Update on Asthma Management in Pregnancy

WHEC Practice Bulletin and Clinical Management Guidelines for healthcare providers. Educational grant provided by Women's Health and Education Center (WHEC).

The course of asthma during pregnancy is variable. Pregnancy can influence asthma severity in unpredictable ways with early studies suggesting that roughly equal proportions of women will worsen, improve or have unchanged asthma control during pregnancy. Evidence suggests the both chronic asthma, and acute asthma exacerbations remain undertreated in pregnancy. Recent landmark clinical trials in non-pregnant individuals have shown that, even for patients with mild disease, using as-needed inhaled corticosteroids combined with long-acting bronchodilators as rescue therapy dramatically reduces exacerbations. Clinicians should actively discourage discontinuation or de-escalation of asthma therapies during pregnancy and educate women on safety and importance of these medications for both themselves and their offsprings. Asthma exacerbations during pregnancy confer additional risk, so they must be promptly recognized and treated with systemic corticosteroids and bronchodilators. Asthma treatment recommendations have been updated in recent years after several landmark clinical trials demonstrated the benefits of inhaled corticosteroids-based regimens for all patients, even those with mild asthma. In addition, increasing use of biologic therapies in asthma raises questions about their role and safety in the treatment of severe asthma during pregnancy.

The purpose of this literature reviewed article (*WHEC Practice Bulletin*), is to provide an overview of asthma in pregnancy, with a focus on its potential adverse health effects and the core principles of asthma evaluation and treatment in pregnancy. This article also reviews the outcomes, evaluation, and treatment of asthma in pregnancy, with a focus on risk reduction through assessment of disease control and optimization of evidence-based asthma treatment strategies. Maternal asthma is associated with a number of adverse pregnancy outcomes that can affect the health of both pregnant mothers and their children. Despite advances in our understanding of asthma and its treatment, national surveys suggest that maternal asthma is often poorly controlled.

Prevalence

An analysis of U.S. health care claims database found the 16 – 28% of asthma is poorly controlled during pregnancy.[1] Asthma affects 3 – 10% of pregnant women in the U.S., and it is most common chronic respiratory disorder during pregnancy.[2] Among pregnant women with poor asthma control, up to 40-50% do not use any controller inhaler therapy.[3] Up to 40% of pregnant women report an asthma exacerbation in the past year, and nearly 20% experience and exacerbation requiring medical intervention.[4] A more recent study of 308 pregnant women found that 40% experienced worsened asthma control with pregnancy, and it did not identify any whose control improved. Subsequent pregnancies may follow a similar asthma for a majority of women.[5] Asthma treatment recommendations have been updated in recent years after landmark clinical trials demonstrated the benefit of inhaled corticosteroid (ICS)-based regimens for all patients, even those with mild asthma.

Definitions and Terminology

The terminology used to classify asthma severity and control varies depending on the context.
Disease control: it refers to the burden of asthma symptoms and risk of complications such as exacerbations and impaired lung function, which may be mitigated by treatment and other interventions.
Uncontrolled disease: it is that with a high symptom burden, frequent or serious exacerbations, or impaired lung function and may be related to inadequate treatment, comorbidities, environmental factors, or refractory disease.

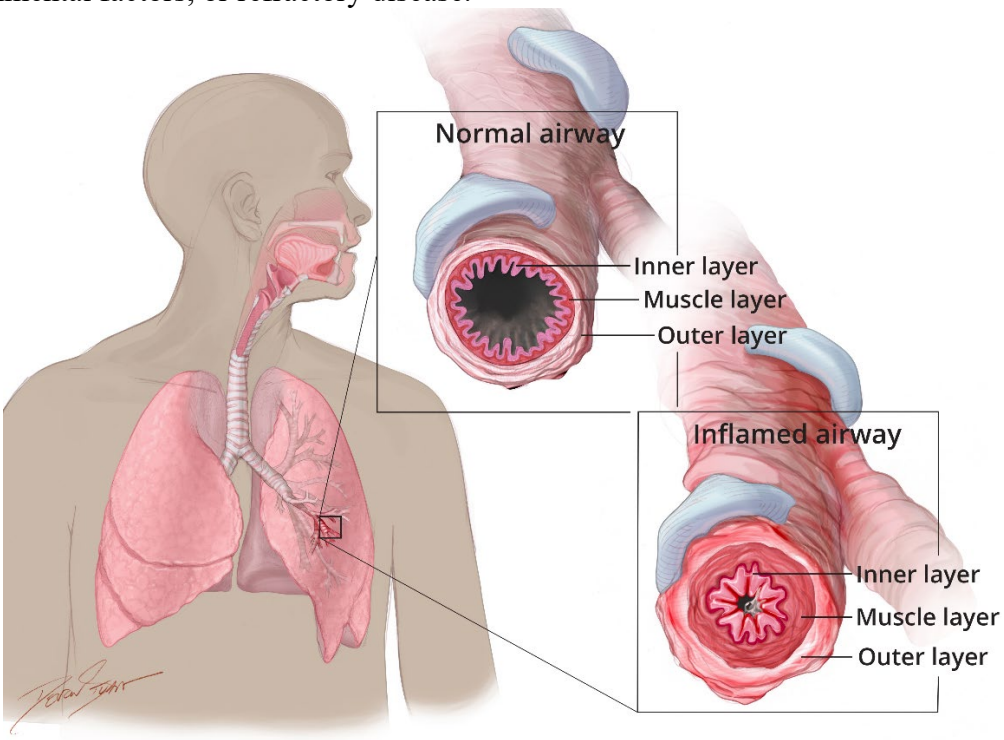

Figure 1. Airway in the lungs narrowing from an asthma attack. A normal airway is wide, compared with the narrowed, inflamed, airway typical of an asthma attack. (Source: National Heart, lung, and Blood Institute [NIH]).

Classification of asthma severity is defined by the intensity of treatment required to achieve disease control. These definitions are consistent with those used by national and international society guidelines.[6]
Mild Asthma: it refers to disease controlled by only as-needed therapy or low-dose daily inhaled corticosteroid (ICS).
Moderate Asthma: it is controlled with low- or medium-dose ICS plus long-acting β agonist (ICS-LABA) combination therapy.
Severe Asthma: it requires or remains uncontrolled by combination high-dose ICS-LABA therapy.

Pregnancy and Respiratory Physiology

During pregnancy, the respiratory system is influenced by numerous hormonal and mechanical changes. Progesterone and estrogen increase throughout gestation, affecting the respiratory

system in several important ways. Beginning in the first trimester, there is a marked increase in minute ventilation attributed predominantly to the central effects of progesterone, increasing the tidal volume of each breath.[7] As a result, serum carbon dioxide (CO_2) levels decrease, producing a chronic and compensated respiratory alkalosis, which facilitates off-loading of fetal CO_2. There is also a small increase in arterial oxygen tension, which compensates for increases in oxygen consumption and basal metabolic rate during pregnancy. Progesterone also affects the airways, exerting a mild bronchodilatory effect and causing hyperemia and edema of the airway mucosa.[7]

Pregnancy also changes respiratory system compliance through effects on the diaphragm and chest wall. As the gravid uterus expands, it causes an upward displacement of the diaphragm (up to 5 cm) and a resultant decrease in resting lung volumes. These effects are most pronounced during the third trimester. As a result of these normal changes, up to 70% of women endorse a sensation of dyspnea by 30 weeks of gestation. Often called "physiologic dyspnea of pregnancy," it is most pronounced during the third trimester. It is important to note that dyspnea of pregnancy is an isolated symptom, whereas dyspnea that occurs as part of asthma is typically paroxysmal and frequently accompanied by cough, chest tightness, wheezing, and responsiveness to rescue inhaler use.

Pathophysiology of Asthma

The pathophysiology of asthma is complex and varies significantly between patients. In general, airway inflammation causes bronchial smooth muscle constriction (*see figure 1)* and excessive mucus production, leading to luminal narrowing and obstruction. For some patients, often referred to as those with T-helper cell type-2 high or allergic asthma, this inflammation is driven by pathways that involve eosinophils and inflammatory mediators such as immunoglobulin E (IgE), interleukin (IL)-4, and IL-5.[8] Recognition of these inflammatory pathways has led to the development of targeted biologic therapies, which are increasingly used in the treatment of severe asthma.

Symptoms and Diagnosis

Symptoms are typically intermittent and include wheezing, cough, chest tightness, and dyspnea. They may be triggered by exposures such as allergens, smoke and other irritants, cold air, exercise, or respiratory viruses.[9] Symptoms at night can be worse or waking-up are common complaints in asthma.

Lung Function Testing in Pregnancy:

Lung function testing most commonly involves spirometry, which measures expiratory volumes and flows, and can include measurements of lung volumes and diffusion capacity for carbon monoxide. They do not change significantly with pregnancy. However, subtle changes can occur in the measurement of testing lung volumes in the second or third trimesters as result of upward displacement of the diaphragm by the gravid uterus, with mild reductions in functional residual capacity, expiratory reserve volume, and residual volume (*see figure 2*).[10] The total lung capacity does not change because of an increase in the inspiratory capacity during pregnancy.[10]

In active asthma, airflow obstruction causes a slowed and prolonged exhalation. This can be measured by spirometry, which shows a decrease in the air exhaled in the first second (forced expiratory volume in 1 second [FEV_1]) relative to the toral air exhaled (forced virtal capacity [FVC]), reducing the FEV_1:FVC ratio to less than 0.7. This can be visualized with a flow-volume loop that is characeristically drawn out or "scooped." In asthma, the obstruction may be reversible, as evidenced by a significant improvement in FEV_1 or FVC after the administration of inhaled bronchodilators. Lung volumes in asthma are typically normal, although they can increase in severe cases as a result of hyperinflation and air trapping. The diffusion capacity for carbon monoxide is normal or even increased in asthma.[11] The presence of variable airflow obstruction on spirometry is important in confirming a diagnosis of asthma.

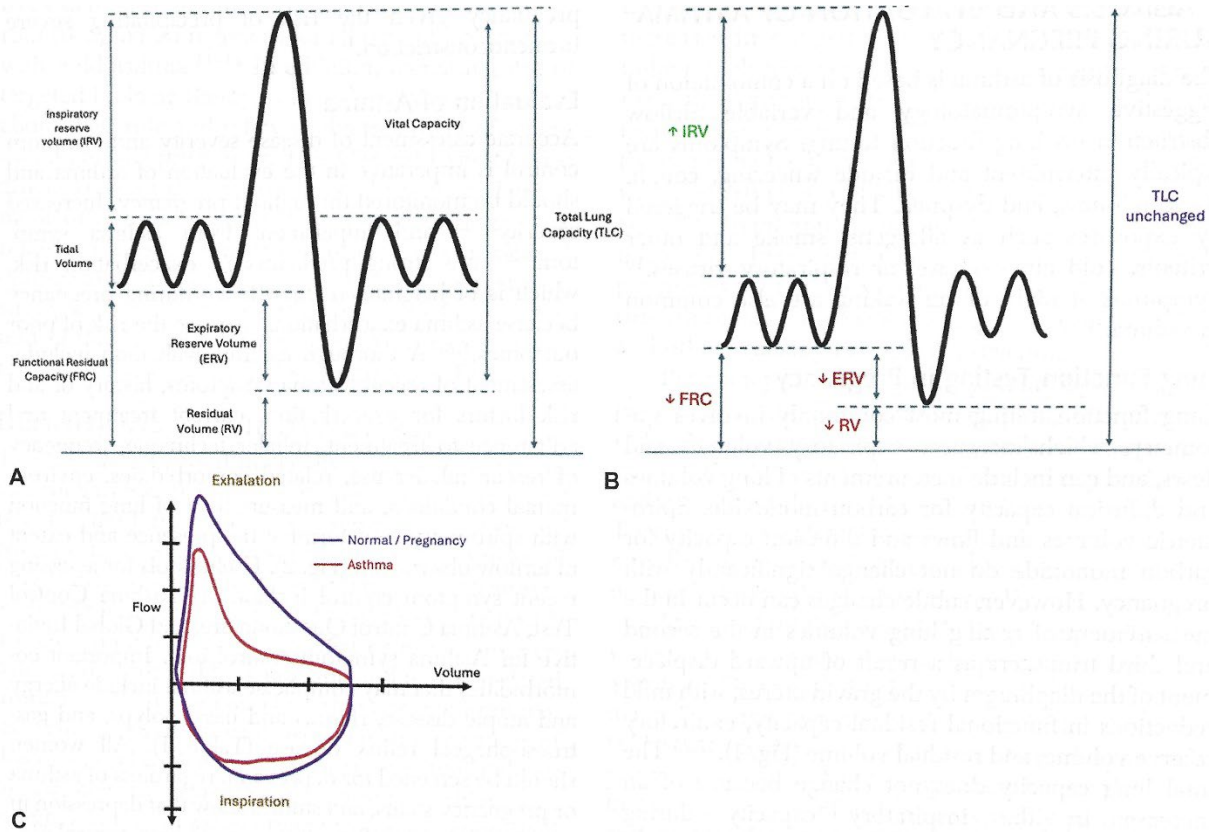

Figure 2. Pulmonary function test in pregnancy and asthma. **A.** Representation of normal lung volumes. **B.** Pregnant women breathe at lower resting lung volumes. Total lung capacity is unchanged. **C.** Illustration of spirometry, comprising inspiration followed by a forced expiratory maneuver, on a flow-volume loop. **Abbreviations**: total lung capacity (TLC); forced vital capacity (FVC); forced expiratory volume in 1 second (FEV_1); expiratory reserve volume (ERV); residual volume (RV).

It is important to recognize that normal lung function tests do not rule out a diagnosis of asthma. Bronchoprovocation testing, wherein airway hyperresponsiveness is elicited by administration of a trigger (typically methacholine), is not recommended in pregnancy, given the risk of precipitating severe bronchoconstriction.[12]

Maternal and Fetal Outcomes

Literature comparing pregnant women with asthma, and with those without asthma, demonstrate that maternal asthma is associated with adverse maternal, perinatal, and pediatric outcomes. Possible explanation include chronic or intermittent maternal hypoxia influencing placental oxygen delivery and fetal oxygenation, adverse effects of increased inflammatory mediators in maternal asthma, or even underlying dysfunction of smooth muscle common to both the airways and myometrium.[13] Pregnant women with asthma report increased respiratory viral infections and may have higher rates of pulmonary embolism and urinary tract infections. In addition, a recent cohort study found an association between maternal asthma and postpartum depression.[14]

Maternal asthma has been associated with small increases in risk of neonatal hospitalization and death, neonatal respiratory distress, transient tachypnea of the newborn, and congenital malformations, including cleft lip.[15] In addition to these neonatal outcomes, large cohort studies have shown that uncontrolled asthma confers increased risk of bronchitis and early onset of asthma in their children. This risk of wheezing and atopy may further increased by respiratory viral infections during pregnancy.

Antenatal Surveillance

Although the association of maternal asthma with adverse pregnancy and neonatal outcomes is clear, there are currently no formal recommendations or guidelines for antenatal surveillance specific to women with asthma. We suggest an emphasis on routine obstetric care with a heightened clinician suspicion for both maternal complications and adverse neonatal outcomes, particularly for those with moderate to severe asthma. In cases of moderate-to-severe asthma, a growth ultrasonogram in the third trimester would be reasonable to consider given the increased risk of having a neonate with small-for-gestation birth weight. A thorough asthma evaluation should be performed for all pregnant women with asthma, and symptom control should be reassessed at each visit. Maternal asthma alone should not dictate mode of delivery.

Commonly used Asthma Medications in Pregnancy

Inhaled Corticosteroids (ICSs): They are the back-bone of asthma treatment and supported by decades of literature. In pregnancy, ICS use is associated with reduced risk of preterm delivery and reduced risk of asthma exacerbations.[16] Inhaled corticosteroids should be started at the time of diagnosis, even for patients with mild disease, because studies suggest that early ICS therapy improve lung function recovery.[17] Common ICS medications used are:

Budesonide – 200 to 400 micrograms (low); 400 to 800 micrograms (medium); more than 800 micrograms (high) dosage, 1 – 2 puffs, 1 – 2 times daily. It is safe throughout pregnancy by consensus of numerous trials, large cohort studies, and meta-analysis.
Fluticasone – 100 to 250 micrograms (low); 251 to 500 micrograms (medium); more than 500 micrograms (high), 1 – 2 puffs, 1 – 2 times daily. Large cohort studies demonstrate overall safety and similar safety to those budesonide included in meta-analysis of ICS class as whole, which suggests safety. [18]
Mometasone – 200 to 400 micrograms (low-medium); more than 400 micrograms (high); 1-2 puffs, 1 – 2 times daily. Included in meta-analyses of ICS class as whole, which suggests safety. Few drug-specific studies are available.

Beclomethasone – 100 to 200 micrograms (low); 201 to 400 micrograms (medium); more than 400 micrograms (high), 1 -2 puffs, 2 times daily. Drug-specific meta-analysis mostly reassuring about its safety, included in meta-analyses of ICS class as whole, which suggests safety.[19]
Ciclesonide – 80 to 100 micrograms (low); 161 to 320 micrograms (medium); more than 320 micrograms (high), 1 – 2 puffs 2 times daily. No drug-specific studies.

Rapid-onset Inhaled Corticosteroid – long-acting β agonist (ICS-LABA)

Budesonide-formoterol – 80 to 4.5 micrograms (low); 160 to 4.5 micrograms (medium), 1 – 2 puffs 2 times daily or PRN. More limited data, but cohort studies suggest that ICS-LABA combination has pregnancy safety profile similar to that of ICS.
Mometasone-formoterol – 100 to 5 micrograms (low-medium); 200 to 5 micrograms (high), 2 puffs 2 times daily or PRN. Safety profile similar to ICS.

Leukotriene Receptor Antagonist

Drugs inhibiting the actions of leukotrienes, endogenous mediators of bronchoconstriction and airway inflammation, are common adjunct therapies for asthma. They may be particularly useful for patients with asthma symptoms related to allergies, exercise, or non-steroidal and anti-inflammatory drugs.[20]
Montelukast – 10 mg oral dose once daily. Reassuring pregnancy safety profile overall, with no difference in rates of congenital anomalies or pregnancy loss. Cohort studies with conflicting results on association with low-birth-weight and preterm birth.[21] Food and Drug Administration (FDA) black box warning for adverse neuropsychiatric effects and sleep disturbances.

Monoclonal Antibody Therapies (Biologics)

The landscape of therapy for severe asthma has changed in recent years with the development of targeted monoclonal antibody therapies against specific inflammatory mediators such as IgE, IL-4, and IL-5. Literature on the safety of biologic therapies in pregnancy is limited.

Omalizumab (anti-IgE) – 75 to 375 mg, subcutaneous every 2 to 4 weeks. Best studied of biologics in pregnancy, EXCEPT cohort (230 exposed) found no difference in rates of malformations or low birth weight. Increased rates of premature birth seen but may be attributable to severity of asthma or higher obesity rate in exposed cohort.[22]
Dupilumab (anti-IL-4Rα) – 400 to 600 load followed by 200- and 400-mg maintenance. Subcutaneous (SC) every 2 weeks. Insufficient evidence with small cohort studies and case reports or series, regarding safety during pregnancy.
Mepolizumab (anti-IL-5) – 100 mg SC every 4 weeks. Insufficient evidence, only limited case reports regarding the safety during pregnancy.
Benralizumab (anti-IL-5Rα) – 30 mg SC every 4 to 8 weeks. Insufficient evidence, only limited case reports regarding safety during pregnancy.
Reslizumab (anti-IL-5) – 3 mg/kg Intravenous every 4 weeks. No studies or case reports.
Tezepelumab (anti-TSLP) – 210 mg SC every 4 weeks. No studies or case reports. TSLP (thymic stromal lymphoprotein)

Systemic Corticosteroids

Treatment of exacerbations of asthma in pregnancy parallels that of non-pregnant patients. Clinicians should promptly administer short-acting bronchodilator and systemic corticosteroids.
Prednisone, Methylprednisolone and Dexamethasone – Acute exacerbations: Prednisone 40 to 50 mg (or equivalent) for 5 to 7 days assess response and consider extending course with taper if needed; oral or intravenous. Benefits of corticosteroids for acute exacerbations strongly outweigh risks, particularly given shorter duration of treatment. Fetal drug exposure lowest with prednisone, prednisolone. Epidemiologic studies of chronic corticosteroid exposure during pregnancy, most in patients with autoimmune disease, have found that; inconsistent associations with cleft lip and palate.[23] Possible increased risk of gestational diabetes (very limited body of evidence).[24] Health care professional education, highlighting the importance of prompt and aggressive management of acute asthma in pregnancy, is crucial to closing the treatment gap.

Management of Status Asthmaticus and Life-Threatening Exacerbations

As in any exacerbation, prompt and repeated bronchodilator treatments and systemic corticosteroids are imperative; however, patients with life-threatening asthma exacerbations frequently require additional forms of respiratory support. Supplementary oxygen should be given to maintain and oxygen saturation about 95%, a higher target for pregnant women than other adults given the added importance of maintaining fetal oxygen deliver. Severe maternal hypoxia can be devastating effects on the fetus, including fetal or neonatal death and ischemic brain injury.[25] The following interventions are taken in the management of asthma exacerbation in pregnancy:

Inhaled bronchodilators -Nebulized solution preferred, if possible. Albuterol 0.083% 2.5 to 5 mg, with or without ipratropium bromide. Can give initially up to 3 successive doses every 20 minutes, then every 1 – 4 hours as needed. Continuous nebulized albuterol considered for life-threatening cases (10-15 mg/hour).
Systemic glucocorticoids – Administer promptly. Prednisone 40 to 60 once daily is typical. Intravenous (IV) methylprednisolone can be considered for life-threatening cases.
Supplemental oxygen corticosteroids – Target oxygen saturation 95% or higher. Hypovolemia often accompanies asthma exacerbations; low threshold for IV fluids.
Systemic bronchodilators – Inhaled bronchodilators are the priority, but trials of adjuncts are reasonable for severe cases. IV magnesium sulfate (2 g infusion every 20 minutes). Terbutaline subcutaneous (SC); 0.25 mg every 20 minutes, up to 3 doses.
Noninvasive ventilation (NIV) – Consider trial only under supervision of experienced clinicians. Prepare for intubation in case of failure. Contraindicated if severe distress, hemodynamic instability, altered mental status, high aspiration risk, unable to tolerate interface, or craniofacial fractures.
Endotracheal intubation and mechanical ventilation – Indicated for those with severe distress, refractory hypoxemia or hypercarbia, poor response, or contraindications to NIV. Ideally performed by clinician with expertise in obstetric airway management.
Ventilatory strategies – Allow complete exhalation to avoid dynamic hyperinflation. Low respiration rate (8 to 12 breaths/minute); High inspiration flow rate; avoid decelerating breath waveform and low tidal volume (TV). Lung protective ventilation: TV 6 – 8 mL/ideal body

weight; Titrate to atrial blood gas goals: $PaCO_2$ 28-32 mm Hg (normal for pregnancy); $PaCO_2$ 70 mm Hg or higher.
Venovenous ECMO (extracorporeal membrane oxygenation) - For extreme respiratory failure unresponsive to intubation and ventilator strategies above (very rare). Continuous fetal monitoring required and position in lateral decubitus position.

Obstetric consultation

Severe maternal hypoxia can have devastating effects on the fetus, including fetal or neonatal death and ischemic brain injury. Involving the obstetric team, particularly for severe exacerbations and other high-risk scenarios is essential. Determine need for and frequency of fetal monitoring, and assess safety of continuing pregnancy, and if viable, consider timing and method of delivery. For critical cases, preparations for emergency delivery should be in place. Regular, open communication between intensive care unit (ICU) and obstetrics teams are strongly recommended.

Patients with respiratory distress or who are not responding appropriately to noninvasive respiratory support must be emergently considered for endotracheal intubation and invasive ventilation. Intubation resulting from anatomic and physiologic changes of pregnancy, must notably oropharyngeal and tracheal hyperemia and edema, the increased risk of aspiration.[26]
In rare cases, patients who are unable to be adequately oxygenated or ventilated despite invasive mechanical ventilation may be considered for ECMO at centers with this expertise. Limited evidence indicates that ECMO can be performed safely during pregnancy as a form of life-support, but requires continuous fetal monitoring and positioning in the lateral decubitus position to optimize blood flow.[27]

Global Initiative for Asthma (GINA)

GINA was established in 1993 by the National Heart, Lung, and Blood Institute (NHLBI) and the World Health Organization (WHO) to increase asthma awareness and translate scientific evidence into improved asthma care worldwide.[28] GINA publishes annual updates to its report on the Global Strategy for Asthma Management and Prevention and summaries recommendations for clinical practice and supporting evidence. It is important to understand that while GINA strives to be a globally relevant voice, recommendations for asthma care need to be adapted to local conditions, resources, and services. Talk with your healthcare provider about what is right for you. Through resources such as evidence-based strategy documents for asthma management, and events such as the annual celebration of World Asthma Day, GINA is working to improve the lives of people with asthma in every corner of the globe.

Severe Asthma is a debilitating form of asthma, which afflicts up to 10% of asthma sufferers. It can develop often in association with allergies, or come on later in life in relation to respiratory infections, hormonal changes or environmental exposures. Patients with severe asthma typically have the lowest quality of life, the highest risk for morbidity and mortality, and consume the majority of healthcare resources. Unlike “usual” asthma, severe asthma often does not responds well to currently available medications. Thus, the lives of patients with severe asthma are often dramatically impacted by the burden of their disease.

Summary

Asthma is common in pregnancy and can negatively affect both maternal and neonatal outcomes. Asthma is diagnosed through a combination of characteristic symptoms and variable obstruction on lung function testing. Treatment of asthma in pregnancy should prioritize the use ICS combination inhalers, which are safe and effective in reducing symptoms and risk of exacerbation. Disease control should be reassessed throughout the pregnancy, with treatment adjusted according. For more than 20 years, Severe Asthma Research Program; http://www.severeasthma.org/ has transformed out knowledge of severe asthma. Many people have asthma that is difficult to control, even after adding new medicines or increasing dosage. Studies are looking at new approaches to improve asthma treatment options, including repurposing and approved drug to treat severe asthma, understanding why medicines work, and using personalized medicine. In patients with severe asthma, joint care by an asthma specialist and obstetrics will result in the safest, most efficacious care.

Suggested Reading

1. World Health Organization (WHO)
   Asthma
   https://www.who.int/news-room/fact-sheets/detail/asthma

2. Centers for Disease Control and Prevention (CDC)
   Work Related Asthma
   https://www.cdc.gov/niosh/asthma/about/

3. National Institutes of Health (NIH)
   Asthma Research
   https://www.nhlbi.nih.gov/research/asthma

4. Women's Health and Education Center (WHEC)
   Asthma in Pregnancy
   http://www.womenshealthsection.com/content/obsmd/obsm008.php3

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