CHEST

Asthma Outcomes and Management During Pregnancy

Catherine A. Bonham, MD; Karen C. Patterson, MD; and Mary E. Strek, MD

Asthma during pregnancy poses a common, increasingly prevalent threat to the health of women and their children. The present article reviews recent insights gained from the epidemiology of asthma during pregnancy, demonstrating the many short- and long-term risks to mother and fetus incurred by poorly controlled maternal asthma. We further discuss emerging evidence that active management of asthma during pregnancy can positively influence and perhaps completely mitigate these poor outcomes. Recent high-quality trials examining best methods for asthma treatment are reviewed and synthesized to offer an evidence-based pathway for comprehensive treatment of asthma in the outpatient setting. Safe and effective medications, as well as nonpharmacologic interventions, for asthma during pregnancy are discussed, and treatment options for related conditions of pregnancy, including depression, rhinitis, and gastroesophageal reflux, are presented. Throughout, we emphasize that an effective treatment strategy relies on a detailed patient evaluation, patient education, objective measurement of asthma control, and frequent and supportive follow-up. The cardiovascular and respiratory physiology of pregnancy is reviewed, as well as its implications for the management of patients with asthma, including patients requiring intubation and mechanical ventilation. For the situation when outpatient asthma management has failed, an approach to the critically ill pregnant patient with status asthmaticus is detailed. Multidisciplinary teams that include pulmonary specialists, obstetricians, primary care providers, nurses, pharmacists, and asthma educators improve the care of pregnant women with asthma.

CHEST 2018; 153(2):515-527

KEY WORDS: asthma; critical care; pregnancy; primary medicine

Asthma is the most common respiratory disorder to complicate pregnancy, and it remains a high-risk condition despite advances in therapy. We review recent literature on epidemiology, outcomes, physiology and treatment of asthma during pregnancy, including care of patients with status asthmaticus in the ICU.

Physiologic Changes in Pregnancy

Numerous cardiovascular changes occur in pregnancy to meet the metabolic demands

ABBREVIATIONS: ACQ = Asthma Control Questionnaire; ACT = Asthma Control Test; $ECCO_2R$ = extracorporeal carbon dioxide removal; ECMO = extracorporeal membrane oxygenation; ICS = inhaled corticosteroid; IT = immunotherapy; LABA = long-acting beta-agonist; RR = relative risk; SABA = short-acting beta-agonist

AFFILIATIONS: From the Section of Pulmonary and Critical Care Medicine (Drs Bonham and Strek), University of Chicago, Chicago, IL; the Division of Pulmonary, Allergy and Critical Care Medicine (Dr Patterson), University of Pennsylvania, Philadelphia, PA; and Brighton and Sussex Medical School (Dr Patterson), University of Sussex, Brighton, United Kingdom.

FUNDING/SUPPORT: Dr Bonham was supported by the National Institutes of Health/National Heart, Lung, and Blood Institute [Grant T32 HL007605, followed by Grant K12 HL119995] during preparation of the manuscript.

CORRESPONDENCE TO: Catherine A. Bonham, MD, University of Chicago, Pulmonary and Critical Care Medicine, 5841 S Maryland Ave, Room W652B, MC 6076, Chicago, IL 60637; e-mail: catherine.bonham@uchospitals.edu

DOI: https://doi.org/10.1016/j.chest.2017.08.029

of the fetus, placenta, and mother, and to prepare the mother for delivery (Table 1).[1,2] These changes include an increase in cardiac output, stroke volume, and heart rate.[1] The gravid uterus causes a significant fall in cardiac output in the supine compared with left lateral position in the third trimester, due to compression of the vena cava and decreased venous return. This change is clinically important for the care of pregnant women, who benefit hemodynamically from left lateral positioning.[3] Respiratory changes[2] include an increase in minute ventilation that occurs primarily by an increase in tidal volume but not respiratory rate, resulting in a compensated respiratory alkalosis. Pregnancy also affects chest wall compliance with a fall in functional residual capacity as pregnancy progresses. Increasing dyspnea in late pregnancy is associated with a reduction in expiratory reserve volume,[4] although an increase in inspiratory capacity results in total lung capacity remaining in the normal range. Healthy pregnant women show no change in FEV_1 and a very modest increase in FVC, approximately one-tenth of 1 L, after 14 to 16 weeks' gestational age, and no significant change in the FEV_1/FVC ratio throughout pregnancy.[5] Therefore, in pregnant women with asthma, any decline in these spirometric parameters should be concerning.

Oxygen delivery to the fetus depends on uterine artery blood flow and maternal oxygen content.[6] Because uterine artery blood flow is near maximal at baseline, the fetus is critically dependent on adequate maternal cardiac output for optimal oxygen delivery. Maternal fetal oxygen transfer occurs by an elegant concurrent exchange mechanism, with the difference in oxygen tension between the maternal and fetal circulations in the placenta determining oxygen transfer. Thus, maximization of maternal oxygen saturation and maintenance of maternal cardiac output best ensures appropriate fetal oxygen delivery when maternal respiratory compromise occurs.

Renal and GI adaptations to pregnancy affect the absorption and clearance of medication by increased plasma volume and glomerular filtration rate, and decreased albumin and gastric motility.[7] Higher and/or more frequent dosing of medications may be indicated depending on the mechanisms of metabolism and clearance. It is important to recognize that the placenta is not a barrier, and most medications cross the placenta.

TABLE 1] Physiologic Changes in Pregnancy

Parameter	Change	Amount
Heart rate	Increases	10%-30%
Stroke volume	Increases	…
Systemic vascular resistance	Decreases	20%-30%
Cardiac output	Increases	30%-50%
Blood pressure	Decreases	10%-20%
Respiratory rate	May increase	Minimally
Tidal volume	Increases	…
Minute ventilation	Increases	20%-40%

Epidemiology

In the United States, 5% to 8% of pregnant women have asthma, and the prevalence of asthma is increasing.[8,9] Worldwide, asthma affects 2% to 13% of pregnancies.[10,11] Asthma is the most common respiratory condition of pregnancy, with increasing health-care utilization and cost.[12] The relationship between asthma status and pregnancy outcomes is complex, in part due to higher rates of smoking, obesity, and other comorbidities in patients with asthma that are independently associated with higher maternal and fetal obstetric risk.[9] Studies that control for these and other important variables are best suited to measure the true impact of asthmatic airway physiology and asthma treatment strategy on obstetric outcomes. Differences in study design, reference populations, asthma phenotypes, and evolving treatment regimens have led to conflicting reports. The present review highlights findings from large, mainly contemporary studies that summarize common and demonstrable asthma-related risks of pregnancy (Table 2).[9,13-21]

Maternal Outcomes

Asthma is strongly associated with preeclampsia,[9,13,14] placental abruption and placenta previa,[9,15] and obstetric hemorrhage.[9,15] Decades of research have linked asthma to increased rates of cesarean delivery.[13,15] Rejno et al[13] reported that asthma is associated with unplanned, emergency cesarean deliveries (adjusted OR, 1.29 [95% CI, 1.23-1.34]). Asthma severity is associated with some adverse obstetric outcomes but not others; risk of cesarean delivery is higher for patients with severe asthma vs mild asthma.[15] A large cohort study of > 15,000 Canadian women with asthma found an increased risk of spontaneous abortion.[19] The key question of whether asthma treatment can affect poor obstetric outcomes was addressed in a meta-analysis by

TABLE 2] Maternal and Fetal Adverse Outcomes Related to Asthma

Maternal	Perinatal	Fetal
Antepartum and postpartum hemorrhage	Placenta previa	Death
Cesarean delivery	Placental abruption	Hospitalization
Gestational diabetes mellitus	Premature rupture of membranes	Low birth weight
Gestational hypertension		Small for gestational age
Preeclampsia		Cleft lip/palate

Murphy et al,[14] which showed that the relative risk (RR) of preterm delivery and preterm labor is reduced by active asthma management. Prospective trials are needed to demonstrate the efficacy of increased asthma control in all asthma severity types and for other crucial maternal and fetal end points.

In addition to obstetric complications, asthma is associated with multiple comorbid maternal conditions. In a meta-analysis of publications from 1975 to 2012, maternal asthma was associated with an increased risk of gestational diabetes (RR, 1.39 [95% CI, 1.17-1.66]).[15] Notably, women who received active asthma management had a risk of gestational diabetes that was similar to that of nonasthmatic control subjects (RR, 1.08 [95% CI, 0.81-1.46]), and in a comparison of asthma subgroups, bronchodilator use was associated with a significantly lower rate of gestational diabetes (RR, 0.64 [95% CI, 0.57-0.71]). In a retrospective cohort study of > 220,000 pregnancies, patients with asthma had an 11% increased odds of gestational diabetes.[9] This study was also the first to report an increased risk of pulmonary embolism among patients with asthma (OR, 1.71 [95% CI, 1.05-2.79]). The overall low rate of pulmonary embolism (affecting 0.06% of nonasthmatic pregnancies and 0.12% of asthmatic pregnancies) may complicate efforts to detect a significantly different incident rate in other studies.

Among pregnant patients, the frequency and severity of respiratory viral infections are higher for those with asthma. In a survey of 285 pregnant patients, 71% of women with asthma compared with 46% of women without asthma had at least 1 common cold during pregnancy.[22] Among all pregnant women, influenza is associated with increased morbidity; during pandemic influenza infections, increased mortality is also observed, especially in the second trimester.[23] These risks are even higher for pregnant patients who have asthma. In a matched cohort study of 297 pregnancies with hospital admission for respiratory symptoms during influenza season, asthma was the most important risk factor for admission, and the adjusted OR for admission among those with asthma was a striking 10.63 (95% CI, 8.18-13.81); confirmation of pulmonary infection was documented in fewer than one-half of cases, however.[24] Over nine nonpandemic seasons, asthma was the most important risk factor for hospitalization due to respiratory cause among pregnant patients.[25] During the H1N1 pandemic season, asthma was the most common comorbidity (present in 23% of cases) reported in pregnant women who developed influenza A infection, and 44% of pregnant women who died of H1N1 influenza had asthma.[26]

Just as asthma affects pregnancy outcomes, pregnancy affects asthma. Pregnancy is associated with new-onset asthma and, in patients with preexisting disease, the severity of asthma can worsen during pregnancy.[27,28] Kircher et al[29] found that day-to-day disease control was worse during pregnancy for 36% of patients with asthma. Asthma exacerbation rates are higher during pregnancy, particularly for patients with a history of severe asthma. In a study of 1,739 patients, 52% of those with severe asthma experienced an exacerbation during pregnancy, compared with an exacerbation rate of 26% for those with moderate asthma and 13% for those with mild asthma.[28] Triggers for exacerbations include treatment nonadherence and viral infections.[16,30] Exacerbations of asthma, especially when severe enough to warrant hospitalization, are associated with increased rates of maternal complications.[16] As highlighted in the following discussions, they also have an impact on fetal outcomes.

Poorly Controlled Maternal Asthma Results in Poor Pediatric Outcomes

Pediatric complications associated with poorly controlled maternal asthma are numerous and long-lasting, including low birth weight and small-for-gestational-age infants,[13,21] with the risk of low birth weight increased with increasing asthma severity.[13] A large cohort of 36,587 women with asthma has also

demonstrated increased prevalence of congenital malformations in those experiencing severe asthma exacerbations during the first trimester.[20] A meta-analysis of studies from 1975 to 2012 reported significant associations between maternal asthma and neonatal death (RR, 1.49), neonatal hospitalization (RR, 1.50), cleft lip/palate (RR, 1.30), and minor malformations (RR, 1.11) but not major malformations or stillbirth.[17] Exacerbations, use of bronchodilators, or use of inhaled corticosteroid (ICS) were not associated with congenital malformation.

Another meta-analysis of studies from 1975 to 2012 found that maternal oral corticosteroid use was associated with low birth weight and preterm delivery, with moderate to severe asthma associated with increased small-for-gestational-age infants.[18] A recent prospective cohort study highlighted recurrent uncontrolled asthma as a greater contributor to poor perinatal outcomes than exacerbations.[31] This study defined recurrent uncontrolled asthma as an Asthma Control Questionnaire (ACQ) score $>$ 1.5 on two or more occasions. The same study observed a remarkable effect when pregnancies were stratified according to fetal sex: women pregnant with female fetuses were at increased risk for small-for-gestational age infants, whereas male fetuses had a tendency toward preterm birth. This clinical observation is supported by translational science elucidating how the placenta and growing fetus can adapt to early pregnancy stress, such as uncontrolled asthma, in a sex-specific manner.[32] While future research illuminates these biological mechanisms, the study by Grzeskowiak et al[31] highlights the need to seek good daily control of asthma during the course of pregnancy, rather than simply focusing on exacerbation prevention and management.

Childhood Asthma Risk Is Mitigated by Maternal Asthma Control

Children born to mothers with asthma are more likely to have asthma themselves. Murphy et al[33] followed up a cohort of 42 women with asthma who reported respiratory symptoms during pregnancy, 26 of whom had polymerase chain reaction-confirmed viral respiratory infection. Infants of these women were significantly more likely to have wheezing symptoms, treatment with albuterol, and eczema reported by their parents at 12 months, compared with infants of asthmatic mothers without laboratory-confirmed prenatal viral infection. Importantly, in a follow-up study of women who completed a randomized controlled trial of asthma intervention,[34] Mattes et al[35] showed that reducing exacerbations during pregnancy resulted in fewer episodes of bronchiolitis in the infants at 12 months vs standard maternal asthma management (OR, 0.08). Infants from this cohort exhibited significantly different peripheral blood DNA methylation compared with infants whose mothers did not have asthma.[36] Further research is needed to elucidate the impact of such fetal epigenetic modifications as well as placental adaptations[32] to the stress of maternal asthma.

Treatment

Asthma Management Improves Maternal and Fetal Outcomes

Excellent prenatal care with attention to maintaining asthma control is the cornerstone to achieving improved maternal and fetal outcomes (Table 3). A meta-analysis of studies conducted between 1975 and 2009 showed that the RR of preterm delivery and preterm labor was reduced by active asthma management to avoid asthma exacerbations.[14] Murphy et al[37] reported significant improvements in all aspects of asthma self-management following two asthma educator visits, with reductions in nocturnal symptoms and rescue medication use in women with severe asthma. Recently, the Management of Asthma With Supportive Telehealth of Respiratory Function in Pregnancy (MASTERY) study took a modernized education approach, demonstrating improved asthma control and quality of life in pregnant women who used a handheld respiratory device and an Android smartphone to conduct telehealth visits.[38] Further exploration of telehealth is needed to determine if it can affect morbidity and mortality associated with asthma in pregnancy.

Several other studies have been conducted to determine the best treatment algorithm and best individual to lead the treatment team. The Multidisciplinary Approach to Management of Maternal Asthma (MAMMA) study followed up 60 women randomized to a pharmacist-led intervention group vs usual care and was successful in decreasing the ACQ score but not hard end points, including oral corticosteroid use, hospitalization, emergency visits, or days off work.[39] A prospective cohort study testing a nurse-led asthma management service reported a decrease in the RR of exacerbations but only a near-

TABLE 3] Components of Effective Asthma Therapy in Pregnancy

Monthly assessment of asthma control using objective measures
• Structured asthma history using a validated questionnaire (eg, ACQ, ACT, GINA)
• Monitoring of lung function by spirometry or peak expiratory flow
• Fetal monitoring after 32 wks
Patient education
• Preconception education for all women with asthma who are of reproductive age
• Inhaler technique
• Written asthma action plan
• Specifically address teratogen concerns and risks of medication discontinuation
Avoidance of environmental triggers
• Cigarette smoking
• Animal allergens
• House dust mites
• Cockroaches
• Indoor mold
• Fireplaces, wood-burning stoves, and unvented heating devices
• Perfumes, cleaning agents, and aerosol sprays
• Pollen
• Air pollution
Treatment of comorbid conditions
• Rhinitis
• Gastroesophageal reflux disease
• Depression
• Allergy
Pharmacologic therapy for asthma

ACQ = Asthma Control Questionnaire; ACT = Asthma Control Test; GINA = Global Initiative for Asthma.

significant trend toward exacerbation rate reduction and controlled asthma after two or more visits.[40] A double-blind, randomized controlled trial of active asthma management using a treatment algorithm guided by fractional exhaled nitric oxide measurement succeeded in improving exacerbation rates (0.288 vs 0.615 per pregnancy), maternal quality of life, and neonatal hospitalization rates (8% to 17%).[34] Taken together, these studies show that a diverse group of providers can be involved in asthma interventions which improve symptom control and maternal quality of life. Treatment approaches that incorporate quantitative data, such as fractional exhaled nitric oxide, have been most successful at reducing exacerbations and hospitalizations. Further studies using randomized controlled designs are needed.

Medication Discontinuation and Safety

Data from the National Health and Nutritional Examination Survey show that pregnant women report much less frequent use of albuterol than nonpregnant women of the same age, suggesting medication discontinuation during pregnancy.[41] Medication discontinuation may be due to excessive perceived teratogenic risk, which in one survey of mothers with asthma was estimated at 42% for oral corticosteroids, 12% for ICS, and 5% for short-acting beta-agonists (SABAs).[42] Women who reduce their asthma medication use during pregnancy are twice as likely to experience increased days of wheeze (OR, 2.17), particularly in areas of high nitrogen dioxide air pollution and in warm months.[43] Enrollment in an asthma management program with monthly visits increased asthma control and medication adherence, measured according to a prescription fill rate, from 28% to 46%, although the same women self-reported adherence rates of up to 73%.[44] In terms of counseling regarding medication safety, it should be noted that the US Food and Drug Administration has updated its pregnancy and lactation labeling guidelines. As of June 30, 2015, the pregnancy letter categories A, B, C, D, and X have been removed in favor of a descriptive label format.

Treatment of Related Symptoms and Comorbidities

Atopy and Allergy

National Asthma Education and Prevention Program guidelines[45] suggest counseling on lifestyle modifications for women with allergic and atopic asthma, including avoidance of animal dander, house dust mites, cockroaches, pollens, and indoor mold. Specific interventions include encasement of mattress and pillows in an allergen-impermeable cover, washing bedding weekly in water $> 130^{\circ}$F, reduction of indoor humidity to $< 50\%$, and removal of carpeting and pets ideally from the home but at a minimum from the bedroom. All women with asthma and all pregnant women should avoid tobacco smoke and reduce exposures to pollutants and irritants, including wood-burning stoves and fireplaces, unvented stoves or heaters, perfumes, cleaning agents, and sprays. Traffic pollution, especially preconception and in the first trimester, is associated with a higher

risk for preterm birth and preeclampsia in women with asthma.[46,47]

Continuation of subcutaneous and sublingual immunotherapy (IT) for inhalant allergens as well as venom IT during pregnancy seems safe, based on four small studies[48-51] reviewed by Oykhman et al.[52] The most recent study assessed sublingual IT vs control ICS or SABA use in 280 women; the investigators found no significant difference in perinatal outcomes, congenital malformations, or systemic reactions to IT for 185 pregnant women, 24 of whom received IT for the first time during pregnancy.[50] Due to concern for systemic reactions and a paucity of data, current US and European guidelines do not support initiation of IT in pregnancy, except in special circumstances such as previous anaphylaxis to Hymenoptera venom.[53,54] Interestingly, IT-induced IgG antibodies cross the placenta,[55] and higher IgG to inhaled allergens in cord blood is associated with less atopy in children.[56] However, the theoretical advantage of IT for preventing allergy and asthma in offspring has not been proven and is a topic of ongoing research.[57]

Rhinitis

Hormonal changes during pregnancy can produce nonallergic rhinitis. Rhinitis occurs in 65% of pregnant women with asthma and is associated with poor asthma control and quality of life.[58] Women with allergic rhinitis benefit from trigger avoidance, intranasal lavage with hypertonic saline solution three times daily,[59] and intranasal corticosteroid sprays. Intranasal corticosteroid sprays are ineffective in nonallergic rhinitis of pregnancy,[60] although other forms of rhinitis are responsive to corticosteroids. Intranasal corticosteroids are safe in pregnancy, with some clinicians choosing intranasal budesonide over others because of the safety data available. No change in pregnancy outcome was seen in a trial of pregnant women using intranasal fluticasone.[60]

Leukotriene receptor antagonists such as montelukast are generally accepted as safe.[45] Intranasal antihistamines or oral second-generation antihistamines, including cetirizine or loratadine, are also considered safe.[61] Local vasoconstriction with oxymetazoline can be used, at usual dosing and for $\leq$ 3 days to avoid rebound rhinitis. However, oral decongestants such as pseudoephedrine and phenylephrine should be avoided, especially in early pregnancy, as their systemic vasoconstriction has teratogenic effects.[62]

Gastroesophageal Reflux Disease

Gastroesophageal reflux disease exacerbates asthma[63] and is more severe in pregnant women with asthma compared to pregnant women without asthma.[64] First-line treatment is lifestyle modifications, including elevation of the head of the bed and avoidance of trigger foods and eating before bedtime. Antacids such as sucralfate, followed by a histamine$_2$-receptor antagonist such as ranitidine, may be used. Sodium bicarbonate is generally avoided due to concerns regarding metabolic alkalosis. Proton pump inhibitors may also be considered.[65]

Depression

Compared with women with asthma who do not report depression, women with self-reported depression and anxiety have an increased likelihood and incidence of uncontrolled asthma in pregnancy, although their exacerbation rate remains unchanged.[66] Depression screening and treatment are indicated in all women regardless of asthma or pregnancy status. The effect of depression treatment on asthma outcomes in pregnant women has not been studied.

Treatment of Asthma With Preventive Medications

The pharmacologic cornerstone of tightly controlled asthma rests upon titration of ICS and long-acting beta-agonist (LABA) inhalers, judicious use of oral corticosteroids, and appropriate continuation of adjunct therapies (Tables 4 and 5). Significant teratogenic effects of these medications, extensively reviewed in the National Asthma Education and Prevention Program guidelines,[45] are a perennial concern not well supported by large, well-controlled, and well-designed studies. The possible teratogenic risk of uptitration of medication is outweighed by the significant harm to mother and fetus when asthma is uncontrolled. For example, in one large study of over 36,000 pregnancies the prevalence of congenital malformation increased from 12.0% to 19.1% among asthmatic women with severe exacerbations during the first trimester vs women with asthma who did not experience an exacerbation.[20]

Titration of Daily Inhaler Regimen

Similar to management of asthma outside of pregnancy, frequent re-assessment of symptoms guides a stepwise approach to inhaler use. Use of validated tools, such as the Asthma Control Test (ACT), the ACQ, and the Global Initiative for Asthma (http://ginasthma.org/2017-gina-report-global-strategy-for-asthma-management-and-prevention/) classification, facilitates

TABLE 4] Asthma Inhalers Used in Pregnancy Are Titrated to Asthma Severity

Asthma Severity	Symptoms	PEF (% of Personal Best) or FEV_1 (% Predicted)	Drug Class	Comments
Mild intermittent	≤ 2 d/wk or ≤ 2 nights/mo	≥ 80%	SABA	Use as rescue therapy in all categories of asthma Most safety data available for albuterol
Mild persistent	3-6 d/wk or ≥ 3 nights/mo	≥ 80%	Low-dose ICS	Most safety data available for budesonide, but no evidence that other ICS are less safe or efficacious
Moderate persistent	Intermittent daily or ≥ 4 nights/mo	61%-79%	Medium-dose ICS or ICS/LABA combination	Increasing ICS dose vs adding LABA to ICS has been shown to be equally safe LABA should not be used as monotherapy Most safety data available for salmeterol, but no evidence that other LABA are less safe or efficacious
Severe persistent	Continuous daily or nightly	≤ 60%	High-dose ICS/LABA Oral steroid if needed	Chronic oral steroids should be administered at the lowest dose and for the shortest period needed, particularly in the first trimester

This information was adapted from the National Asthma Education and Prevention Program expert panel report on managing asthma during pregnancy. ICS = inhaled corticosteroid; LABA = long-acting beta-agonist; PEF = peak expiratory flow; SABA = short-acting beta-agonist.

quantitative symptom assessment. Recently, a pregnancy-specific ACT (the p-ACT) was validated for telephone administration.[67] Importantly, for primary health-care settings in which spirometry may not be readily available, the ACQ and Global Initiative for Asthma assessments correlate with spirometric lung function.[68] Measurement of baseline spirometry is advised by guidelines, however, and aids in ruling out asthma mimics. Stepwise titration of controller therapies can also be guided by peak expiratory flow, which increases with each trimester in women without asthma[5] and also in women with asthma when it is well controlled.[69] Prior to adding therapy or increasing dosage, inhaler technique should be assessed and corrected. Up to one-third of dry powder inhaler users make insufficient inspiratory effort, and one-fourth of metered-dose inhaler users actuate before inhalation. These mistakes and others were associated with poor asthma control in the Critical Inhaler Mistakes and Asthma Control (CRITIKAL) study.[70]

The emphasis on SABA, ICS, and LABA therapy is borne out by epidemiologic studies of prescribing patterns across Europe, which show that SABA and

TABLE 5] Asthma Therapies Used in Addition to Inhaler Medications

Drug Category	Drug	Comments
Leukotriene receptor antagonists	Montelukast Zafirlukast	Most safety data available for montelukast
Xanthine derivative	Theophylline	Monitor serum levels for toxicity Increases toxic effect of formoterol
Monoclonal antibody	Omalizumab	Should not be started during pregnancy due to risk of anaphylaxis
Allergen immunotherapy	Subcutaneous Sublingual Venom	Should not be started during pregnancy due to risk of anaphylaxis, except in Hymenoptera venom sensitivity Maintenance dose immunotherapy should be continued
5-lipoxygenase inhibitor	Zileuton	Teratogenicity in animal studies and thus contraindicated in pregnancy

This information was adapted from the National Asthma Education and Prevention Program expert panel report on managing asthma during pregnancy.

ICS monotherapy are the most popular regimens in pregnant women.[71,72] A decline in LABA therapy was observed in most regions, perhaps due to practitioners increasing ICS in lieu of adding LABA for moderate persistent asthma. A study of 1,744 nonpregnant patients with asthma found LABA addition more effective than increased ICS for reducing asthma exacerbation rates and SABA use.[73] Until more efficacy data are available for pregnant women, practitioners considering stepping up to ICS/LABA vs higher dose ICS must balance the potential efficacy of combination ICS/LABA therapy against their concerns regarding adding a second drug in pregnant women with moderate asthma. Two studies have indicated that ICS/LABA seems as safe as higher dose ICS. Eltonsy et al[74] found no difference in congenital malformation for combination ICS/LABA vs increased-dose ICS. Cossette et al[75] also showed that ICS/LABA and low to moderate dose ICS did not affect perinatal outcomes.

Budesonide is the ICS with the greatest amount of safety evidence; however, other ICS are also safe and should be continued if a pregnant patient whose asthma is well controlled is already using them. A retrospective study of > 5,000 pregnancies exposed to first-trimester ICS showed no increase in the overall risk of major congenital malformations for fluticasone propionate vs other ICS.[76] Another study of salmeterol vs formoterol and fluticasone vs budesonide revealed no evidence of greater safety for one LABA or ICS over another.[77]

Other Asthma Medications

The leukotriene receptor antagonists montelukast and zafirlukast are considered safe medications due to reassuring animal data[45] and no evidence of major congenital malformations in humans.[78,79] In contrast, zileuton was associated with teratogenicity in animal studies and should be avoided.[45]

Theophylline can be continued in pregnancy, but its use carries the added burden of monitoring to ensure that serum concentrations remain between 5 and 12 μg/mL to avoid toxicity.[45] Its use can also increase the risk of formoterol toxicity.

Omalizumab pregnancy registry data (The Xolair Pregnancy Registry [EXPECT]) indicate no increase in major congenital malformations, prematurity, or small-for-gestational-age births, but omalizumab should not be started in pregnancy due to risk of anaphylaxis.[80]

Exacerbation Treatment

Treating an acute exacerbation of asthma is similar for pregnant and nonpregnant patients (Table 6). The first step in management is to identify the severity of the exacerbation and risk factors for respiratory failure. If close clinical follow-up is arranged, patients with mild exacerbations can be managed as an outpatient or discharged from the ED. For moderate and severe cases, inpatient monitoring is warranted.

Beta-agonist bronchodilators and systemic corticosteroids are mainstays of treatment of acute exacerbations.[81] Bronchodilators in patients with unstable disease can be delivered initially up to every 20 min; in severe cases, continuous delivery can be provided in an ICU setting. Systemic corticosteroids should be provided at the usual doses (Table 6) and early in the course of an exacerbation. Failure to adequately treat an acute exacerbation poses a much higher risk for the pregnant patient and fetus than does utilization of these standard medications. Although systemic corticosteroids are associated with some risk, including a small increased risk (from 0.1% to 0.3%) of cleft palate if given in the first trimester, the risks associated with unstable asthma are deemed higher. As previously discussed, risks of poorly controlled asthma include preeclampsia and low birth weight, and in severe cases maternal and fetal demise.[30,45] In contrast to the standard treatments, epinephrine infusions may compromise utero-placental perfusion and should be avoided. Helium-oxygen mixtures (heliox) are of low risk, but demonstrated efficacy for pregnant patients is lacking.[82] Similarly, the efficacy of IV magnesium in acute exacerbations remains unclear for pregnant and nonpregnant patients alike, especially for nonsevere exacerbations; pregnancy per se, however, is not a contraindication to its use if serum levels are monitored (not to exceed 5 nmol/L) and respiratory fitness is serially assessed.

An assessment of oxygenation, potential respiratory fatigue, and circulating volume is critical. Oxygen saturation should be maintained > 95%. Because pregnant patients normally have a physiologic compensated respiratory alkalosis with a P_{CO_2} range of 28 to 32 mm Hg, a seemingly normal P_{CO_2} on blood gas testing represents an acute respiratory acidosis and typically signals impending respiratory failure. Frank acidemia is a sign of imminent danger to mother and fetus. Both cases warrant ICU-level care and should include close monitoring of the mother and fetus by obstetrics.

TABLE 6] Acute Exacerbation Treatment in Pregnancy Mirrors Treatment in Nonpregnant Patients

1. Beta$_2$-agonist bronchodilation with one of the following:
• Albuterol MDI 4-8 puffs every 20 min up to 1 h, then every 1 to 4 h as needed
• Albuterol 0.083% 2.5-5 mg nebulized every 20 min for 3 doses, then every 1 to 4 h as needed
• Albuterol continuous nebulization 10-15 mg/h
2. Anticholinergic added to beta$_2$-agonist therapy:
• Ipratropium bromide nebulized 0.5 mg every 20 minutes for 3 doses, then as needed, given simultaneously with albuterol
3. Oxygen to maintain saturation $>$ 95%
4. Consider fetal monitoring if pregnancy has reached viability
5. Assess volume status and use oral rehydration or IV fluids to maintain euvolemia and adequate maternal cardiac output
6. Initiate systemic glucocorticoids without delay for patients in severe exacerbation, or who are already on chronic oral glucocorticoids, or who have mild to moderate symptoms not responsive to steps 1-5 within the first hour:
• Mild exacerbation that can be managed safely at home: oral prednisone 40 to 60 mg/d for 3 to 10 d
• Hospitalization: Oral prednisone as above, or equivalent-dose IV methylprednisolone until PEF 70% of predicted or personal best, then taper
• Critically ill: high-dose IV methylprednisolone 120-180 mg/d in three or four divided doses for 48 h, then 60-80 mg/d, tapered as patient improves
7. Adjunct therapies for patients poorly responsive to the above:
• Magnesium sulfate 2 g IV over 20 minutes. Assess baseline serum magnesium level if renal insufficiency present
• Terbutaline 0.25 mg subcutaneous every 20 min for up to three doses
8. Plan early and expert intubation and mechanical ventilation for patients in severe distress poorly responsive to the above, or who exhibit arterial pH $<$ 7.35, arterial P_{CO_2} above the normal pregnancy range of 28-32 mm Hg, or arterial P_{O_2} $<$ 70
• Monitor intensely for hyperinflation and breath stacking on mechanical ventilation, particularly in the hours immediately following intubation, as this ventilator interaction may precipitate sudden cardiovascular collapse. Disconnection from the ventilator circuit to allow exhalation for 30 to 60 s may be required. Patients who are highly active on the ventilator and show signs of hyperinflation should be deeply sedated.
• Facilitate avoidance of hyperinflation using a prolonged expiratory time ventilation strategy, including low tidal volumes (6-8 mL/kg), low respiratory rate (8-12 breaths/min), and high inspiratory flow rate (up to 100 L/min)
• Titrate ventilation to achieve normal pH, normal pregnancy P_{CO_2} of 28-32 mm Hg, and normal P_{O_2}. If hyperinflation does not permit titration to normal pregnancy P_{CO_2}, hypercapnia may be tolerated.

MDI = metered dose inhaler. See Table 4 legend for expansion of other abbreviation.

The successful use of noninvasive positive pressure ventilation in pregnancy has been described in small case series and case reports for indications other than asthma[83,84] and in one case report in a pregnant woman with asthma exacerbation.[85] Aspiration and precipitous deterioration are major concerns with the use of noninvasive ventilation in pregnant women, and given the paucity of data, noninvasive ventilation cannot be conclusively recommended in all pregnant women presenting with an asthma exacerbation. The use of noninvasive ventilation in select cases may be appropriate in the hands of an experienced clinician. Intubation and mechanical ventilation are indicated for any sign of respiratory failure, whether from hypercarbia, hypoxemia, or respiratory fatigue. Intubation should be performed by a practitioner well versed in the biologic changes of pregnancy, which increase intubation risks due to pregnancy-related airway hyperemia, aspiration, and precipitous development of hypoxemia. If necessary, euvolemia should be maintained with IV fluids, and hypotension that may ensue with positive pressure ventilation and sedation should be anticipated.

Ventilator settings must be adjusted to minimize air-trapping, also known as dynamic hyperinflation, or auto-positive end expiratory pressure (auto-PEEP), which creates exceedingly high intrathoracic pressures resulting in hypotension and volutrauma/barotrauma. Low minute ventilation with prolonged expiratory time avoids hyperinflation[86] and is achieved with low tidal volumes (6-8 mL/kg), low respiratory rate (8-12 breaths/min), and high inspiratory flow rates (up to 100 L/min in some cases). Although maintenance of normal pregnancy P_{CO_2} of 28 to 32 mm Hg is ideal, hypercapnia may be unavoidable, and tolerance of P_{CO_2} levels sometimes as high as 100 mm Hg has become the accepted ventilator strategy in patients with asthma who are not pregnant.[87,88] Permissive hypercapnia in pregnancy is controversial, as carbon dioxide transfer from fetal to

maternal circulation is gradient dependent, and fetal acidosis reduces oxygenation of fetal hemoglobin. However, fetal acidosis produced by maternal hypercapnia in the absence of hypoxia may be tolerated differently or better than fetal metabolic acidosis produced by hypoxic insult; indeed, the umbilical artery lactate level is a more discriminant measure of neonatal morbidity than pH alone.[89] A case series of five women ventilated by using a permissive hypercapnia strategy reported good pregnancy outcomes, including deliveries of apparently healthy term neonates.[90]

For patients who fail the aforementioned ventilator strategies and maximum pharmacologic treatments, extracorporeal membrane oxygenation (ECMO) has been described in nonpregnant patients with asthma[91] and in one case report of a pregnant woman with asthma.[92] A case series of 12 pregnant and postpartum women who underwent ECMO for ARDS due to H1N1 influenza reported 66% mortality in mothers and 71% in fetuses, with maternal mortality due to bleeding complications.[93] Consideration of ECMO in pregnancy should be undertaken in extreme circumstances at a center experienced in ECMO delivery. Other modalities of extracorporeal life support include extracorporeal carbon dioxide removal ($ECCO_2R$) devices, which are currently being tested at the frontier of mechanical ventilation for ARDS.[94] $ECCO_2R$ cannula placement is less traumatic than ECMO and can be used without a pump. With further study, $ECCO_2R$ may prove useful in conditions such as status asthmaticus, in which full oxygenation and circulatory support via the traditional ECMO circuit are not required.

Overall, improving the status of the mother is the most important intervention for the fetus. In addition to therapies aimed at normalizing pulmonary and cardiovascular function, involvement of an obstetrician is recommended because fetal monitoring may be indicated. A case series of 10 nonasthmatic women who gave birth while undergoing mechanical ventilation showed modest improvement in respiratory function for some, but not all, with no characteristics identifying which patients benefit from delivery of the fetus.[95]

Conclusions

Effective management of asthma in pregnancy offers the rewarding opportunity to positively influence the health of both mother and child. Studies continue to indicate that poor asthma control, particularly early in pregnancy, drives abnormal placental development and epigenetic changes in the fetus, modifying obstetric outcomes as well as downstream rates of childhood asthma. Thus, comprehensive education, modification of environmental triggers, and titration of asthma medication should ideally begin prior to conception in all women with asthma who are of reproductive age. During pregnancy, worsening asthma symptoms should be minimized aggressively via medication uptitration rather than risk poor asthma control and asthma exacerbations. Treatment guided by a supportive multidisciplinary team, objective data, and frequent clinic visits facilitates improved outcomes.

Acknowledgments

Financial/nonfinancial disclosures: None declared.

Role of sponsors: The authors were supported by no outside sponsors, except NIH research grant sponsorship to Dr Bonham. The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

Other contributions: The authors wish to thank Dr Jesse Hall, MD, for his reading and commentary on the critical care portions of this manuscript, Ms Nancy Trojan for her administrative assistance, and Drs John G. Bush, MD, and Ann M. LaBarge, MD, for their assistance during preparation of this manuscript.

References

1. Petersen JW, Liu J, Chi YY, et al. Comparison of multiple non-invasive methods of measuring cardiac output during pregnancy reveals marked heterogeneity in the magnitude of cardiac output change between women. *Physiol Rep*. 2017;5(8). pii: e13223.
2. LoMauro A, Aliverti A. Respiratory physiology of pregnancy: physiology masterclass. *Breathe (Sheff)*. 2015;11(4):297-301.
3. Rossi A, Cornette J, Johnson MR, et al. Quantitative cardiovascular magnetic resonance in pregnant women: cross-sectional analysis of physiological parameters throughout pregnancy and the impact of the supine position. *J Cardiovasc Magn Reson*. 2011;13:31.
4. Sroczynski T, Gawlikowska-Sroka A, Dzieciolowska-Baran E, Poziomkowska-Gesicka I. Causes of respiratory ailments in pregnancy. *Eur J Med Res*. 2010;15(suppl 2):189-192.
5. Grindheim G, Toska K, Estensen ME, Rosseland LA. Changes in pulmonary function during pregnancy: a longitudinal cohort study. *BJOG*. 2012;119(1):94-101.
6. Longo LD. Respiratory gas exchange in the placenta. In: *Comprehensive Physiology*. 2011:351-401. http://onlinelibrary.wiley.com/doi/10.1002/cphy.cp030418/full. Accessed October 3, 2017.
7. Soma-Pillay P, Nelson-Piercy C, Tolppanen H, Mebazaa A. Physiological changes in pregnancy. *Cardiovasc J Afr*. 2016;27(2):89-94.
8. Kwon HL, Triche EW, Belanger K, Bracken MB. The epidemiology of asthma during pregnancy: prevalence, diagnosis, and symptoms. *Immunol Allergy Clin North Am*. 2006;26(1):29-62.
9. Mendola P, Laughon SK, Mannisto TI, et al. Obstetric complications among US women with asthma. *Am J Obstet Gynecol*. 2013;208(2):127.e1-127.e8.
10. Jolving LR, Nielsen J, Kesmodel US, Nielsen RG, Beck-Nielsen SS, Norgard BM. Prevalence of maternal chronic diseases during pregnancy—a nationwide population based study from 1989 to 2013. *Acta Obstet Gynecol Scand*. 2016;95(11):1295-1304.
11. Sawicki E, Stewart K, Wong S, Leung L, Paul E, George J. Medication use for chronic health conditions by pregnant women attending an

Australian maternity hospital. *Aust N Z J Obstet Gynaecol*. 2011;51(4):333-338.

12. Kim S, Kim J, Park SY, et al. Effect of pregnancy in asthma on health care use and perinatal outcomes. *J Allergy Clin Immunol*. 2015;136(5):1215-1223.e1-6.
13. Rejno G, Lundholm C, Gong T, Larsson K, Saltvedt S, Almqvist C. Asthma during pregnancy in a population-based study—pregnancy complications and adverse perinatal outcomes. *PLoS One*. 2014;9(8):e104755.
14. Murphy VE, Namazy JA, Powell H, et al. A meta-analysis of adverse perinatal outcomes in women with asthma. *BJOG*. 2011;118(11):1314-1323.
15. Wang G, Murphy VE, Namazy J, et al. The risk of maternal and placental complications in pregnant women with asthma: a systematic review and meta-analysis. *J Matern Fetal Neonatal Med*. 2014;27(9):934-942.
16. Murphy VE, Gibson P, Talbot PI, Clifton VL. Severe asthma exacerbations during pregnancy. *Obstet Gynecol*. 2005;106(5 pt 1):1046-1054.
17. Murphy VE, Wang G, Namazy JA, et al. The risk of congenital malformations, perinatal mortality and neonatal hospitalisation among pregnant women with asthma: a systematic review and meta-analysis. *BJOG*. 2013;120(7):812-822.
18. Namazy JA, Murphy VE, Powell H, Gibson PG, Chambers C, Schatz M. Effects of asthma severity, exacerbations and oral corticosteroids on perinatal outcomes. *Eur Respir J*. 2013;41(5):1082-1090.
19. Blais L, Kettani FZ, Forget A. Relationship between maternal asthma, its severity and control and abortion. *Hum Reprod*. 2013;28(4):908-915.
20. Blais L, Kettani FZ, Forget A, Beauchesne MF, Lemiere C. Asthma exacerbations during the first trimester of pregnancy and congenital malformations: revisiting the association in a large representative cohort. *Thorax*. 2015;70(7):647-652.
21. Mendola P, Mannisto TI, Leishear K, Reddy UM, Chen Z, Laughon SK. Neonatal health of infants born to mothers with asthma. *J Allergy Clin Immunol*. 2014;133(1):85-90.e1-4.
22. Murphy VE, Powell H, Wark PA, Gibson PG. A prospective study of respiratory viral infection in pregnant women with and without asthma. *Chest*. 2013;144(2):420-427.
23. Meijer WJ, van Noortwijk AG, Bruinse HW, Wensing AM. Influenza virus infection in pregnancy: a review. *Acta Obstet Gynecol Scand*. 2015;94(8):797-819.
24. Hartert TV, Neuzil KM, Shintani AK, et al. Maternal morbidity and perinatal outcomes among pregnant women with respiratory hospitalizations during influenza season. *Am J Obstet Gynecol*. 2003;189(6):1705-1712.
25. Schanzer DL, Langley JM, Tam TW. Influenza-attributed hospitalization rates among pregnant women in Canada 1994-2000. *J Obstet Gynaecol Can*. 2007;29(8):622-629.
26. Siston AM, Rasmussen SA, Honein MA, et al. Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. *JAMA*. 2010;303(15):1517-1525.
27. Bidad K, Heidarnazhad H, Pourpak Z, Ramazanzadeh F, Zendehdel N, Moin M. Frequency of asthma as the cause of dyspnea in pregnancy. *Int J Gynaecol Obstet*. 2010;111(2):140-143.
28. Schatz M, Dombrowski MP, Wise R, et al. Asthma morbidity during pregnancy can be predicted by severity classification. *J Allergy Clin Immunol*. 2003;112(2):283-288.
29. Kircher S, Schatz M, Long L. Variables affecting asthma course during pregnancy. *Ann Allergy Asthma Immunol*. 2002;89(5):463-466.
30. Murphy VE, Clifton VL, Gibson PG. Asthma exacerbations during pregnancy: incidence and association with adverse pregnancy outcomes. *Thorax*. 2006;61(2):169-176.
31. Grzeskowiak LE, Smith B, Roy A, Dekker GA, Clifton VL. Patterns, predictors and outcomes of asthma control and exacerbations during pregnancy: a prospective cohort study. *ERJ Open Res*. 2016;2(1). pii: 00054-2015.
32. Meakin AS, Saif Z, Jones AR, Aviles PFV, Clifton VL. Review: placental adaptations to the presence of maternal asthma during pregnancy. *Placenta*. 2017;54:17-23.
33. Murphy VE, Mattes J, Powell H, Baines KJ, Gibson PG. Respiratory viral infections in pregnant women with asthma are associated with wheezing in the first 12 months of life. *Pediatr Allergy Immunol*. 2014;25(2):151-158.
34. Powell H, Murphy VE, Taylor DR, et al. Management of asthma in pregnancy guided by measurement of fraction of exhaled nitric oxide: a double-blind, randomised controlled trial. *Lancet*. 2011;378(9795):983-990.
35. Mattes J, Murphy VE, Powell H, Gibson PG. Prenatal origins of bronchiolitis: protective effect of optimised asthma management during pregnancy. *Thorax*. 2014;69(4):383-384.
36. Gunawardhana LP, Baines KJ, Mattes J, Murphy VE, Simpson JL, Gibson PG. Differential DNA methylation profiles of infants exposed to maternal asthma during pregnancy. *Pediatr Pulmonol*. 2014;49(9):852-862.
37. Murphy VE, Gibson PG, Talbot PI, Kessell CG, Clifton VL. Asthma self-management skills and the use of asthma education during pregnancy. *Eur Respir J*. 2005;26(3):435-441.
38. Zairina E, Abramson MJ, McDonald CF, et al. Telehealth to improve asthma control in pregnancy: a randomized controlled trial. *Respirology*. 2016;21(5):867-874.
39. Lim AS, Stewart K, Abramson MJ, Walker SP, Smith CL, George J. Multidisciplinary Approach to Management of Maternal Asthma (MAMMA): a randomized controlled trial. *Chest*. 2014;145(5):1046-1054.
40. Grzeskowiak LE, Smith B, Roy A, Dekker GA, Clifton VL. An observational study of the impact of an antenatal asthma management service on asthma control during pregnancy. *Eur J Obstet Gynecol Reprod Biol*. 2016;197:48-53.
41. Tinker SC, Broussard CS, Frey MT, Gilboa SM. Prevalence of prescription medication use among non-pregnant women of childbearing age and pregnant women in the United States: NHANES, 1999-2006. *Matern Child Health J*. 2015;19(5):1097-1106.
42. Powell H, McCaffery K, Murphy VE, et al. Psychosocial outcomes are related to asthma control and quality of life in pregnant women with asthma. *J Asthma*. 2011;48(10):1032-1040.
43. Gent JF, Kezik JM, Hill ME, et al. Asthma medication use during pregnancy, wheeze and estimated exposure to ambient nitrogen dioxide. *Eur Respir J*. 2015;45(2):538-540.
44. Baarnes CB, Hansen AV, Ulrik CS. Enrolment in an asthma management program during pregnancy and adherence with inhaled corticosteroids: the 'Management of Asthma during Pregnancy' program. *Respiration*. 2016;92(1):9-15.
45. National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program Asthma Pregnancy Working Group. NAEPP expert panel report. Managing asthma during pregnancy: recommendations for pharmacologic treatment-2004 update. *J Allergy Clin Immunol*. 2005;115(1):34-46.
46. Mendola P, Wallace M, Liu D, Robledo C, Mnnist T, Grantz KL. Air pollution exposure and preeclampsia among US women with and without asthma. *Environ Res*. 2016;148:248-255.
47. Mendola P, Wallace M, Hwang BS, et al. Preterm birth and air pollution: critical windows of exposure for women with asthma. *J Allergy Clin Immunol*. 2016;138(2):432-440.e5.
48. Metzger WJ, Turner E, Patterson R. The safety of immunotherapy during pregnancy. *J Allergy Clin Immunol*. 1978;61(4):268-272.
49. Shaikh WA. A retrospective study on the safety of immunotherapy in pregnancy. *Clin Exp Allergy*. 1993;23(10):857-860.
50. Shaikh WA, Shaikh SW. A prospective study on the safety of sublingual immunotherapy in pregnancy. *Allergy*. 2012;67(6):741-743.

51. Schwartz HJ, Golden DB, Lockey RF. Venom immunotherapy in the Hymenoptera-allergic pregnant patient. *J Allergy Clin Immunol*. 1990;85(4):709-712.
52. Oykhman P, Kim HL, Ellis AK. Allergen immunotherapy in pregnancy. *Allergy Asthma Clin Immunol*. 2015;11:31.
53. Cox L, Nelson H, Lockey R, et al. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol*. 2011;127(suppl 1):S1-S55.
54. Pitsios C, Demoly P, Bilo MB, et al. Clinical contraindications to allergen immunotherapy: an EAACI position paper. *Allergy*. 2015;70(8):897-909.
55. Flicker S, Marth K, Kofler H, Valenta R. Placental transfer of allergen-specific IgG but not IgE from a specific immunotherapy-treated mother. *J Allergy Clin Immunol*. 2009;124(6):1358-1360.e1.
56. Jenmalm MC, Bjorksten B. Cord blood levels of immunoglobulin G subclass antibodies to food and inhalant allergens in relation to maternal atopy and the development of atopic disease during the first 8 years of life. *Clin Exp Allergy*. 2000;30(1):34-40.
57. Lieberman J. Should we encourage allergen immunotherapy during pregnancy? *Expert Rev Clin Immunol*. 2014;10(3):317-319.
58. Powell H, Murphy VE, Hensley MJ, Giles W, Clifton VL, Gibson PG. Rhinitis in pregnant women with asthma is associated with poorer asthma control and quality of life. *J Asthma*. 2015;52(10):1023-1030.
59. Garavello W, Somigliana E, Acaia B, Gaini L, Pignataro L, Gaini RM. Nasal lavage in pregnant women with seasonal allergic rhinitis: a randomized study. *Int Arch Allergy Immunol*. 2010;151(2):137-141.
60. Ellegard EK, Hellgren M, Karlsson NG. Fluticasone propionate aqueous nasal spray in pregnancy rhinitis. *Clin Otolaryngol Allied Sci*. 2001;26(5):394-400.
61. Kallen B. Use of antihistamine drugs in early pregnancy and delivery outcome. *J Matern Fetal Neonatal Med*. 2002;11(3):146-152.
62. Werler MM. Teratogen update: pseudoephedrine. *Birth Defects Res A Clin Mol Teratol*. 2006;76(6):445-452.
63. Harding SM. Gastroesophageal reflux: a potential asthma trigger. *Immunol Allergy Clin North Am*. 2005;25(1):131-148.
64. Bidad K, Heidarnazhad H, Pourpak Z, Shayestefar G, Moayeri H, Zendehdel N. Gastroesophagial reflux disease and asthma in pregnant women with dyspnea. *Iran J Allergy Asthma Immunol*. 2014;13(2):104-109.
65. van der Woude CJ, Metselaar HJ, Danese S. Management of gastrointestinal and liver diseases during pregnancy. *Gut*. 2014;63(6):1014-1023.
66. Grzeskowiak LE, Smith B, Roy A, et al. Impact of a history of maternal depression and anxiety on asthma control during pregnancy. *J Asthma*. 2017;54(7):706-713.
67. Palmsten K, Schatz M, Chan PH, Johnson DL, Chambers CD. Validation of the Pregnancy Asthma Control Test. *J Allergy Clin Immunol Pract*. 2016;4(2):310-315.e1.
68. de Araujo GV, Leite DF, Rizzo JA, Sarinho ES. Asthma in pregnancy: association between the Asthma Control Test and the Global Initiative for Asthma classification and comparisons with spirometry. *Eur J Obstet Gynecol Reprod Biol*. 2016;203:25-29.
69. Beckmann CA. Peak flow values by gestation in women with asthma. *Clin Nurs Res*. 2008;17(3):174-181.
70. Price DB, Román-Rodríguez M, McQueen RB, et al. Inhaler errors in the CRITIKAL study: type, frequency, and association with asthma outcomes. *J Allergy Clin Immunol Pract*. 2017;5(4):1071-1081.e9.
71. Charlton RA, Pierini A, Klungsoyr K, et al. Asthma medication prescribing before, during and after pregnancy: a study in seven European regions. *BMJ Open*. 2016;6(1):e009237.
72. Beau AB, Didier A, Hurault-Delarue C, Montastruc JL, Lacroix I, Damase-Michel C. Prescription of asthma medications before and during pregnancy in France: an observational drug study using the EFEMERIS database. *J Asthma*. 2017;54(3):258-264.
73. Delea TE, Hagiwara M, Stempel DA, Stanford RH. Adding salmeterol to fluticasone propionate or increasing the dose of fluticasone propionate in patients with asthma. *Allergy Asthma Proc*. 2010;31(3):211-218.
74. Eltonsy S, Forget A, Beauchesne MF, Blais L. Risk of congenital malformations for asthmatic pregnant women using a long-acting beta(2)-agonist and inhaled corticosteroid combination versus higher-dose inhaled corticosteroid monotherapy. *J Allergy Clin Immunol*. 2015;135(1):123-130.
75. Cossette B, Forget A, Beauchesne MF, et al. Impact of maternal use of asthma-controller therapy on perinatal outcomes. *Thorax*. 2013;68(8):724-730.
76. Charlton RA, Snowball JM, Nightingale AL, Davis KJ. Safety of fluticasone propionate prescribed for asthma during pregnancy: a UK population-based cohort study. *J Allergy Clin Immunol Pract*. 2015;3(5):772-779.e3.
77. Cossette B, Beauchesne MF, Forget A, et al. Relative perinatal safety of salmeterol vs formoterol and fluticasone vs budesonide use during pregnancy. *Ann Allergy Asthma Immunol*. 2014;112(5):459-464.
78. Nelsen LM, Shields KE, Cunningham ML, et al. Congenital malformations among infants born to women receiving montelukast, inhaled corticosteroids, and other asthma medications. *J Allergy Clin Immunol*. 2012;129(1):251-254.e1-6.
79. Sarkar M, Koren G, Kalra S, et al. Montelukast use during pregnancy: a multicentre, prospective, comparative study of infant outcomes. *Eur J Clin Pharmacol*. 2009;65(12):1259-1264.
80. Namazy J, Cabana MD, Scheuerle AE, et al. The Xolair Pregnancy Registry (EXPECT): the safety of omalizumab use during pregnancy. *J Allergy Clin Immunol*. 2015;135(2):407-412.
81. Hanania NA, Belfort MA. Acute asthma in pregnancy. *Crit Care Med*. 2005;33(suppl 10):S319-S324.
82. Chan AL, Juarez MM, Gidwani N, Albertson TE. Management of critical asthma syndrome during pregnancy. *Clin Rev Allergy Immunol*. 2015;48(1):45-53.
83. Al-Ansari MA, Hameed AA, Al-jawder SE, Saeed HM. Use of noninvasive positive pressure ventilation during pregnancy: case series. *Ann Thorac Med*. 2007;2(1):23-25.
84. Allred CC, Matias Esquinas A, Caronia J, Mahdavi R, Mina BA. Successful use of noninvasive ventilation in pregnancy. *Eur Respir Rev*. 2014;23(131):142-144.
85. Dalar L, Caner H, Eryuksel E, Kosar F. Application of non-invasive mechanical ventilation in an asthmatic pregnant woman in respiratory failure: a case report. *J Thorac Dis*. 2013;5(1):97-100.
86. Leatherman JW, McArthur C, Shapiro RS. Effect of prolongation of expiratory time on dynamic hyperinflation in mechanically ventilated patients with severe asthma. *Crit Care Med*. 2004;32(7):1542-1545.
87. Bellomo R, McLaughlin P, Tai E, Parkin G. Asthma requiring mechanical ventilation. A low morbidity approach. *Chest*. 1994;105(3):891-896.
88. Peters JI, Stupka JE, Singh H, et al. Status asthmaticus in the medical intensive care unit: a 30-year experience. *Respir Med*. 2012;106(3):344-348.
89. Tuuli MG, Stout MJ, Shanks A, Odibo AO, Macones GA, Cahill AG. Umbilical cord arterial lactate compared with pH for predicting neonatal morbidity at term. *Obstet Gynecol*. 2014;124(4):756-761.
90. Elsayegh D, Shapiro JM. Management of the obstetric patient with status asthmaticus. *J Intensive Care Med*. 2008;23(6):396-402.
91. Mikkelsen ME, Woo YJ, Sager JS, Fuchs BD, Christie JD. Outcomes using extracorporeal life support for adult respiratory failure due to status asthmaticus. *ASAIO J*. 2009;55(1):47-52.

92. Steinack C, Lenherr R, Hendra H, Franzen D. The use of life-saving extracorporeal membrane oxygenation (ECMO) for pregnant woman with status asthmaticus. *J Asthma*. 2017;54(1):84-88.

93. Nair P, Davies AR, Beca J, et al. Extracorporeal membrane oxygenation for severe ARDS in pregnant and postpartum women during the 2009 H1N1 pandemic. *Intensive Care Med*. 2011;37(4):648-654.

94. Combes A, Pesenti A, Ranieri VM. Fifty years of research in ARDS. Is extracorporeal circulation the future of acute respiratory distress syndrome management? *Am J Respir Crit Care Med*. 2017;195(9):1161-1170.

95. Lapinsky SE, Rojas-Suarez JA, Crozier TM, et al. Mechanical ventilation in critically-ill pregnant women: a case series. *Int J Obstet Anesth*. 2015;24(4):323-328.