Anesthesia for the Pregnant Patient with Asthma

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5.1 Epidemiology and Effect of Asthma on Maternal and Fetal Outcomes

Asthma remains to be the most common respiratory problem in pregnant patients despite new developments in assessment and pharmacological and non-pharmacological interventions [1–3]. Asthma prevalence in pregnant patients is estimated between 3.2% and 8.4% in the United States [4]; however reported incidence may vary geographically [5]. Moreover, this prevalence is shown to increase in recent years, similar to asthma prevalence in general which translates to an important health burden [6].

The sole effect of the disease on outcomes is difficult to determine as several other comorbidities are associated with maternal asthma such as obesity, higher smoking, and alcohol consumption as well as increased incidence of other chronic diseases [6, 7]. Possible effects of therapy on outcomes further complicate the issue.

When studies or systematic reviews controlling for these confounding factors are considered, the effect of asthma on maternal and fetal adverse events can be summarized in Table 5.1. Of note, these outcome studies are largely retrospective analysis of databases so that increased observation frequency (i.e., increased doctor visits) and hence increased possibility of detecting adverse outcomes compared to non-asthmatic counterparts should be taken into account. Additionally, although studies conclude higher incidence of adverse outcomes in uncontrolled maternal asthma, not all studies could report an association between asthma control level and outcomes [8]. These underline the need for large, prospective studies.

Even though not demonstrated in Table 5.1, respiratory viral infections are more frequently encountered in asthmatic pregnant patients compared to non-asthmatics which can deteriorate maternal health, cause asthma exacerbations, increase

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Table 5.1 Maternal asthma-related adverse outcomes

Maternal	Peripartum	Fetal
Spontaneous abortion specifically in pregnant women with uncontrolled asthma	Pulmonary embolism	Low birth weight
	Maternal ICU admission	Small for gestational age
	Antepartum and postpartum hemorrhage due to placenta previa and placental abruption	Hyperbilirubinemia
Gestational hypertension, preeclampsia, eclampsia		Respiratory distress syndrome, transient tachypnea of newborn or asphyxia
Gestational diabetes mellitus	Premature contractions, preterm delivery	Intracerebral hemorrhage in term infants
Breech presentation		Anemia for term infants
		Congenital malformations
Cesarean section		Cleft lip with or without cleft palate
		Neonatal hospitalization, ICU admission
		Neonatal death

ICU intensive care unit

hospitalization, and increase risk of preeclampsia [9]. Respiratory viral infections can also increase asthma and subsequently wheezing risk in the offspring [10]. Influenza A pandemic in 2009 (H1N1) has clearly demonstrated that pregnant patients are at higher risk of morbidity and mortality during influenza infections and risk is further increased with maternal asthma [11].

5.2 Pathophysiology and Effect of Pregnancy on Maternal Asthma

Asthma is a chronic disease of bronchial hyperreactivity and inflammation. Combined effects of muscle spasm, airway inflammation, and mucus plugging result in edema, airway flow limitation, and remodeling of the tissues [12]. Different underlying etiologies have been proposed for this disease such as innate immunity imbalance between T-helper cells Th1, Th2, and Th17 (mainly due to Th2 inflammation [13], genetics, environmental factors, and exaggerated cholinergic activity). Pathological changes lead to clinical symptoms of partially/completely reversible bronchoconstriction [14].

Pregnancy has a complex effect on asthmatic patients. In terms of hormones, progesterone increases minute ventilation and causes bronchodilation via cyclic adenosine monophosphate (cAMP) pathway with resultant amelioration of asthmatic symptoms [15]. Yet, progesterone is also held responsible for changes in beta (ß)-2 adrenoreceptor responsiveness and airway inflammation [16].

Regarding immunological changes, pregnancy is a state of so-called physiological immunosuppression. This immunosuppression is vital for fetus to control maternal immune response against its expressed paternal antigens [13]. Immunosuppression

of pregnancy is characterized by abundance of Th2 cells and regulatory T cells (Treg) that inhibit natural killer (NK) cells. NK cells offer protection against viral diseases. Increase of Treg cells in healthy pregnancy may explain viral infection susceptibility of the pregnant patients. Interestingly, there are conflicting immunological changes in asthmatic pregnant patients. There are findings of blunted lymphocyte activation (particularly CD4 and CD8 cells) in well-controlled asthmatic pregnant patients compared to nonpregnant asthmatics or healthy pregnant patients [17]. Contrary to this blunted response, there is an increase peripheral interferon (IFN)-γ-producing cells and interleukin (ILN)-4 levels [18]. Serum levels of inflammatory heat shock protein (Hsp)-70 [19] and lower levels of Treg cells in maternal asthma compared to healthy pregnant counterparts are also noted [20]. All these complex changes are speculated to be involved in maternal and fetal adverse outcomes of asthma such as preeclampsia and intrauterine growth retardation [21].

A study by Schatz et al. reviewing prospectively maintained asthma diaries and monthly spirometry showed that asthma clinic worsened in 35%, improved in 28%, and remained the same in 33% of pregnant asthma patients [22]. This study was the base of "one-third" rule stating that asthma progress can increase, decrease, or be left unchanged in one-third of pregnant patients. In this study, patients with progressed symptoms were particularly affected between 25 and 32 weeks of gestation. Luckily, asthma attack incidence and severity was decreased in the last month of pregnancy, and exacerbations were rare during labor [22].

5.3 Diagnosis

Characteristic symptoms of asthma (i.e., wheezing, cough, shortness of breath, and feeling of tightness in chest) can demonstrate intensity differences over time (symptoms usually worse at night or early in the morning) and can be triggered by a variety of causes (Table 5.2). On auscultation, wheezing can be heard, but its absence does not exclude diagnosis. For definitive diagnosis, at least a partially reversible airway obstruction should be demonstrated such as an increase greater than 12% (or 200 mL) in forced expiratory volume in 1 s (FEV_1) with bronchodilator short-acting ß-2 agonist (SABA) administration [12].

Pregnancy affects spirometry so that functional residual capacity (FRC, decreased by 17–20%), residual volume (RV, decreased by 20–25%), tidal volume (TV, increased by 30–50%), and expiratory reserve volume (ERV, decreased by 5–15%) are changed with resultant increased minute volume (MV) by 30–50%. Yet, FEV_1 and peak expiratory flow rate (PEFR) are unchanged in healthy pregnant women making these two measurements distinctive for asthma diagnosis and management [14]. There is also very modest increase in forced vital capacity (FVC) in healthy pregnant women, so that FEV_1/FVC ratio remains the same throughout pregnancy [14].

Spirometry, not handheld peak flow meters, should be performed for diagnosis though latter measurements can effectively monitor asthma progress. Peak expiratory flow rate (PEFR) is roughly 380–550 L/min in an otherwise healthy parturient.

Table 5.2 Asthma triggers and comorbidities

Trigger/comorbidity	Suggestion
Viral respiratory infections	Consider prevention by annual inactive influenza vaccination Consider antiviral medications during influenza pandemics for postexposure prophylaxis and treatment of infected individuals
Obesity	Counsel for weight control
Smoking	Patients should be questioned for smoking and advised and assisted to quit. Regular follow-up of smoking status should commence in doctor visits. In heavy-smoker pregnant asthmatic patients (>10 cigarettes/day), transdermal nicotine patches should be considered [24]
Indoor (e.g., mold, house dust mite, cockroach, animal dander, or secretory products) or outdoor (e.g., pollen) environmental triggers	Avoid triggers such as animal dander, house dust mites, cockroaches, pollens, and indoor mold. For indoor allergens mattress and pillow encasement in allergen-impermeable cover, washing bedding weekly in hot water, reduction of indoor humidity to <50%, and removal of carpeting and pets can offer protection
Irritants (e.g., tobacco smoke, strong odors, air pollutants, occupational chemicals, dusts and particulates, vapors, gases, and aerosols)	Avoid triggers. Starting immunotherapy (IT) for allergens not recommended for pregnant patients due to risk of anaphylaxis [23]
Emotions (e.g., fear, anger, frustration, hard crying, or laughing) and stress, depression	Depression can increase likelihood of uncontrolled asthma [1] and should be treated
Drugs (e.g., aspirin; and other nonsteroidal anti-inflammatory drugs, ß-blockers including eye drops, others)	Avoid triggers
Food, food additives, and preservatives (e.g., sulfites)	
Changes in weather, exposure to cold air	
Comorbid conditions (e.g., sinusitis, rhinitis, gastroesophageal reflux disease (GERD))	Discussed in diagnosis section

Asthma triggers and comorbidities should be identified, and patients should be educated for avoidance or treatment

Patients can self-monitor daily progress comparing measurements with their "personal best values" acquired in doctor visits as suggested by National Asthma Education and Prevention Program (NAEPP) of National Heart, Lung, and Blood Institute [12] and American College of Obstetricians and Gynecologists (ACOG) [23]. Severity of asthma is classified based on the occurrence of symptoms and these measurements as listed in Table 5.3.

In spite of the fact that bronchoprovocation with methacholine, histamine, or exercise challenge is used in suspicion of asthma for individuals with normal

Table 5.3 Asthma severity classification as advised by NAEPP [12] and ACOG [23]

Severity	Symptom	Nighttime awakening	Interference with normal activity (limitation of daily activity)	FEV_1 or peak flow (predicted % of personal best)	ACT score
Intermittent (well controlled)	≤2 days/week	≤Twice/month	None	>80%	≥20
Mild persistent (not well controlled)	>2 days/week but not daily	>Twice/month	Minor	>80%	16–19
Moderate persistent (not well controlled)	Daily	>Once / week	Some	60–80%	16–19
Severe persistent (very poorly controlled)	Throughout the day	≥4 times/week	Extreme	<60%	<15

This table can be used for both assessing severity in asthmatic patients who are not receiving long-term medications and controlling management to step up or down in patients with long-term medications. FEV_1 is forced expiratory volume in 1 s. ACT is Asthma Control Questionnaire [30]

spirometry, it is not recommended for pregnant patients [24]. Rather, a trial of therapy is advised in patients whom asthma suspicion could not be verified by spirometry. Similarly, skin testing for allergens is not recommended due to possibility of systemic anaphylaxis. If and when deemed necessary, immunoglobulin E antibodies for allergens can be tested in blood [25].

Differential diagnosis includes all causes of dyspnea in pregnancy including dyspnea of pregnancy (physiological dyspnea), gastroesophageal reflux, allergic rhinitis with postnasal drip, bronchitis, pneumonia, congestive heart failure, cardiomyopathy, pulmonary edema, amniotic fluid embolism, pulmonary embolism, and airway obstruction [25]. Of these, dyspnea of pregnancy is the most commonly seen in early pregnancy in 70% of the women [26], yet in this situation wheezing, cough, productive sputum, or chest tightness is not encountered.

Gastroesophageal reflux and non-allergic rhinitis due to hormonal changes in pregnancy can further exacerbate maternal asthma and should be treated accordingly [1]. For patients with allergic rhinitis, several recommendations such as avoiding triggers, intranasal hypertonic saline lavage, and intranasal corticosteroids are effective, but corticosteroids are shown to have no benefit in pregnancy-related non-allergic rhinitis. Other medications such as leukotriene receptor antagonist montelukast, intranasal or oral antihistamines, or local vasoconstrictor oxymetazoline have been used successfully in treatment of rhinitis. Oral decongestants with pseudoephedrine or phenylephrine should not be given specifically in early pregnancy as systemic vasoconstriction is linked with teratogenicity. For gastroesophageal reflux, lifestyle modifications coupled with antacids such as sucralfate or histamine $(H)_2$ receptor antagonists such as ranitidine can be used. Lifestyle modifications can be

summarized as avoidance of triggering foods (e.g., coffee) or feeding within 3 h of bedtime, eating in smaller portions, and elevation of the head of the bed while sleeping [23].

In the recent years, use of exhaled nitric oxide (NO) has been suggested for diagnosis and management of asthma. Respiratory epithelium is the origin for exhaled NO via inducible NO synthase (iNOS). In asthmatic patients, expression of iNOS and subsequently fractional exhaled NO (FeNO) is increased due to Th2 cytokines [27]. Unfortunately, smoking can interfere with FeNO results, and its effectiveness needs further testing in pregnant population [28].

5.4 Medical Management

5.4.1 Components of Medical Management

Experts in NAEPP and Global Initiative for Asthma (GINA) [29] emphasize four important components of medical management as listed below:

1. Objective monitoring and assessment: Asthma severity and progress should be controlled using objective measures and patients' reported symptoms within 2–4 weeks with validated tools such as Asthma Control Questionnaire [30] (Table 5.3). Measurement of baseline spirometry, coupled with PEFR measurements (twice/day in frequent symptom reporting patients), can help achieve this goal. For pregnant patients, an early ultrasound of the fetus (12–20 weeks) can provide a basis for subsequent development that can be compared. These patients should be followed up every 1–2 weeks till asthma control is achieved. Once asthma is well controlled, follow-up period can be lengthened to once a month.
2. Avoidance or control of triggering factors (Table 5.2).
3. Patient education: Patients should be educated to early recognize exacerbations with self-management tools and home-management plan [12]. Furthermore, despite evidence of adverse outcomes in uncontrolled asthma, pregnant patients are shown to reduce their asthma medications due to perceived threats of medications to fetus [16]. Physicians should emphasize importance of treatment and inform the patient on the risk of acute and chronic hypoxia both to mother and fetus. Another important goal of education is to instruct on correct use of inhalational technique [31].
4. Pharmacotherapy.

5.4.2 Pharmacotherapy

Guidelines [12, 23] and reviews of asthma management [1, 32] advise a stepwise approach in medications and titration of daily inhaler regimen (Table 5.4). According to this, the goal of the therapy is to encounter minimal or no chronic symptoms day/night and minimal or no exacerbations with no limitation of daily activity and to

obtain normal lung functions. Although short-acting ß-2 agonist (SABA)—preferably albuterol 2–6 puffs repeatable in 20 min—may ensure a quick relief for symptoms, the main goal is to minimize its use. In this regard, the need for 1 canister of SABA/month should alert the physician to step up in treatment. Physicians are also urged to place a low priority on stepping down the treatment till delivery is concluded [12, 23].

Inhaled corticosteroids are the mainstay of therapy in maternal asthma with an established good safety track [33, 9, 34]. Majority of studies are with budesonide for which the US Food and Drug Administration (FDA) has categorized as B in drugs for pregnancy, yet other agents such as fluticasone or beclomethasone [35] have reassuring profile. Steps have defined ICS doses as low, medium, and high (Table 5.4). Daily drug doses of budesonide for comparison in low, medium, and high administration are 200–600, 600–1200, and >1200 mcg/day, respectively [32].

Short-acting ß-2 agonist (SABA) are rescue therapy for acute asthma exacerbations. In contrast, long-acting inhaled ß-2 agonists (LABA) are "add-on controller therapy" for patients whose symptoms cannot suppress with medium dose of ICS. They are not given as monotherapy, and their safety profile is expected to be like SABA due to shared similarities in pharmacology. LABA agents (namely, salmeterol and formoterol) are not different from each other regarding the risk of low birth weight [36]. However, there are concerns on bronchodilator use in pregnancy as they are linked with esophageal atresia [37], gastroschisis [38], orofacial defects [39], and cardiac abnormalities [40] in the newborn. Albuterol, formoterol, and

Table 5.4 Medical management of asthma: stepwise approach

Asthma severity	Preferred treatment	Alternative treatment
Step 1: mild intermittent	No daily medications required, possibility of severe exacerbation with long asymptomatic periods in between, a trial of systemic corticosteroids is recommended in such case	
Step 2: mild persistent	Low-dose inhaled corticosteroid	– Cromolyn, leukotriene receptor antagonist – Sustained release of theophylline to serum concentration of 5–12 mcg/mL
Step 3: moderate persistent	– Low-dose inhaled corticosteroid and long-acting inhaled ß-2 agonist (salmeterol) *or* – Medium-dose inhaled corticosteroid – If needed (particularly in patients with recurring severe exacerbations): medium-dose inhaled corticosteroid and long-acting inhaled ß-2 agonist	– Low-dose inhaled corticosteroid and either theophylline or leukotriene receptor antagonist – If needed: medium-dose inhaled corticosteroid and either theophylline or leukotriene receptor antagonist
Step 4: severe persistent	– High-dose inhaled corticosteroid and long-acting inhaled ß-2 agonist – If needed: systemic corticosteroids long term (2 mg/kg/ day, generally not to exceed 60 mg/day)	– High-dose inhaled corticosteroid and sustained-release theophylline to serum concentrations of 5–12 mcg/mL

Adapted from [32] and [12]

salmeterol are classified as in Category C by the FDA [41]. Still, evidence against ß-agonists should be treated with caution since their use is necessitated in severe exacerbations which by itself can cause fetal problems. Indeed, contrary to findings of previous studies, a large database review of could not find any evidence of increased risk of congenital malformations in patients exposed to asthma medication during gestation [42].

Leukotriene receptor antagonists montelukast and zafirlukast antagonize effects of leukotrienes C4, D4, and E4 on airway smooth muscle by suppressing inflammation and bronchoconstriction. There is a paucity of information regarding these agents. A small study with montelukast and zafirlukast could not find any relationship with their use and maternal (pregnancy loss, gestational diabetes, preeclampsia, or low maternal weight gain) or fetal (preterm delivery, low Apgar scores, reduced measures of birth length, or head circumference in the newborns) adverse events [43]. Unlike montelukast and zafirlukast which are shown in category B by the FDA, zileuton is shown to be unsafe in animal studies and not given to pregnant asthmatics [12].

Xanthine derivative theophylline and cromolyn are alternative treatments in persistent mild asthma as they have proven to be inferior to ICS [2]. Theophylline can also be an alternative add-on agent for moderate and severe persistent asthma (Step 3 and 4) for chronic administration as it is not effective in acute exacerbations [14]. Its use is limited due to adverse effects (insomnia, heartburn, palpitations, nausea) and narrow therapeutic range affected by concomitant medications (cimetidine, lorazepam, and erythromycin) and changes in pregnancy (decreased protein binding and decreased metabolism) resulting in the need for serum level controls [2].

Omalizumab is recombinant DNA-derived humanized immunoglobulin (Ig)G1k monoclonal antibody. It binds to human immunoglobulin E in the blood, reducing inflammation. Although this drug is Category B due to animal safety studies and no reported incidence of major congenital malformations, prematurity, or small-for-gestational-age births in its registry [44], it is not prescribed during pregnancy.

Lastly oral corticosteroids are reserved for severe asthma management in pregnancy as their use has been linked with preeclampsia, orofacial defects, congenital malformations, low birth weight, and preterm delivery [45, 46]. Once more, one cannot safely conclude whether these unwanted observations were due to corticosteroid exposure or were due to asthma severity. However, in severe persistent asthma, risk of uncontrolled disease to mother and fetus clearly outweighs aforementioned risks [29].

5.4.3 Management of Acute Exacerbation

Management of acute exacerbation during pregnancy at home and at health institutions is different from each other [32]. For brevity, the latter is displayed (Fig. 5.1).

Initial evaluation of the patient should aim in ensuring the well-being of the mother and fetus. In this regard, oxygen administration, left lateral positioning of the patient, initiating hydration, and avoiding hypotension are prioritized [1, 32].

In severely distressed patients who are not responsive to medical treatment and who exhibit acute respiratory failure with arterial pH <7.35, arterial carbon dioxide

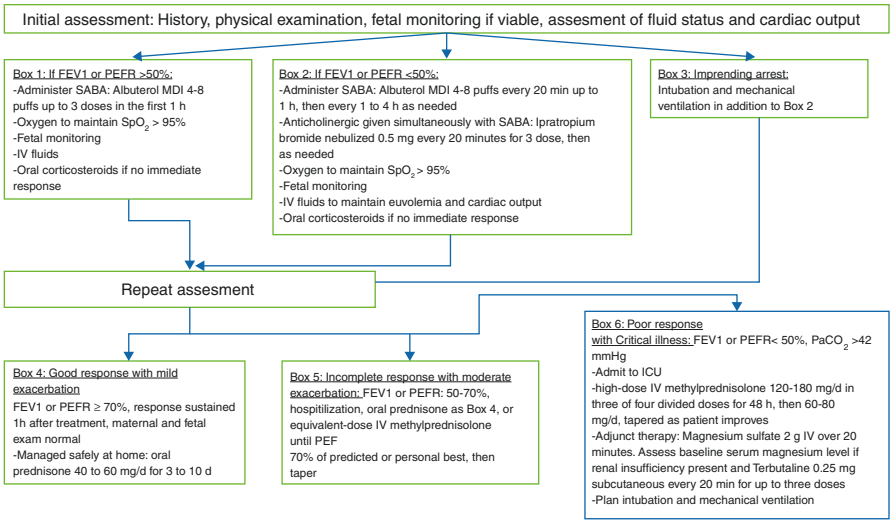

Fig. 5.1 It shows acute exacerbation treatment in pregnancy mirroring that in nonpregnant patients, adapted from [1] and [32]

partial pressure ($PaCO_2$) >42 mmHg, and arterial oxygen partial pressure (PaO_2) <70 mmHg, early intubation and mechanical ventilation must be considered. In such a case, ventilator settings should be carefully managed to avoid dynamic hyperinflation and auto-positive end-expiratory pressure (auto-PEEP) with air trapping. Dynamic hyperinflation not only leads to ineffective ventilation and increases risk of barotrauma but also causes hemodynamic instability. General goals for mechanical ventilation can be stated as low tidal volume (6–8 mL/kg), low respiratory rate (8–12 breaths/min), and high inspiratory flow rates (up to 100 L/min) to prolong expiratory time. In order to achieve these goals, hypercapnia is permitted in nonpregnant asthmatic patients, though permissive hypercapnia is controversial in pregnant patients due to fetal acidosis and reduced oxygenation of fetal hemoglobin. Yet, in a series of four patients, hypercapnia was well tolerated [47].

As a last resort, in patients in whom pharmacological treatment and mechanical ventilation have failed, extracorporeal membrane oxygenation (ECMO) may be considered. There are nonpregnant asthmatic patients reported in ECMO registry [48], but there is yet only one report of such a treatment in pregnant patient with successful results [49].

5.5 Obstetric Management

Several aspects of obstetric management need to be emphasized in asthmatic patients. Asthma medication continuation during labor and in the postpartum period is a must. There is also no contraindication to the use of prednisone, theophylline, cromolyn, inhaled corticosteroids, or ß-2 agonists during breastfeeding [23]. If the

patient is on systemic corticosteroids, intravenous corticosteroid such as 100 mg hydrocortisone at 8-h intervals during labor should be given to prevent adrenal crisis. If the patient is on steroids, blood glucose levels should be monitored to avoid maternal hyperglycemia effects on fetus [25].

If there is preterm labor danger, magnesium and terbutaline may offer additional bronchodilator effects as tocolytic agents, but indomethacin should be avoided since it may cause bronchospasm specifically in aspirin-sensitive patients [25].

Agents that should be avoided also include bronchoconstricting drugs such as prostaglandin (PG) F2α (dinoprost), ergotamine, and other ergot derivatives. In contrast, PGE1 (misoprostol) and PGE2 (dinoprostone) are deemed safe to use [12, 50, 51]. Oxytocin should be preferred for labor induction and postpartum hemorrhage control [25].

Physicians should be cautious of low-dose aspirin prescription to prevent preeclampsia, as it may trigger bronchospasm in aspirin-sensitive patients. Labetalol, a combined α- and ß-receptor antagonist, commonly used to control blood pressure in preeclamptic patients, can also cause bronchospasm and should be avoided. Of note, vasodilator agents like calcium channel blockers, nitroprusside and nitroglycerin, or hydralazine are safe in terms of bronchoconstriction but have the potential to cause hypoxemia via disturbed hypoxic pulmonary vasoconstriction in asthmatic patients [52].

5.6 Anesthetic Management

Main aims of preoperative evaluation are stratifying risks, optimizing treatment, and minimizing complications of asthma. Patients should be carefully questioned for severity of the disease on symptom frequency, nighttime awakening, limitation of daily activity, and self-measured peak expiratory flow rate if they are measuring. In fact, a correlation between American Society of Anesthesiologists (ASA) physical status classification and asthma severity classification proposed by NAEPP (Table 5.3) [12] can be established with ASA Classes 2, 3, and 4 corresponding to mild, moderate, and severe disease, respectively, in nonpregnant patients [53]. Patients should also be interrogated about the course of the disease during pregnancy, compliance to their pharmacotherapy, date of last exacerbation, smoking habit if any, and any recent pulmonary infections. Patients with severe uncontrolled asthma will be at the highest risk for adverse outcomes [53].

Physical examination may reveal wheezing with or without prolonged expiratory time on chest auscultation. A simple way to understand if exhalation is prolonged is to auscultate the trachea while the patient is instructed to forcefully exhale [54]. If this forced expiratory time is longer than 6 s, it may correlate with decreased FEV_1/FVC ratio. Of note, if the patient is in severe stress with very limited airflow, wheezing may be inaudible. In such a condition, signs of respiratory distress such as increased respiratory rate, use of accessory respiratory muscles, and/or pulsus paradoxus (>20 mmHg) due to exaggerated intrathoracic pressure swings should be looked for [55].

If the patient is stable with no symptoms, there is no need for pulmonary function tests [56], as measurements return to normal values between the attacks. However, in case of a respiratory distress, chest X-ray, arterial blood gas analysis, and spirometry are essential in differential diagnosis and management. Chest X-ray may reveal pulmonary congestion, edema, or infiltrates for differential diagnosis, whereas hyperinflation of the lungs could support diagnosis of asthma. Arterial blood gas analyses in healthy pregnant women reveal a metabolically compensated respiratory alkalosis with $PaCO_2$ of ~30 (28–32) mmHg at term. A chronically elevated $PaCO_2$ in asthmatic pregnant patient may point out uncontrolled disease status [57]. Additionally, at early stages of acute respiratory distress, further decrease in $PaCO_2$ with signs of increased ineffective ventilation efforts can be observed. However, $PaCO_2$ accumulation >42 mmHg with progressive hypoxia, acidosis, and exhaustion should alert the clinician for aggressive precautions.

5.6.1 Anesthetic Management for Labor and Vaginal Delivery

For the asthmatic laboring parturient, analgesia gains a greater importance as pain could trigger disease symptoms. In patients whose symptoms are triggered by exercise or stress, it is also essential to prevent tachypnea and anxiety. Analgesia and relief of anxiety should be accomplished with minimal respiratory depression and sedation of the mother and fetus [58].

Systemic opioids, though inferior to neuraxial techniques in terms of analgesia, are long known to effectively suppress respiratory drive and cough reflex and prevent tachypnea. They may be of benefit in patients with contraindication to neuraxial anesthesia in whom hyperpnoea can be deleterious. In fact, recently opioid receptors in pulmonary neuroendocrine cells and sensory C-fibers are becoming attractive targets to relieve refractory dyspnea in cancer patients [59]. There is some concern for morphine as large boluses over a short period of time can cause histamine release and bronchoconstriction. This concern may not reflect truth as moderate dose of morphine was able to prevent bronchoconstriction in a bronchoprovocation volunteer study with mild asthma [59]. However, morphine is not a usually preferred systemic opioid for labor analgesia due to its difficulty in titration, long elimination half-life, and potent metabolite accumulation [59]. Synthetic opioids (fentanyl, remifentanil) may be preferred as systemic opioids in asthmatic patients [54], but the latter is associated with a significant risk for maternal respiratory depression and arterial desaturation when used in healthy laboring women [59]. Physicians should be aware of the fact that systemic opioid administration in an already respiratory-compromised patient may result in respiratory arrest.

Epidural or intrathecal opioid administration particularly in the first stage of labor can effectively maintain analgesia without any motor block. As stated in a comprehensive review about obstetric setting [60], maternal respiratory depression with neuraxial opioids is rare in doses used, and large doses of intrathecal lipophilic opioids (>10 mcg sufentanil or >50 mcg fentanyl) would only increase this risk without any increased analgesic effect. However, patients under risk (patients who

have received systemic opioids or magnesium, patients with respiratory compromise) should be identified and closely monitored as respiratory depression is reported even in small doses [61].

Lumbar epidural local anesthetic administration in asthmatic laboring parturient can provide effective analgesia and suppress maternal hyperventilation caused by painful uterine contractions. Epidural analgesia using bupivacaine and fentanyl was reported to enhance effectiveness of bronchodilators in a case of laboring parturient in status asthmaticus [62]. Moreover, if emergency cesarean section is needed, presence of epidural catheter can facilitate epidural anesthesia avoiding the need for airway instrumentation. Epidural block extension higher than thoracic dermatomes could potentially lead problems in patients with respiratory compromise. But this is normally not a concern for labor analgesia, where dilute local anesthetics are used to aim an upper sensory block level of T10 dermatome.

5.6.2 Anesthetic Management for Cesarean Section

As mentioned above, regional anesthesia should be preferred for cesarean section to avoid airway instrumentation. Tracheal intubation has shown to evoke bronchoconstriction in volunteers with bronchial hyperreactivity [63]. This bronchoconstriction is an efferent response to reflex mechanism where stimulus is sensed via irritant receptors and carried by afferent parasympathetic fibers. In closed claims analysis of ASA in 1990, nearly all bronchospasm complaints were related with tracheal intubation [64]. Indeed, when similar procedures are compared, regional anesthesia is associated with fewer respiratory complications compared to general anesthesia [65].

Motor blockade of abdominal muscles during spinal anesthesia may decrease PEFR [66], but this is probably not important in asymptomatic asthma patients. It can become a point of concern when high and dense block in neuraxial anesthesia blocks accessory inspiratory muscles in patients who are dependent on these to sustain minute ventilation. However, some argue against such a possibility, as high epidural block did not result in significant vital capacity changes in respiratory-compromised mastectomy patients [67].

Second concern of high thoracic blockade is related to pulmonary sympathetic denervation with unopposed parasympathetic system causing bronchoconstriction. Yet, high thoracic epidural anesthesia did not result in such an outcome and even attenuated the response to provocation in a controlled study [68]. Still, albeit rare, there are reports of bronchospasm under regional anesthesia necessitating careful monitoring of block level [69]. Last concern is related to reduced output of adrenal medulla due to blockade of T6-L2 spinal segments. But this is not a valid theory. Although epinephrine is an effective bronchodilator, its release is not stimulated during bronchospasm [70].

General anesthesia, hence airway instrumentation, may be mandated in pregnant patients with contraindications to neuraxial anesthesia, or in patients with severe respiratory distress [71].

Need for awake intubation in obstetric anesthesia is very rare, but when indicated premedication with ß-2 agonist inhalation (even with patients' own inhaler) and local anesthetic (topical or airway blocks) can help in abolishing airway reflexes. In such a situation, risk of aspiration due to loss of reflexes should be taken into account. Intravenous lidocaine is also effective in blunting reflex response to intubation [63, 72].

Preoxygenation with adequate duration prior to induction is a must. Intubation is generally performed after rapid sequence induction with propofol and/or ketamine. Propofol has been shown to induce less bronchoconstriction than thiopentone [73, 74]. Similarly, ketamine, by directly acting on bronchial smooth muscle and potentiating catecholamine effects, has bronchodilator properties. Although there is one report of inhalation anesthesia induction [75], it is usually not preferred due to concerns of slow induction with possibility of aspiration.

For muscle relaxant choice, succinylcholine or rocuronium can be safely used for rapid sequence induction. Another alternative is vecuronium, but agents that cause histamine release such as atracurium and mivacurium should be avoided. An important point to remember is that reversal of neuromuscular agent with neostigmine at the end of the surgery could also increase secretions and trigger hyperreactivity. But this can be suppressed with atropine or glycopyrrolate. The use of sugammadex (a cyclodextrine derivative designed to encapsulate rocuronium and vecuronium) can present unique opportunities in reversing these agents at the end of operation in patients with respiratory diseases and are advocated for changes in rapid sequence induction in pregnancy [76–78]. Although an animal study on the effect of sugammadex on bronchial tonus could not demonstrate any negative effects [79], cases of laryngospasm and intraoperative anaphylaxis have recently been reported [80, 81].

Inhalational anesthesia with halogenated agents is typically used for general anesthesia maintenance, as they are effective bronchodilators also attenuating histamine-induced bronchospasm. Their effects are explained by increase intracellular c-AMP via ß-adrenergic stimulation [82]. Bronchodilator effects are dose-dependent and agent specific. There is animal data that sevoflurane inhibits allergic airway inflammation [83]. It may be preferred to desflurane as it has been shown to be superior in reducing respiratory resistance [84]. Desflurane has also been noted for bronchoconstricting effects in smokers [84]. One caveat with inhalational agents is their potential dose-dependent relaxation effect on uterine musculature [85].

Extubation and emergence is another discerning time period for asthmatic patients when bronchospasm could occur. Despite this, extubation in deep plane of anesthesia to avoid endotracheal tube stimulation carries aspiration risk.

Postoperative care should focus on adequate pain relief where trunk blocks could offer the benefit of decreasing opioid requirement. Administration of humidified oxygenation and short-acting bronchodilators may be necessary in postoperative care unit. If there is sustained exacerbation unresponsive to treatment, transfer to intensive care unit for noninvasive or invasive mechanical ventilation support may be required [32].

Key Learning Points

- Asthma is related with a series of maternal and fetal adverse outcomes. Therefore, severity and triggering factors in parturients should be assessed by a multidisciplinary team, and stepwise medical approach should be tailored according to individual needs.
- Patients should be informed that medication discontinuation, triggering agents, smoking, and/or respiratory viral infections could result in acute exacerbations with hazardous consequences.
- Anesthesiologists as well as obstetricians should avoid drugs or techniques that would provoke bronchoconstriction. In this regard, neuraxial analgesia/anesthesia—hence avoidance of airway instrumentation—should be preferred in stable patients.
- For unstable patients, rescue drugs as well as continued monitoring and possible need for mechanical ventilation should be anticipated.

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