was most prominent between weeks 29-36.
- Asthma was generally less severe during the last four weeks of pregnancy.
- Substantial asthma symptoms were uncommon during labor and delivery.
- The course of asthma in successive pregnancies in an individual patient tended to be similar.

Physiologic changes in pregnancy[3]:

Measurement	***Change***
Forced vital capacity	None
Forced expiratory volume in 1 second	None
Minute ventilation	Increased by ~50%
Tidal volume	Increased by ~40%
Diaphragm elevation	~4cm near term
Total lung capacity, expiratory reserve volume, residual volume, functional residual capacity	All decreased

ABGs:

- Minute ventilation increases during pregnancy due to increased levels of progesterone and exceeds metabolic demands. This causes
    - Primary respiratory alkalosis
    - Compensatory renal loss of bicarbonate (decreased to 18-21)
    - Decreased $PaCO_2$ (typical range 28-30 mmHg) and an increased PaO_2(typical range 100-106 mm Hg)
- Normal pH during pregnancy is 7.4 to 7.45, with slightly elevated pO2 of 100-105 mmHg.
- A $PaCO_2$>35mmHg or a PaO_2<70 represents more severe compromise

Effect of Uncontrolled Asthma on Pregnancy

While a maternal diagnosis of asthma minimally increases the risk of maternal-fetal complications, this risk rises dramatically if maternal asthma is not controlled. A study of over 100,000 pregnant asthmatic women demonstrated a significantly higher risk of:

- Congenital malformations
- Preterm births
- Low birth weight
- Pregnancy-induced hypertension/pre-eclampsia
- Infant pneumonia/asthma[3]

Question 2: What are the safety data or potential adverse effects of commonly used maintenance therapy in asthma (i.e., short-acting beta-agonists (SABA), long-acting beta-agonists (LABA), and inhaled corticosteroids (ICS))? What about systemic corticosteroids? What about biologics? Are patients more likely to be adherent to medication therapy during pregnancy? What do these categories mean?

Approximately half of the pregnant women who were on asthma therapy before pregnancy are likely to ***stop or decrease*** their use of their asthma medications on their own or under the advice of a healthcare provider.[4]

General Take Home: Maintaining asthma control has been shown to benefit both mom and baby. Treatment of asthma is safer than uncontrolled asthma.[2]

Maintenance Medications[1] – SABA/LABA/ICS have minimal adverse effects on pregnancy and should be continued. Emphasis on non-pharmacologic control should also be maintained.

Albuterol– Most large studies have shown no increased risk of major birth defects. A few have shown a moderately increased risk of cleft lip/palate, gastroschisis, esophageal atresia, cardiac defects, or omphalocele.

LABA – Always used in combination with ICS due to the risk of sudden death in asthmatics taking a LABA as monotherapy. Preferred choices include Salmeterol and Formoterol. A study of 841 pregnant asthmatics taking a LABA with an ICS showed no increased risk of birth defects compared with those taking only an ICS.

ICS – A meta-analysis published in 2013 found no increase in stillbirth, congenital malformations, or rate of c-section in those with maternal ICS use vs. those without.

Because of the initial available human data from a Swedish cohort study, budesonide is considered the preferred ICS. Still, new data suggests that if a non-pregnant woman responds well to fluticasone, and it is indicated, it should be continued.[5]

Oral steroids – A recent US National Birth Defects Prevention study showed no increased risk for cleft lip/palate with the use of oral steroids in the first trimester. No other major birth defects were noted.

LAMA – Some animal studies have shown teratogenicity. There is currently no human data surrounding its safety in pregnancy.[6]

Leukotriene modifiers – Large studies have not demonstrated an increased risk of major birth defects in exposed pregnancies.

Biologics – All currently available biologics will cross the placenta. Omalizumab has the most data in pregnancy, with no concerns for teratogenicity. This is typically the preferred biologic in pregnancy as it has the most data. Animal studies of mepolizumab and bevacizumab have not shown any adverse outcomes, and limited data surrounding mepolizumab in human pregnancies have not demonstrated adverse maternal or fetal outcomes. Initiation while pregnant is not recommended due to the small risk of anaphylaxis with these medications.[3,7]

Question 3: How do you counsel your patient on SABA/LABA and ICS risks while breastfeeding?

In general, inhaled drugs do not result in significant systemic drug levels. Infant exposure to these medications through breastfeeding is markedly less than in utero. The amount ingested would generally be <3% of a weight-based therapeutic dose. Systemic steroids are not significantly excreted in breast milk, but to further reduce infant exposure avoiding feeds for a few hours after each dose could be considered.[8]

Question 4: What about smoking cessation therapy?

35-75% of women who smoke quit while pregnant.[9,10] Most who quit do so independently without intervention during the first trimester. Quitting early is best, but quitting any time is good. Evidence from 5 cohort studies shows no harm to fetuses resulting from smoking cessation interventions compared to mothers who smoked. This includes the following:

> **Behavioral Therapies:** A review of 97 study groups showed a statistically significant association with smoking cessation in later pregnancy with evidence that postpartum smoking abstinence continued for up to 18 months.
>
> **Nicotine replacement therapy** has no clear evidence of fetal harmfulness, but data are unclear. The NRT inhaler may be associated with birth weight, while the patch did not.[11]
>
> **Bupropion and Varenicline –** Cochrane Database meta-analysis in 2020 showed no evidence that buproprion was effective in smoking cessation in pregnancy, and minimal studies exist looking at safety data. Fewer placebo-controlled studies exist evaluating Varenicline.[12]

Question 5: What are the management principles during an acute asthma exacerbation in pregnancy?

The mean gestational age for acute asthma exacerbation is in the second trimester. Surprisingly, exacerbations during labor and delivery are not common.[3] Due to the increased minute ventilation during pregnancy, normal blood gas has a PaCO2 of 28-30. Therefore, PaCO2 >35 mmHg or PaO2 <70 mmHg during an acute asthma exacerbation indicates more severe impending respiratory failure.[13] The following interventions can be used:

1. Oxygen supplementation to keep O2 saturation > 95%.
2. Beta Agonists bronchodilators via MDI or nebulizers
3. Inhaled ipratropium
4. Systemic Glucocorticoids – Use is similar to nonpregnant patients, and benefits with risks should be balanced.
5. Intervenous Magnesium is well studied in pregnancy at 2gm over 20 minutes.
6. Subcutaneous terbutaline at 0.25mg every 20 minutes for 3 doses

Recommendation for treatment of acute asthma exacerbation in pregnant patients remains essentially the same as in nonpregnant adults, with the caveat that special attention should be paid to O2 saturations less than 95% to prevent fetal hypoxemia.

Question 6: What medications are effective for allergic rhinitis?

Glucocorticoid nasal sprays are highly effective for allergic rhinitis. Safety data is extrapolated from ICS data, and a large 2016 study confirms this.[14] First-generation oral histamines have significant safety data, especially chlorpheniramine. Among second-generation oral histamines, loratadine and cetirizine have reassuring human data.[15]

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Pre-test/Post-Test Questions:

1. Many physiologic changes occur in a woman's body during pregnancy. Which of the following is true regarding typical physiologic changes seen on PFTs:

    a. RV and FRC are typically decreased
    b. FEV1 typically decreases in the late 2nd and throughout the 3rd trimester
    c. FEV1/FVC ratio decreases
    d. VC increases

2. A 28-year-old female with a history of asthma is 22 weeks pregnant. She has a history of asthma and was previously well-maintained on inhaled steroids but has not been treated with regular inhaled therapies in the last 2 years. She reports a recent increase in symptoms, with symptoms on average 3 days a week. She denies any nighttime symptoms. She requires the use of her albuterol inhaler about 3 days a week. Which of the following would you recommend in terms of therapy?

    a. Initiate low-dose budesonide
    b. Defer initiation of inhaled steroids, given the risk to the fetus
    c. Continue albuterol as needed alone
    d. Start low dose fluticasone-salmeterol
    e. Start oral prednisone and monitor for symptom improvement

3. A 31-year-old female with a history of asthma is referred to you by OB/GYN to evaluate and treat her poorly controlled asthma. She is 2 weeks postpartum, and her delivery was uncomplicated. Her baby is home and doing well. She notes that she has had significant wheezing and chest tightness since starting with some upper respiratory viral symptoms a week prior. In your best assessment, she has an acute asthma exacerbation, but you believe she can be managed safely as an outpatient. You do not think she warrants antibiotics but requires additional medical therapy beyond her current albuterol PRN. Which of the following is FALSE regarding outpatient management of an asthma exacerbation in this patient?

    a. Inhaled steroids are likely compatible with this setting
    b. Oral/systemic prednisone concentrations are high in breast milk and should be avoided.
    c. She can safely continue her albuterol inhaler
    d. Influenza vaccines are safe to administer to the breastfeeding mother