

Management of Critical Asthma Syndrome During Pregnancy

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Abstract One-third of pregnant asthmatics experience a worsening of their asthma that may progress to a critical asthma syndrome (CAS) that includes status asthmaticus (SA) and near-fatal asthma (NFA). Patients with severe asthma before pregnancy may experience more exacerbations, especially during late pregnancy. Prevention of the CAS includes excellent asthma control involving targeted early and regular medical care of the pregnant asthmatic, together with medication compliance. Spontaneous abortion risk is higher in pregnant women with uncontrolled asthma than in non-asthmatics. Should CAS occur during pregnancy, aggressive bronchodilator therapy, montelukast, and systemic corticosteroids can be used in the context of respiratory monitoring, preferably in an Intensive Care Unit (ICU). Systemic epinephrine should be avoided due to potential teratogenic side-effects and placental/uterine vasoconstriction. Non-invasive ventilation has been used in some cases. Intratracheal intubation can be hazardous and rapid-sequence intubation by an experienced physician is recommended. Mechanical ventilation parameters are adjusted based on changes to respiratory mechanics in the pregnant patient. An inhaled helium–oxygen gas admixture may promote laminar airflow and improve gas exchange. Permissive hypercapnea is controversial, but may be unavoidable. Sedation with propofol which itself has bronchodilating properties is preferred to benzodiazepines. Case reports delineating good outcomes for both mother and fetus despite intubation for SA suggest that multidisciplinary

ICU care of the pregnant asthmatic with critical asthma are feasible especially if hypoxemia is avoided.

Keywords Asthma · Pregnancy · Intensive care · Status asthmaticus · Near-fatal asthma

Introduction

Asthma per se is one of the commonest chronic medical illnesses that complicate pregnancy, occurring in up to 8.8 % of women [1, 2]. One-third of pregnant asthmatics improve, one-third remain stable, but the remaining third demonstrate a clinical worsening of their asthma [3–5]. Those who worsen are rendered at risk for developing a critical asthma syndrome, i.e., status asthmaticus (SA) and near-fatal asthma (NFA). Worsening during pregnancy may be related to pre-pregnancy baseline severity, with patients with moderate and severe asthma, in particular, demonstrating more exacerbations [6–8]. Gluck et al. [3] reported on similarities of an individual's asthma course during the first and subsequent pregnancies. Asthma symptoms and hence worsening usually peak in the late second or early third trimester, but exacerbations are rare during labor and peripartum [3, 5, 9, 10]. The optimal management of a critically ill pregnant patient due to worsening asthma can be challenging, with both mother and fetus at risk, especially from hypoxemia. Therefore, subspecialist management within a multidisciplinary Intensive Care Unit (ICU), including intensivists, asthma specialists, neonatologists, and obstetricians experienced in high-risk pregnancies, is vital for ultimate safety and success. This approach is particularly important if non-invasive ventilation (NIV) or mechanical ventilation after intratracheal intubation becomes necessary.

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Management of the Pregnant Asthmatic

The best treatment for pregnant asthmatics is excellent asthma control, including asthma education, compliance with asthma action plan, smoking cessation [11, 12], and most important, preventing exacerbations. At-risk patients should be identified early and close follow-up instituted. In fact, Maselli et al. [13] suggest that all asthmatics who become pregnant should be considered as high-risk, and followed and managed as such.

Acute Exacerbations and Indications for Admission to the ICU

Emergency department (ED) evaluation of dyspnea in an asthmatic patient must include acute exacerbation of asthma and whether a critical asthma syndrome is present, e.g., status asthmaticus (SA) or near-fatal asthma. Other causes of acute dyspnea must be excluded including pulmonary embolism, cardiogenic pulmonary edema, acute lung injury (ALI)/acute respiratory distress syndrome (ARDS), pneumonia, and pneumothorax amongst other possibilities.

CAS, once diagnosed, can be defined as an acute and severe asthma exacerbation that does not respond promptly to intensive bronchodilator therapy. It can progress to NFA, where respiratory failure has ensued [14]. Timely diagnosis and management is therefore of paramount importance because both mother and fetus are at risk for morbidity and mortality from hypoxemia. A multidisciplinary team approach as previously described should be adopted.

Overall, Cydulka et al. [15] found that 12.6 % of pregnant asthmatic women presented to the ED, and hospitalization occurred in 1.6 %. ICU admission should be considered for patients whose asthma continues to worsen despite maximal bronchodilator therapy. This includes patients whose FEV1 is <25 % predicted, or if it improves less than 10 % after treatment [13].

Physiological Changes of Pregnancy

These include an increase in the transverse diameter of the chest, and the subcostal angle widens from 68° to 103°. The diaphragm also ultimately rises by 4 cm due to an enlarging uterus. These changes result in a decrease of residual volume (RV) by 20 % but only a 5 % decrease in total lung capacity (TLC). Chest wall compliance and hence total respiratory compliance decreases by about 30 %, but lung compliance per se remains unchanged [16–18].

Ventilatory Management

Non-invasive ventilation may be an alternative under the right clinical circumstance, and may support ventilation whilst corticosteroids and maximal bronchodilator therapy take effect [9, 19]. The use of NIV is however controversial, and the case report that Dalar et al. [19] described involved a 28-year-old female in her 16th week of pregnancy with preceding influenza, the development of lobar pneumonia, and reported worsening of asthma with hypoxemic respiratory failure ($\text{PaO}_2/\text{FiO}_2$ ratio 250, APACHE II score 20). NIV administration was found to be successful in this patient. Caution regarding gastric distension whilst on NIV needs to be emphasized, especially if subsequent intubation takes place [9].

Progressive or unremitting hypoxemia, respiratory acidosis, maternal fatigue, alteration in mental status, and other causes for increased work of breathing despite maximal bronchodilator therapies and NIV are indications for intubation and mechanical ventilation (MV) [13]. Amelioration or indeed prevention of continued hypoxia to the mother and especially the fetus remains of paramount priority and importance [14].

Intubation, if indicated, in the pregnant asthmatic may be up to eight times more difficult when compared to non-pregnant women secondary to soft tissue edema [20]. In a recent study in the UK, the failure rate incidence for tracheal intubation in obstetric cases was 1 in 224 (95 % CI 179–281) with univariate analysis showing index cases to be both older and heavier with a higher body-mass index, and a Mallampati score >1. The laryngeal mask airway was the most commonly used airway in 39 of 57 cases, and gastric aspiration occurred in 4 % or 8 % index cases [20]. Reduced functional residual capacity (FRC) and increased oxygen consumption with diminished oxygen reserve can cause alarmingly rapid desaturation when the pregnant patient is apneic. Therefore, skilled intensivists or anesthesiologists should ideally perform the intubation procedure in these challenging cases. Adequate preoxygenation avoiding severe respiratory alkalosis and aerophagia is helpful [13]. Rapid-sequence protocols should be utilized [14, 21]. This may include use of non-depolarizing neuromuscular blocking agents such as rocuronium, and sedatives such as etomidate or ketamine [14]. Intratracheal intubation via the oral route should be favored over the nasal route because of hyperemia from capillary engorgement of the upper respiratory tract resulting in a narrower airway. A smaller-sized endotracheal tube may be necessary [22, 23].

Mechanical ventilation can be initiated with a target tidal volume (TV) of 6–10 ml/kg once the pregnant asthmatic patient is intubated. However, a TV of 12 ml/kg in intubated asthmatics did not show any increased complication rates [24]. Ideally an alveolar plateau pressure of 30 cm H₂O is not exceeded with any increase in TV [17]. The priority is to maintain adequate maternal oxygenation with a PaO_2 of approximately 65 mm Hg [25]. Permissive hypercapnia together

with a reduction in dynamic hyperinflation have likely contributed to the improvement in mortality for status asthmaticus patients [9, 26] although the concept of permissive hypercapnea in a pregnant patient with status asthmaticus is controversial, with minimal data available regarding its use in the intubated pregnant asthmatic. Indeed a high $p\text{CO}_2$ can have deleterious effects on uterine blood flow [27]. In addition, permissive hypercapnea may shift the fetal oxyhemoglobin dissociation curve to the right with impaired oxygenation of fetal hemoglobin and contribute to fetal respiratory acidosis [6, 9, 17]. However, Elsayegh et al. [9] showed that three of four pregnant patients intubated for status asthmaticus with hypercapnia and PaCO_2 's varying between 57 to 145 mm Hg had excellent pregnancy outcomes despite hypercapnia. The fourth patient elected to have termination of her pregnancy instead.

Dynamic hyperinflation in CAS can be ameliorated with prolonged expiratory times associated with a lower set respiratory rate, higher peak inspiratory flow rate and lower TVs. This may remedy the dyssynchrony between the pregnant patient and the ventilator and ameliorate volutrauma and barotrauma.

Invasive Hemodynamic Monitoring

Hemodynamic monitoring via a pulmonary artery catheter in the pregnant asthmatic is not usually indicated. If utilized however, the incidence of complications may be reduced due to younger age and lack of comorbid illnesses [22, 28]. Table 1 outlines the expected hemodynamic findings in a patient during late pregnancy. In the pregnant state, a decrease in systemic vascular resistance and pulmonary vascular resistance with a concomitant higher heart rate and stroke volume and hence an increased cardiac output are noted. The pulmonary capillary wedge pressure remained unchanged when compared to the non-pregnant state [22, 29]. Body surface area nomograms in pregnancy may not be routinely available, and hence hemodynamic data corrected for body surface area may not be applicable [22, 30].

Table 1 Normal hemodynamic parameters in the third trimester, giving mean ($\pm$ standard deviation) values and the change relative to values in the non-pregnant state (From Lapinsky et al. [22])

	Mean value	Change from non-pregnant value
Heart rate	83 $\pm$ 10 beats/min	10–30 % increase
Mean arterial pressure	90 $\pm$ 6 mmHg	No change
Central venous pressure	4 $\pm$ 2.5 mmHg	No change
Pulmonary capillary wedge pressure	7.5 $\pm$ 2 mmHg	No change
Cardiac output	6.2 $\pm$ 1 L/min	30–50 % increase
Systemic vascular resistance	1,200 $\pm$ 260 dyne cm s^{-5}	20–30 % increase
Pulmonary vascular resistance	75 $\pm$ 22 dyne cm s^{-5}	20–30 % decrease

Bronchodilator Therapy

Asthma drugs themselves may also impact the risk of congenital anomalies. Schatz et al. [31] studied 824 pregnant asthmatics exposed to oral corticosteroids, and found that pre-eclampsia rates were increased twofold. No increase in fetal congenital malformations was noted. In addition, no data linking inhaled steroids to adverse effects on the fetus have been noted [17]. Montelukast also did not appear to increase the baseline rate of major fetal malformations in a multicenter prospective comparative study of infant outcomes [32]. A matched cohort study based on the United Kingdom's General Practice Research database also found that asthma drugs overall did not increase the risk of fetal congenital abnormalities, when taken during the first trimester of pregnancy. The prevalence of a congenital anomaly among pregnant women not exposed to asthma drugs, and those exposed was 27.8 (95 % CI 25.4–30.6/1,000 pregnancies and 31.3 (95 % CI 27.7–35.5/1,000 pregnancies) respectively (RR 1.1, 95 % CI 1.0–1.3) [33]. However, some increased risk of specific abnormalities were found in association with specific asthma drugs, for example cleft lip or palate associated with long-acting beta-agonists. These findings were, however, not statistically significant, as they were based on small numbers (Table 2). Of note, systemic administration of epinephrine, a combined alpha and beta agonist, is not recommended because of potential teratogenic effects and placental or uterine vasoconstriction. Terbutaline, a pure beta-2 agonist, may be given subcutaneously instead as a means of systemic delivery [13, 14].

Bronchodilators remain the cornerstone of treatment in the acutely ill pregnant asthmatic in the ED and ICU. Such patients will likely benefit from continuous aerosolized delivery of beta-agonists by nebulizer (0.5 m–1.0 mg/h); as this can be associated with a more rapid clinical improvement versus intermittent nebulization at 2.5 mg every 2–4 h. Such drug delivery may be augmented with Heliox as the carrier gas at 70:30 or 80:20 helium–oxygen gas mixture. Helium per se lowers gas density and increases its viscosity, helping to convert turbulent airflow to laminar flow with a concomitant decrease in the Reynolds number to a value less than 2,000, above which turbulent airflow is thought to occur [14, 27, 34].

Table 2 Relative Risks of various anomalies according to maternal use of asthma drug during early pregnancy^a (From Vasilakis-Scaramozza C. et al. [33])

	No. of Cases	No. in Exposure category	Crude relative risk (95 % CI)
Musculoskeletal anomalies			
No exposure	35	15,840	Reference
Any exposure	19	7911	1.1 (0.6–1.9)
Short-acting β_2 agonist	18	7061	1.0 (0.5–2.1)
Long-acting β_2 agonist	2	424	1.9 (0.4–9.1)
Inhaled corticosteroid	13	4735	1.2 (0.5–2.5)
Oral corticosteroid	2	666	1.1 (0.2–5.2)
Other exposure	1	543	0.7 (0.1–5.2)
Cleft lip or palate			
No exposure	16	15,840	Reference
Any exposure	11	7911	1.4 (0.6–2.9)
Short-acting β_2 agonist	9	7061	1.4 (0.5–4.1)
Long-acting β_2 agonist	1	424	2.4 (0.3–21.8)
Inhaled corticosteroid	5	4735	0.7 (0.2–2.6)
Oral corticosteroid	1	666	1.3 (0.1–14.0)
Cardiovascular anomalies			
No exposure	67	15,840	Reference
Any exposure	38	7911	1.1 (0.8–1.7)
Short-acting β_2 agonist	36	7061	1.3 (0.8–2.1)
Long-acting β_2 agonist	2	424	1.0 (0.2–4.4)
Inhaled corticosteroid	23	4735	1.0 (0.6–1.7)
Oral corticosteroid	3	666	0.9 (0.3–3.2)
Other exposure	2	543	0.8 (0.2–3.2)
Multiple anomalies			
No exposure	34	15,840	Reference
Any exposure	24	7911	1.4 (0.8–2.4)
Short-acting β_2 agonist	23	7061	1.2 (0.6–2.2)
Long-acting β_2 agonist	2	424	1.4 (0.3–6.3)
Inhaled corticosteroid	18	4735	1.6 (0.8–3.2)
Oral corticosteroid	2	666	0.9 (0.2–3.9)
Other exposure	1	543	0.5 (0.1–4.4)

CI confidence interval

^a Exposure categories are not mutually exclusive. Controlling for potential confounders did not materially change the crude estimates

These effects of a helium–oxygen mixture can therefore decrease airway resistance to airflow especially in the more distal airways, decrease peak inspiratory pressures and improve gas exchange. Helium, as an inert gas, is not absorbed across the respiratory tract and is therefore not expected to have toxic effects on the mother or fetus. George et al. [27] described the first case report describing the successful use of a helium–oxygen mixture for mechanical ventilation in a 15-year-old girl with a second trimester intrauterine pregnancy with status asthmaticus and ARDS. The patient was discharged home 5 days after extubation, and subsequently delivered a full-term healthy male infant.

The effectiveness of concomitant inhaled ipratropium (category B) with nebulized albuterol in status asthmaticus in adults remains unclear. However, Louie et al. suggest that it may benefit critically ill asthmatics with chronic obstructive pulmonary disease (COPD) physiology and a forced

expiratory volume in 1 s (FEV1) of <50 % by increasing FEV1 to an increased degree when compared to albuterol alone, and also by decreasing the hospitalization rate [14, 35].

Systemic corticosteroids, administered orally or intravenously, can reduce mortality. For example intravenous (iv) methylprednisolone 60 mg every 6 h reduces the incidence of fatal asthma [14]. Intravenous montelukast, a leukotriene receptor antagonist, may allow patients with acute asthma to receive less beta agonists and demonstrate fewer treatment failures when compared to placebo without unexpected adverse events. The intravenous preparation of montelukast is however currently not available in the USA [14, 36].

Methylxanthines, either theophylline or aminophylline (both category C), are drugs with narrow therapeutic windows, and lack proven additional efficacy. They are therefore not routinely employed in the critically ill pregnant asthmatic [14].

Magnesium sulfate (category A) likely bronchodilates by inhibiting bronchial smooth muscle calcium channels and by blocking parasympathetic tone in the tracheobronchial tree [14]. Intravenous magnesium sulfate, also commonly used to treat preeclampsia, reduced hospitalizations in severe asthmatics when compared to placebo in the emergency department [37]. Newborns may show signs of magnesium toxicity, however, in terms of respiratory and/or neuromuscular depression.

Inhaled general anesthetics such as isoflurane (category C) and sevoflurane (category B) can provide further bronchodilation in asthmatic patients with progressive CAS despite maximal bronchodilator therapy. Therefore these agents are used under extreme circumstances only, with the more popular choice of propofol as an intravenous sedative but also with bronchodilator properties.

Ketamine (category B) is a dissociative anesthetic that causes bronchorrhea and bronchodilatation, and hence may be useful especially in NFA. However, its side effects of hallucinations may require concurrent benzodiazepine administration (category D/X), and other side effects of tachycardia and hypertension require close observation and management as clinically indicated [14].

Other ICU Medications

Asthma drugs notwithstanding, the critically ill pregnant asthmatic often requires sedation and sometimes paralysis. The safety of continuous sedation in pregnant patients is unclear. Nevertheless, propofol, a sedative-hypnotic, is category B and was used by Elsayegh et al. in their intubated pregnant asthmatic patients as their main form of sedation [9]. The authors noted that hypotension, a common side effect of propofol would risk decreasing uteroplacental blood flow, and that higher doses might lead to a reduction in uterine muscle tone [38]. However, no teratogenic effects were seen [39]. The potential bronchodilating effects of propofol confer an added advantage to its use in the pregnant asthmatic patient [14].

Benzodiazepines as sedatives in the ICU cross the placenta and are category D (there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks). They are associated with an increased risk of preterm birth and low birth weight and may have a tentative association with pylorostenosis and alimentary tract atresia [40] late trimester use of benzodiazepines may be associated with the neonatal withdrawal syndrome (i.e., floppy infant syndrome) [9, 41]. Therefore, benzodiazepine use in a pregnant asthmatic patient is best avoided if possible.

The use of opioids as analgesics in the ICU is often unavoidable, despite its category C/D classification. They cross

the placenta, and may affect the neonate neurologically [9, 42]. Caution regarding the daily necessity of opioids use is advised.

Neuromuscular paralysis is sometimes indicated in the intubated pregnant asthmatic because of continued agitation despite maximal sedation. Cisatracurium (category B) has been used by some authors [9] with success, over the short term without untoward effect. However, long-term fetal pharmacological paralysis can be associated with arthrogryposis [43]. Such neuromuscular paralysis should be minimized and removed as soon as clinically indicated, as prolonged weakness may result from its use especially in conjunction with corticosteroids over a prolonged time period [44–46].

Table 3 shows a list of asthma medications and select drugs used in the ICU as classified for safety in pregnancy by the United States Food and Drug Administration (FDA).

Other Treatments in the Critically Ill Pregnant Asthmatic

Pumpless extra-corporeal carbon dioxide (CO₂) removal may be a useful adjunct in NFA where severe hypercapnea and metabolic acidosis persist despite maximal aggressive therapies being given. Elliot et al. [47] reported on the use of a low-resistance, pumpless, gas exchange membrane that relied on an arteriovenous shunt and a sweep flow of oxygen to effect membrane diffusion of oxygen and carbon dioxide in two patients with life-threatening asthma. Successful weaning from mechanical ventilation and a full recovery were noted in both patients, but the utility of this in a pregnant patient is uncertain. However, King et al. [48] reported on the use of extra-corporeal membrane oxygenation (ECMO) utilizing bypass in a pregnant patient with pneumonia, asthma and respiratory failure. The patient was successfully weaned and extubated a few days later, and subsequently, delivered a healthy baby.

Complications

Elevated intrathoracic pressures and hyperinflation may contribute to barotrauma manifesting as pneumomediastinum, subcutaneous air, pneumothorax, and/or pericardial air. Worsening severity of such complications may lead to tension pneumothorax or even cardiac tamponade. Life-saving decompressive measures including chest tube thoracostomy in the case of the former diagnosis may become necessary [14].

Acute resuscitation of the pregnant asthmatic, including cardiopulmonary resuscitation (CPR) involves attention to body position as the gravid uterus in the supine position can mechanically diminish venous return. Left lateral decubitus positioning of the mother may ameliorate maternal cardiac output and hence blood pressure, and improve placental blood

Table 3 US FDA pregnancy category classification of asthma medications and select drugs used in the ICU (Adapted and updated from Maselli et al. [13])

	FDA pregnancy classification	Evidence for classification
ICS		
Budesonide	B	Studies involving more than 6600 infants demonstrated no association between exposure to orally inhaled budesonide during pregnancy and an increased risk of congenital malformations or other adverse fetal outcomes. There is limited data on pregnancy outcomes after maternal exposure to intranasal budesonide [54].
Beclomethasone	C	There is no evidence linking use of inhaled corticosteroids with adverse fetal outcomes in humans [9, 55]. In animal studies, however, teratogenicity and fetal deaths have been observed. Additional animal findings suggest that infants born of mothers receiving substantial doses during pregnancy should be observed for adrenal suppression [56].
Ciclesonide	C	
Fluticasone	C	
Mometasone	C	
Ipratropium	B	No adequate and well-controlled trials in pregnant women. Animal studies have failed to reveal evidence of teratogenicity [56].
LABA		
Formoterol	C	No adequate and well-controlled studies in pregnant women. Animal reproduction studies of these substances, except for indacaterol, have revealed evidence of teratogenicity as well as other developmental toxic effects. LABAs should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus [56].
Salmeterol	C	
Indacaterol ^a	C	
Aformoterol ^a	C	
Leukotriene inhibitors		
Montelukast	B	No adequate and well-controlled studies in pregnant women. No teratogenicity was observed in animal studies. During worldwide marketing experience, congenital limb defects were rarely reported in the offspring of women treated during pregnancy. Most of these women were also taking other asthma medications during their pregnancy. A causal relationship between these events and montelukast sodium has not been established [56].
Zafirlukast	B	No adequate and well-controlled trials in pregnant women. Animal reproductive studies demonstrated fetal resorption, spontaneous abortion, and maternal toxicity and death [56].
Zileuton	C	No adequate and well-controlled trials in pregnant women. Animal reproductive studies demonstrated reduced body weight, increased skeletal variations, and cleft palates [56].
Mast-cell stabilizers		
Nedocromil	B	No adequate and well-controlled trials in pregnant women. Animal studies have failed to reveal evidence of teratogenicity [56].
Cromolyn	B	
Immunomodulators		
Omalizumab	B	No adequate and well-controlled trials in pregnant women. Animal studies have failed to reveal evidence of teratogenicity [56].
Systemic corticosteroids		
Dexamethasone	C	Conflicting evidence. Some studies showed no increase in birth defects in humans, others showed that their use is associated with gestational diabetes. Use in the first trimester is associated with a threefold increased risk for isolated cleft lip with or without cleft palate, as well as increasing risk of preterm delivery, impaired fetal growth, and preeclampsia. However, due to the major benefit of systemic corticosteroids in severe asthma, the National Asthma Education and Prevention Program (NAEPP) recommends their usage during severe asthma exacerbation [9, 55].
Hydrocortisone	C	
Methylprednisolone	C	
Prednisone	C	
SABA		
Albuterol	C	Considered generally safe during pregnancy. A mainstay of treatment of patients with asthma exacerbation [9, 55].
Levalbuterol	C	
Metaproterenol	C	
Pirbuterol	C	
Terbutaline	C	
Methylxanthines		
Theophylline	C	No adequate and well-controlled studies of either theophylline or aminophylline in pregnant women exist. However, death following fetal tachycardia and metabolic acidosis in the fetus and tachycardia and intractable seizures in the neonate has been reported after aminophylline treatment [57]. Animal reproduction studies of both substances revealed evidence of teratogenicity as well as other developmental toxic effects [56].
Aminophylline	C	

Table 3 (continued)

	FDA pregnancy classification	Evidence for classification
Other bronchodilating agents		
Magnesium sulfate	A	Has not been demonstrated to increase the risk of adverse fetal outcomes if administered during any trimester of pregnancy in humans. The possibility of fetal harm therefore appears remote [56].
Drugs for sedation, analgesia, and paralysis		
Cisatracurium	B	No adequate and well-controlled trials in pregnant women. Animal studies have failed to reveal evidence of teratogenicity [56].
Ketamine	B	
Sevoflurane	B	
Propofol	B	No adequate and well-controlled trials in pregnant women. Animal studies revealed no evidence of teratogenicity. Propofol, however, has been shown to cause maternal deaths and decreased survival during the lactating period. The pharmacological activity (anesthesia) of the drug on the mother is probably responsible for the adverse effects seen in the offspring [56].
Isoflurane	C	No adequate and well-controlled trials in pregnant women. Animal studies revealed possible anesthetic-related fetotoxic effect [56].
Opioids	C/D	Therapeutic opioid use in early pregnancy was reported by 2.6 % of 17,449 case mothers and 2.0 % of 6701 control mothers in one study. Treatment was associated with cardiac defects, spina bifida, or gastroschisis in infants [58].
Benzodiazepines	D/X	Best avoided, if possible. Increased risk of preterm birth and low birth weight and may have a tentative association with pylorostenosis and alimentary tract atresia [40]. Late trimester use may be associated with the neonatal withdrawal syndrome [9, 41].

FDA categories: category B, animal studies show no risk or adverse fetal effects, but controlled human first trimester studies do not avail or confirm adverse effects, no evidence of second or third trimester risk, fetal harm is possible but unlikely; category C, animal studies show adverse fetal effects(s) but no controlled human studies have been done, maternal versus fetal risk should be weighed. FDA has proposed that pregnancy and lactation subsections of labeling include a risk summary and clinical considerations to support patient care decisions and counseling. The proposed regulations will eliminate the current pregnancy categories A, B, C, D, and X (<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/tcm093307.htm>)

FDA US Food and Drug Administration, *ICS* inhaled corticosteroids, *LABA* long-acting β_2 agonist, *SABA* short-acting β_2 agonist

^a FDA-approved for COPD. Not indicated for asthma, but may be of use in critical asthma.

flow. Elevation of the right hip by 15° may help [17, 49]. A body angle of inclination of 27° on an inclined board allows 80 % of the maximal force for chest compression delivery and yet allows significant mechanical relief to venous return [50]. Perimortem Cesarean section at 24–26 weeks of gestation may be necessary if CPR fails. This extreme option may also reverse aorto-caval compromise and allow a satisfactory outcome for both mother and fetus [22, 51].

Tata et al. [52] did show that pregnant women with asthma when compared to pregnant women without asthma had no difference in stillbirths or therapeutic abortions overall. However, the miscarriage risk was higher in the former group (odds ratio (OR), 1.10; 95 % confidence interval (CI), 1.06–1.13). In addition to miscarriage, the risk of depression and cesarean section were moderately increased in pregnant women with severe asthma and previous asthma exacerbation. Blais et al. [53] found that pregnant women with severe or uncontrolled asthma were at higher risk for spontaneous abortions. (OR=1.41; 95 % CI 1.33–1.49) and a decreased risk of induced abortions (OR=0.92; 0.88–0.97). Uncontrolled asthma per se increased the spontaneous abortion risk

by 26 % (95 % CI 14–41 %) and the risk of induced abortions by 11 % (95 % CI 1–21 %).

Conclusion

Successful outcomes for both mother and fetus in the management of critical asthma in the pregnant patient are very feasible as demonstrated by Elsayegh et al. [9]. Attention has to be paid to early and aggressive bronchodilator therapy in ameliorating both maternal and fetal hypoxemia, rapid sequence techniques if intubation becomes necessary, ventilator adjustments based on mechanical changes in the pregnant mother, consideration of helium-oxygen, maternal positioning, or controversially permissive hypercapnea as just a few factors when compared to the non-pregnant patient. These goals are best achieved using a multidisciplinary team approach. However the emphasis must still be on prevention of severe acute asthma exacerbations and their progression to one of the critical asthma syndromes, either SA or NFA. This includes access to appropriate subspecialist

care both in an early and regular manner to assess asthma control and prevent exacerbations.

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