REVIEW ARTICLE

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Asthma and pregnancy

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INTRODUCTION

Asthma during pregnancy is a significant public health issue because it is one of the most potentially serious medical problems to complicate pregnancy. Studies have shown that having asthma during pregnancy puts both mother and baby at risk for complications[1].

Several studies indicate that pregnancies in patients with asthma are associated with an increased risk for adverse obstetric outcomes, such as preeclampsia, gestational diabetes mellitus, cesarean section rate, preterm birth (PB), low birth weight (LBW), and intrauterine growth restriction[2].

Different prevalence rates of asthma during pregnancy are described. In Canada, asthma affects only 0.43% of pregnant women, while this rate can reach 8.4% in the United States. In Brazil, although there are not many studies on the subject, it is estimated that the prevalence of asthma in this population is closer to American standards, ranging from 5 to 8%[3].

An observational study using secondary data from a birth cohort study in the metropolitan area of Aracaju applied a questionnaire to 4,757 women and identified that 299 had a diagnosis of asthma before or during pregnancy, corresponding to a prevalence of 6.3%[4].

ASTHMA DIAGNOSIS IN PREGNANT WOMEN

Asthma is characterized by respiratory symptoms such as shortness of breath, wheezing, cough, and chest tightness that are often worse at night and may vary over time and intensity, together with variable airflow obstruction. Symptoms can be triggered by viral infections, exposure to allergens, smoke, exercise, changes in weather, and irritants. Detailed anamnesis and physical examination support asthma diagnosis. Additionally, documented expiratory airflow limitation and excessive variability in lung function corroborate the diagnosis[5].

Symptoms of asthma are similar in pregnant and nonpregnant patients. However, if a pregnant woman complains of shortness of breath or chest tightness, the asthma diagnosis should be carefully made based only on her symptoms[6]. Frequently, pregnant women complain of shortness of breath or chest tightness (approximately two-thirds) during the pregnancy period[7].

During pregnancy, several physiological and structural changes can contribute to a sensation of dyspnea, such as the dilated uterus, elevated diaphragm, and increased anteroposterior and transverse diameter of the thorax. Such changes are compensated by a reduction of thoracic compliance, and as a result, the functional residual capacity (FRC) and total lung function (TLC) decrease by 20 and 5%, respectively[8].

Spirometry parameters such as forced expiratory volume in first second (FEV1), forced vital capacity (FVC), and FEV1/FVC do not change during pregnancy compared to reference values in the nonpregnancy period. Spirometry may help asthma diagnosis in pregnant women by detecting reversible airway obstruction and helping monitor response to treatment. Bronchial provocation tests are not advisable to be carried out in pregnant women to prevent maternal hypoxia and fetal distress.

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Phenotyping asthma allows optimizing disease management and treatment choice, as well as identifying pharmacological pathways that are more likely to respond positively to treatment. In asthmatic pregnant women, identifying the primary phenotype as allergic or non-allergic may be enough. Serological tests for allergen-specific immunoglobulin E (IgE) are preferred to skin and provocation tests, which should be postponed until after birth because of possible, though rare, anaphylactic reactions[9]. During the pregnancy period, Th2 upregulation and other immunity changes may lead to bronchial asthma exacerbation.

PREGNANCY EFFECTS ON ASTHMA

Data about the specific mechanisms by which pregnancy might affect asthma symptoms and control are still weak. Despite that, it is known that pregnancy can cause worsening of asthma in around 30–40% of women[5,10].

The worsening of asthma, with more frequent exacerbations and poor symptom control that occurs in some pregnancies, is thought to be caused by different factors, including mechanical or hormonal changes[5]. Pregnancy might also increase the susceptibility to viral respiratory infections[11]. On the contrary, sometimes, it might be challenging to differentiate the real worsening of asthma from pregnancy-induced dyspnea. The lung function evaluation, especially FEV1, not substantially affected during pregnancy, along with other associated asthma symptoms, might be a clue for making the difference between these situations[12].

EFFECTS OF ASTHMA ON PREGNANCY

The impact of asthma during pregnancy on maternal, fetal, neonatal, and childhood outcomes has been already demonstrated in several studies. Some data suggest that asthma severity and the intensity of treatment, rather than control or exacerbations, may be related to the increased risk of preeclampsia in asthmatic women[12,13].

Other studies indicate that pregnant women with asthma, in addition to preeclampsia, are at significantly increased risk of outcomes including emergency cesarean section, LBW and PB, and neonatal intensive care unit (NICU) admissions[13].

Uncontrolled asthma can lead to hypoxia and other physiological abnormalities that could decrease fetal blood oxygen and result in abnormal growth and development of the fetus. Acute asthma exacerbations or a recurrent loss of asthma control during pregnancy have been identified as the most significant events to affect fetal morbidity and mortality than inhaled corticosteroids (ICS) use[13,14].

A significantly increased risk of LBW infants was noted in subjects experiencing asthma exacerbation during pregnancy (RR 3.02) and using oral corticosteroids (OC) (RR 1.41) [12]. On the contrary, controlled asthma during pregnancy appears to protect the fetus from adverse outcomes[13,15,16].

ASTHMA SEVERITY AND CONTROL

Asthma control assessment should be part of the anamnesis of all pregnant women diagnosed with asthma. Asthma control can be assessed using simple and easy-to-apply questionnaires, the main ones being Global Initiative for Asthma (GINA), Asthma Control Questionnaire (ACQ-7), and Asthma Control Test (ACT) (Table 1)[5,17].

Medication adherence and inhalation technique should always be evaluated[17]. In 2005, data from Australian pregnant women with asthma demonstrated that in their initial visit with an asthma nurse educator at 20 weeks of pregnancy, women with asthma had poor adherence, with 40% self-reported nonadherence with ICS, insufficient knowledge about asthma medications (42% were inadequate), and poor device technique (16% had inadequate inhaler technique)[18].

In addition, common comorbidities such as rhinitis, gastro-esophageal reflux, overweight/obesity, and smoking which can contribute to worsening asthma, should be identified and managed[17,19].

ASTHMA TRIGGERS AND COMORBIDITIES DURING PREGNANCY

Avoiding exacerbation triggers and proper comorbidities management are critical elements of successful asthma management and control.

Pregnant patients' frequency and severity of respiratory viral infections are higher for those with asthma[7]. Among all pregnant women, influenza is associated with increased morbidity and mortality, especially in the second trimester[7]. During the H1N1 pandemic season, asthma was the most common comorbidity 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[7].

Other triggers are environmental (e.g., dust and pollutants) and occupational exposure. Aspirin, other nonsteroidal anti-inflammatory drugs, and beta-blockers (in oral or ophthalmic formulations) may cause bronchospasm[17].

Pregnancy is a moment of unique psychological variability due to neuroendocrinal changes, excessive maternal weight gain,

Table 1. Definition of asthma control by different instruments.

Instrument/items	Controlled asthma	Partially controled asthma	Uncontrolled asthma
GINA			
Daytime asthma symptoms more than twice/week?	None	1–2 items	3–4 items
Any night waking due to asthma?			
SABA reliever for symptoms more than twice/week?			
Any activity limitation due to asthma?			
ACQ-7			
Number of nocturnal awakenings	≤0.75	0.75 to <1.5	>1.5
Intensity of symptons			
Limitation of activities due to asthma			
Intensity of dyspnea			
Wheezing (how long)			
Rescue medication			
Pre-bronchodilator FEV1			
ACT			
Limitation of activities due to asthma	≥20	15–19	≤15
Dyspnea			
Nocturnal awakenings due to asthma			
Rescue medication			
Self-assessment of asthma control			

GINA: Global Initiative for Asthma; ACQ-7: 7-item Asthma Control Questionnaire – 0-7 points per item; ACT: asthma control test – 0-5 points per item. The ACQ can be used without spirometry; in this case, it is referred to as ACQ-6. If used without spirometry or rescue medication, it is referred to as ACQ-5. Reference: Pizzichini et al.[17].

and additional stress regarding fetus safety[12]. Predictably, anxiety and depression potentially impact patient-related outcomes in 6–15% of pregnant asthmatics, including an increased risk of unplanned caesarian delivery and poor asthma control[20].

Obesity and gastroesophageal reflux are prevalent comorbidities in pregnant asthmatics. Maternal obesity during pregnancy represents a unique phenotype and endotype associated with increased airway obstruction, ICS resistance, upregulation of inflammatory pathways, frequent exacerbations, and increased incidence of asthma in children[21]. Exercise and combined dietary interventions significantly improve asthma control and avoid excessive maternal weight gain throughout pregnancy.

GESTATIONAL COMPLICATIONS IN PREGNANT WOMEN WITH ASTHMA

Asthma is strongly associated with preeclampsia, placental abruption, placenta previa, and obstetric hemorrhage. Decades of research have linked asthma to increased rates of cesarean delivery[7]. In addition to obstetric complications, asthma is associated with multiple comorbid maternal conditions[7]. Pediatric complications associated with poorly controlled maternal asthma include LBW and small for gestational age (SGA), with the risk of LBW increasing with asthma severity[7,16]. Table 2 shows the main gestational complications in pregnant women with asthma and fetus[7].

TAILORED ASTHMA TREATMENT IN THE PREGNANCY

Asthma education is critical to building partnership care during pregnancy. The obstetric population often needs better asthma self-management skills and knowledge, regardless of disease severity[18]. Parents should be aware that poor asthma control in pregnancy increases the risk of maternal complications and poor neonatal outcomes[13,22].

Active self-management education plays a key role in obstetric care by improving treatment adherence, asthma control, and inhaler technique and developing a written plan for unstable asthma.

Maternal smoking during pregnancy significantly increases the risk of suboptimal fetal growth and PB, enhances the risk of asthma exacerbations, impairs the effectiveness of ICS, and increases mortality[23,24]. Smoking cessation programs should

Table 2. Main gestational complications in pregnant women with asthma.

Maternal and obstetric complication	Fetal complications
Miscarriage	Low weight at birth
Gestational diabetes	Restricted intrauterine growth
Premature birth	Congenital malformations
Preeclampsia	Increase in perinatal mortality
Gestational hypertension	Fetal anomalies
Pre and pos partum hemorrhage	
Cesarian delivery	
Pulmonary embolism	
Premature rupture of membrane	

Reference: Bonham et al.[7].

ideally involve a multidisciplinary approach with periodic brief counseling interventions and cognitive behavioral therapy. Data about the safety of pharmacological approaches to smoking cessation in pregnancy are limited[25].

PHARMACOLOGICAL TREATMENT

Pharmacological treatment in asthmatics during pregnancy aims to achieve asthma control and prevent future risks, such as exacerbations, accelerated lung function decline, and adverse effects of treatment[17]. Although drug safety for pregnant women and the fetus is a general concern during pregnancy, the use of ICS, short-acting B2-agonists (SABA), short-acting anticholinergic (SAMA), long-acting B2-agonist bronchodilators (LABA), montelukast, and theophylline is not associated with a significant increase in fetal abnormalities[5,26].

As bronchial inflammation is a critical pathogenic mechanism in asthma, the use of ICS is the mainstay of pharmacological asthma treatment, as monotherapy or in association with LABA[17]. According to GINA, ICS withdrawal is not recommended during pregnancy[5].

Even though LABA monotherapy should be avoided due to increased asthma-related mortality, the combined therapy of ICS/LABA is the preferred option as an add-on therapy for patients who failed to achieve control with low/moderate doses of ICS. There was a recent paradigm shift in the management of mild asthma with the recommendation of a fixed-dose ICS/formoterol as maintenance and reliever therapy[5].

Add-on therapy with tiotropium provides functional gain and reduces exacerbations in uncontrolled asthmatics under moderate-high doses of ICS/LABA[5,17]. The small number of pregnant women with asthma in randomized clinical trials difficult to conclude on the efficacy and safety of long-acting muscarinic antagonist (LAMA) in this population.

Leukotriene receptor antagonists (LTRA) are recommended as an add-on medication to other maintenance therapies in pregnant women[5].

As in the general population, severe asthma in pregnancy is defined by persistent symptoms and/or exacerbations despite proper inhaler technique and good treatment adherence in patients treated with a medium-high dosage of ICS combined with other classes of asthma maintenance therapy[5,27]. Although a study has suggested a relationship between a high dose of ICS and fetal malformations, this should be explained by asthma severity based on the relationships between exacerbations and congenital malformations demonstrated by the same group[28].

Some patients with severe asthma may require regular OC use to achieve adequate asthma control. OC use has been associated with an increased risk of PB and LBW infants in exposed women. An increased risk of orofacial clefts was reported in a meta-analysis of case-control studies, but this increased risk was not confirmed in a large cohort study[15].

Recently, biological agents have been used in patients with severe refractory eosinophilic allergic or non-allergic asthma, but data on the use of these biologics in pregnancy are sparse[2,29]. Omalizumab (anti-IgE therapy) is one of the options for moderate-severe allergic asthma. It is currently the only asthma biological with limited available human safety data from the EXPECT pregnancy registry that reported no increased risk of congenital anomalies, stillbirths, premature birth, and SGA[30].

EXACERBATION MANAGEMENT

Studies showed that nearly half of the pregnant asthmatic women experience exacerbations, and one-fourth will experience severe exacerbations, necessitating emergency department (ED) visits or hospitalizations[29,31].

Early and aggressive interventions are necessary to treat severe acute asthma exacerbations in pregnant women to minimize maternal and fetal hypoxia risk[32].

A short story and focused physical examination should be performed rapidly with particular attention to vital signs, maternal oxygen saturation, lung function, and the work of breathing, as outlined in Table 3[5]. If feasible, fetal monitoring should be performed to evaluate fetal distress[5,33].

Recommended primary pharmacological treatment is similar for both pregnant and general adult populations and includes immediate use of inhaled ß2-agonists, inhaled ipratropium, and timely (within 30–60 min) administration of systemic corticosteroids (prednisone 60 mg orally daily up to 5 days)

Table 3. Initial severity assessment of acute asthma in pregnancy.

Findings	Mild/moderate	Severe
Speaking in	Sentences or phrases	Words or unresponsive
Respiratory rate	18–19/min	>30/min
Heart rate	100–120 beats/min	>120 beats/min
Peak flow/FEV1 (%predicted)	50–75%	<50%
Pulse oximetry (room air)	90–95%	<90%

Reference: GINA[5].

or 2 mg/kg methylprednisolone IV in the ED. Oxygen supplementation is recommended in hypoxemic patients to maintain arterial oxygen saturation between 94 and 98%[29].

Status asthmaticus gravidus is a life-threatening asthma syndrome that may require additional therapy (i.e., magnesium sulfate and Heliox), most of which have limited efficacy data in pregnant patients. Intubation and mechanical ventilation are indicated in patients with refractory respiratory failure[29].

SAFETY OF ASTHMA MEDICATIONS DURING PREGNANCY

Despite the lack of evidence for the adverse effects of asthma treatment in pregnancy, many women and doctors remain concerned[5]. Some published data summarize the evidence for human pregnancy safety data for asthma medications[12,26,34,35]. There is evidence for ICS safety during pregnancy (Evidence A) [26,36]. Budesonide is considered the first-line IC to initiate therapy because it is the most IC studied in pregnancy and shows no increased risk of congenital anomalies or stillbirths. However, another IC may be continued if asthma is controlled[12,26].

SABAs are recommended as safe in pregnancy, with salbutamol being the most studied as a rescue medication. There is evidence for **LABA** safety during pregnancy (Evidence A)[26,36], although **LABAs** are only recommended in fixed-dose combination with ICSs to moderate-severe asthma. There is no preference among available LABAs (i.e., formoterol or salmeterol). No data are available for using ultra LABAs (i.e., indacaterol and vilanterol) during pregnancy[26].

The risk of congenital anomalies of ICS/LABA combination versus high-dose ICS alone in the first trimester was similar in moderate-severe asthma, suggesting safety in pregnancy[37]. On the contrary, there is limited data on ICS/formoterol combination safety as a maintenance and reliever therapy[26].

SAMA associated with **SABA** has been recommended for managing severe asthma exacerbation not responding to SABA monotherapy. No well-controlled studies of tiotropium [LAMA] have been performed in pregnant women[12,26].

The Observational Study of the Use and Safety of Xolair (omalizumab) during Pregnancy Trial (EXPERT)[30] showed similar rates of major congenital anomalies in both groups (omalizumab vs. control). Therefore, treatment may be continued during pregnancy if the benefits outweigh the risks; however, it is not currently recommended to start omalizumab in pregnant women[26,30].

There are no available prospective data regarding the safety of other monoclonal antibodies (i.e., mepolizumab, reslizumab, benralizumab, dupilumab, and tezepelumab) for severe asthma during pregnancy. Animal studies found no teratogenic effects. Pregnancy registries https://mothertobaby.org/ongoing-study/nucalamepolizumab/, https://mothertobaby.org/ongoingstudy/fasenra/, and https://mothertobaby.org/ongoing-study/dupixent/ are ongoing for all of them, except for tezepelumab[26,38].

For the patient who requires OC for asthma control, its benefit in preventing severe exacerbations outweighs the potential risk of congenital abnormalities[26,34,35].

MANAGEMENT DURING LABOR AND DELIVERY

There are no published studies specifically addressing intrapartum management in women with respiratory disease and whether there are any clinical benefits of cesarean section *versus* vaginal birth[35]. Although there is a higher planned cesarean rate among moderate-severe asthmatics compared with mild asthma patients, labor induction is rarely indicated due to asthma[22,39].

Controller asthma medications should be maintained, as well as a reliever, if needed, during labor and delivery[5,35]. Asthma exacerbations are uncommon; however, bronchoconstriction may be induced by hyperventilation during labor and should be managed with SABA[5]. In asthmatics receiving OC, there is a potential risk of maternal hypothalamic-pituitary-adrenal axis suppression and a dose of hydrocortisone intravenously during active labor, or cesarean section should be used[35,40].

Pre-delivery evaluation and multidisciplinary planning are the cornerstones in managing women with respiratory disease[35],

decreasing severe respiratory complications[41], probably to close collaboration between obstetricians and respiratory physicians regarding pregnant asthmatic women[22].

Some obstetric considerations must be made. The use of prostaglandin E2 for labor induction or oxytocin (second and third labor stages) has not been associated with worsening lung function or asthma exacerbation[35]. Nevertheless, ergotamine may cause bronchospasm, particularly in association with general anesthesia. Oxytocin is the uterotonic choice for the active third stage of labor[35,40]. Epidural anesthesia is preferred during delivery because it reduces oxygen consumption and minute ventilation. In an emergency cesarean section, this can be extended into proper anesthesia, avoiding the need for airway management. Ketamine and halogenated anesthetics, with a bronchodilator effect, are preferred if general anesthesia is necessary[40].

Post-partum hemorrhage may be increased in women with asthma[35]. Medications used for its management may affect the respiratory system reinforcing the need for collaboration between the obstetric and respiratory teams to optimize management[35].

CONCLUSION

Asthma during pregnancy is a significant public health issue. Studies have shown that having asthma during pregnancy puts both mother and baby at risk for complications. Although there is concern about the use of asthma medications during pregnancy, disease control and exacerbations prevention outweigh the potential risk. Close collaboration between obstetricians and respiratory physicians is essential to improve clinical outcomes in asthmatic women during pregnancy.

AUTHORS' CONTRIBUTIONS

RMCP: Conceptualization, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. **JEDC:** Conceptualization, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. **LSBC:** Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. **ASM:** Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. **DCB:** Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. **GFG:** Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. **RGF:** Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. **TPB:** Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing.

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