REVIEW ARTICLE

Asthma and pregnancy: a comprehensive approach

Asma e gravidez: uma abordagem completa

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ABSTRACT

Asthma is a chronic inflammatory disease characterized by bronchial hyper-reactivity to various stimuli, culminating with bronchospasm crises. Poorly controlled asthma during pregnancy can lead to hypoxia and the consequent increase in maternal and perinatal mortality, prematurity and fetal growth retardation, hyperemesis, and preeclampsia. The course of asthma during pregnancy is not predictable and improvements, worsening, or stabilization of the framework can occur. The treatment of asthma during pregnancy is similar to the usual treatment. The main objectives of treatment are: to control symptoms by avoiding fetal hypoxia, guide the pregnant women about symptoms and how to avoid triggering factors, treatment of crises and maintenance of a normal or near-normal lung function. Asthma during pregnancy should be monitored monthly, with spirometry in the first prenatal consultation and evaluation of peak flow (peak-flow) in subsequent consultations. The medicines used for asthma are divided into two categories: medications for improving a crisis (acute symptoms) and maintenance medications (avoiding exacerbations-controlling symptoms). The ultrasound should be performed early for adequate pregnancy dating enabling appropriate follow-up of fetal growth. Serial exams on the 2nd and 3rd trimesters are essential if the pregnant woman has moderate or severe asthma or if there is suspicion of fetal growth restriction. Breastfeeding in postpartum should be encouraged, and anti-asthmatic medications maintained.

Key words: Asthma; Asthma/therapy; Pregnancy; Pregnancy Complications.

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RESUMO

A asma é doença inflamatória crônica caracterizada pela hiper-reatividade brônquica a vários estímulos, culminando com crises de broncoespasmo. Na gravidez a asma mal controlada pode ocasionar hipóxia e consequente aumento da letalidade materna e perinatal, prematuridade e retardo no crescimento fetal, hiperemese e pré-eclâmpsia. O curso da asma, durante a gravidez, não é previsível, podendo ocorrer melhora, piora ou estabilização do quadro. O tratamento da asma na gravidez apresenta-se similar ao tratamento habitual. Os objetivos principais do tratamento são: controlar sintomas evitando hipóxia fetal, orientar a gestante sobre sintomas e como evitar fatores desencadeantes, tratamento da crise e de manutenção para manter a função pulmonar normal ou próxima do normal. O monitoramento da asma na gestação deverá ser mensal, com realização de espirometria na primeira consulta de pré-natal e avaliação de pico de fluxo (peak-flow) nas consultas subsequentes. Os medicamentos utilizados para asma são divididos em duas categorias: medicamentos para melhora da crise (sintomas agudos) e medicamentos de manutenção (evitar exacerbações – controle de sintomas). A ultrassonografia deve ser realizada precocemente para adequada datação da gravidez, possibilitando acompanhamento adequado do crescimento fetal. Exames seriados no 2º e 3º trimestres são essenciais se a gestante apresenta asma moderada

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ou grave ou se há suspeita de restrição no crescimento fetal. A amamentação no pós-parto deve ser incentivada e as medicações antiasmáticas mantidas.

Palavras-chave: Asma; Asma/terapia; Gravidez; Complicações na Gravidez.

INTRODUCTION

Asthma is a chronic inflammatory disease characterized by bronchial hyper-reactivity to various stimuli including allergens, climate alterations, drugs, and infections. It has an intermittent and reversible character.[1]

Asthma is the most common obstructive pneumopathy in pregnancy, reaching 3.7 to 8.4% of pregnancies; 0.05 to 2% of pregnant women have severe asthmatic crisis.[2]

Based on this important incidence, we decided to delve into the topic asthma and pregnancy through an extensive review of the literature. After review of articles in Medline (1998-2010), meta-analyses were selected first, which are studies that summarize data from other studies using structured methods. Subsequently, clinical trials and observational cohort studies that compared different types of drugs for treatment of asthma in pregnancy, as well as their side effects and clinical efficacy were evaluated, and studies on pathophysiology of asthma and perinatal results in asthmatic patients comparing with non-asthmatic patients. Brazilian consensus and literature reviews on the subject were also evaluated.

Poorly controlled asthma during pregnancy can lead to hypoxia and the consequent increase in maternal and perinatal mortality, prematurity, fetal growth retardation, hyperemesis, and preeclampsia.[1,3-5]

The course of asthma is not predictable during pregnancy and improvement (1/3 of pregnant women), worsening (1/3 of pregnant women), or clinical stabilization can occur. However, patients with severe asthma tend to worsen and those with the mild form tend to improve. There is a trend of exacerbation between 24 and 36 gestational weeks, whereas crises are unusual during labor due to the elevation of prostaglandins (PGE) and cortisol.[6,7]

PATHOGENESIS

Bronchial inflammation is the main physical pathogenic factor of asthma. It results from complex interactions between mediating inflammatory cells (mast cells, macrophages, eosinophils, and Th2 lymphocytes) and structural cells in the airways. Various inflammatory mediators are released causing alterations in epithelial integrity, increased tonus in the airways, hypersecretion of mucus, and changes in the mucociliary function. The chronic inflammatory process may cause proliferation of epithelial cells and adjacent myofibroblasts in addition to providing deposit of collagen and thickening of the basal membrane culminating with irreversible lesions.[1,8]

Physiological alterations occur during pregnancy that can alter the course of asthma and can be divided into factors that improve and worsen asthma.[9,10] (Table 1)

Table 1 - Gestational Factors that alter the course of asthma

Physiological alterations of pregnancy that modify the course of asthma	
Improve	Worsen
Bronchodilation mediated by progesterone, E prostaglandin and atrial natriuretic peptides	Broncho-constriction mediated by F2α prostaglandin
Increased plasma cortisol	Reduction in functional residual capacity (FRC) in 18% due to elevation of the diaphragm in 4-5 cm, causing closure of small airways and reduction in ventilation perfusion indexes
Reduced levels of IgE	Increased gastro-esophageal reflux

DIAGNOSIS

The diagnosis of asthma must be based on clinical and functional conditions and evaluation of triggering factors of crises.

It is important to evaluate previous history of asthma, frequency, intensity of asthma attacks, and the need to use medicines.[1]

CLINICAL DIAGNOSIS

- symptoms of dyspnea, chronic cough, wheezing, and chest discomfort (one or more symptoms), especially at night and when waking up;[11]
- pulmonary auscultation evidencing wheezing;
- episodic symptoms with spontaneous or drug related improvement;
- crises often triggered by exposure to allergens, physical exercise, climate alterations, or respiratory infections.

Blood tests and chest x-rays are important to ward off associated lung infections.

FUNCTIONAL DIAGNOSTICS – SPIROMETRY

Performance of pulmonary function test using a spirometer.

The functional evaluation of asthma in pregnancy is based on parameters that do not change as a function of gestation:[1]

- **FEV1 –** forced expiratory volume in the 1st second;
- **FVC –** forced vital capacity (after inspiring to total lung capacity, expires quickly and intensely);
- **PEF –** peak expiratory flow (can be evaluated through a portable flowmeter, "peak-flow").

Are indicative of asthma:[1]

- obstruction of the airflow with FEV1 < 80% of predicted (predicted = 380-550 L/min) and FEV1/FVC ratio less than 75;
- obstruction of the airflow that improves significantly after using short-duration bronchodilator;
- 20% increase in FEV1 after using corticosteroids for two weeks;
- diurnal variation in peak expiratory flow (PEF) – difference between PEF measurement in the morning and at night > 20% (calculate average of three measures at every evaluation round in 2-3 weeks);
- increase of 20% in PEF after using short-duration bronchodilator;
- bronchial provocation test with bronchoconstricting agents (histamine or methacholine) positive, performed if normal spirometry in pregnant women with asthma symptoms – it is considered positive if 20% reduction in the value of FEV1 is observed.

GRAVITY CRITERIA

- heart rate > 110 bpm;
- respiratory rate > 30 BPM;
- moderate or intense dyspnea;
- accentuated use of accessory muscles;
- cyanosis, sweating, agitation, or confusion;
- PO_2< 60 mmHg and PCO_2 > 40 mmHg;
- O_2saturation < 95% in room air (equivalent to fetal PO_2 < 60 mmHg, leading to fetal hypoxia);
- respiratory acidosis;
- PFE < 50% of predicted.[1,2]

CLASSIFICATION OF ASTHMA

It is essential to classify asthma for an improved approach to the disease and consequent control avoiding maternal and fetal complications. Asthma is classified as intermittent, mild persistent, moderate persistent, and severe persistent.[1,2] (Table 2)

DIFFERENTIAL DIAGNOSIS IN PREGNANCY

Other diseases presenting acute dyspnea must be considered:[12]

- **hyperventilation in pregnancy –** can be associated with dyspnea, however, without other symptoms of asthma;
- **pneumonia –** there are signs of infection;
- **perinatal cardiomyopathy –** always perform in severe dyspnea clinical frames, cardiac and imaging clinical evaluation;
- **acute lung edema –** search for tocolytic therapy;
- pulmonary embolism;
- amniotic fluid embolism.

Table 2 - Classification of asthma

Parameters		Clinical forms			
		Intermittent	Mild persistent	Moderate persistent	Severe persistent
Clinic	Daytime symptoms	Up to 2x/week	> 2x/week	Daily	Dailycontinuous
	Nocturnal symptoms	Up to 2x/month	> 2x/month	> 1x/week	> 2x/week
	Limitation of activities	Only in a crisis	Discrete (major efforts)	Impaired (medium efforts)	Daily (minimum efforts)
	Crises	Casual and mild	Infrequent	Frequent	Frequent and severe
Spirometry	FEV1 and PEF	> 80% predicted	≥ 80% predicted	60-80% predicted	< 60% predicted
Treatment	Bronchodilator	Up to 1x/week	Up to 2 x/week	2x/week to 2x/day	> 2x/day
	Corticosteroid	No	Occasional – inhaled	Frequent-systemic	Always – systemic

TREATMENT

The treatment of asthma during pregnancy is similar to the usual treatment.

The main goals of treatment are to: control symptoms avoiding fetal hypoxia, guide the pregnant woman about symptoms and how to avoid triggering factors, treatment of crisis, and maintenance to sustain normal or near-normal lung function.[2]

Asthma in pregnancy should be monitored monthly, with spirometry in the first prenatal consultation and evaluation of peak flow (peak-flow) in subsequent consultations. Pregnant women with moderate and severe asthma should evaluate the peak flow at home. The ideal control is considered as PEF ≥ 80%. The expectant mother must schedule an appointment if PEF is 50-80% and seek emergency care if < 50%. Patients with severe asthma must be monitored jointly by the obstetrician and pulmonologist.[2,13]

The medicines used for asthma are divided into two categories: medicines for improving crisis (acute symptoms) and maintenance medications (to avoid exacerbations-control of symptoms). The most widely used bronchodilators are β2-agonists, which provide adequate effect in crises; however, because they do not have an anti-inflammatory effect, they are not indicated as maintenance treatment if used in isolation.

The early use of anti-inflammatory drugs can result in greater lung preservation by preventing the remodeling of airways.[1,14]

The specification of drugs used in the treatment of asthma, divided by the purpose of their use is presented.[14-17] (Table 3)

TREATMENT DURING CRISIS

Terbutaline is considered the safest β 2-agonist (category B), unlike others, category C by the Food and Drug Administration (FDA).[18]

Intravenous hydration is very important during an asthmatic crisis to avoid dehydration.

Pregnancy interruption is indicated if there is maternal-fetal complication.

Crises may occur during labor and should be treated in the same way as those occurring at other times.[2]

Analgesia during labor is crucial because the pain may trigger bronchospasm crises.[2]

The use of EV corticosteroid (hydrocortisone 100 mg 8/8 h) is essential for 24 h after childbirth if the patient received systemic corticosteroid during the previous four weeks.

The use of ergotamine and F2 α prostaglandin can cause bronchospasm.[19]

Table 3 - Treatment of asthma

Crisis	Maintenance
Bronchodilator fast-acting β2 agonist (1 min-4 h of action) • Salbutamol • Terbutalina • Fenoterol	Inhaled corticosteroids • Fluticasone • Budesonide • Beclomethasone • Triamcinolona = Flunisolide (in order of potency) Sistemic corticosteroids • Prednisolone • Prednisone
Anticholinergic (30 min-1 h): Bronchodilator inferior to β2 Agonist, co-adjuvant in severe crisis • Ipratropium bromide	Bronchodilator long duration β2 agonist (12 h of action) • Salmeterol: active in 20 min • Formoterol: fast action, similar to those of short duration
Xanthines Low potency and high risk of side effects Broncho-dilating action and light anti-inflammatory • Aminophylline – Co-adjuvant during crisis, restricted to hospitalized patient	Antagonist for leukotrienes Anti-inflammatories co-adjuvant Montelukast • Zafirlukast
	Xanthines Low potency and high risk of side effects Broncho-dilating action and light anti-inflammatory • Theophylline of slow action
	Cromones Anti-inflammatories co-adjuvant – modest action • Cromolyn sodium: unfavorable posology (4 x/day) • Nedocromil: not available

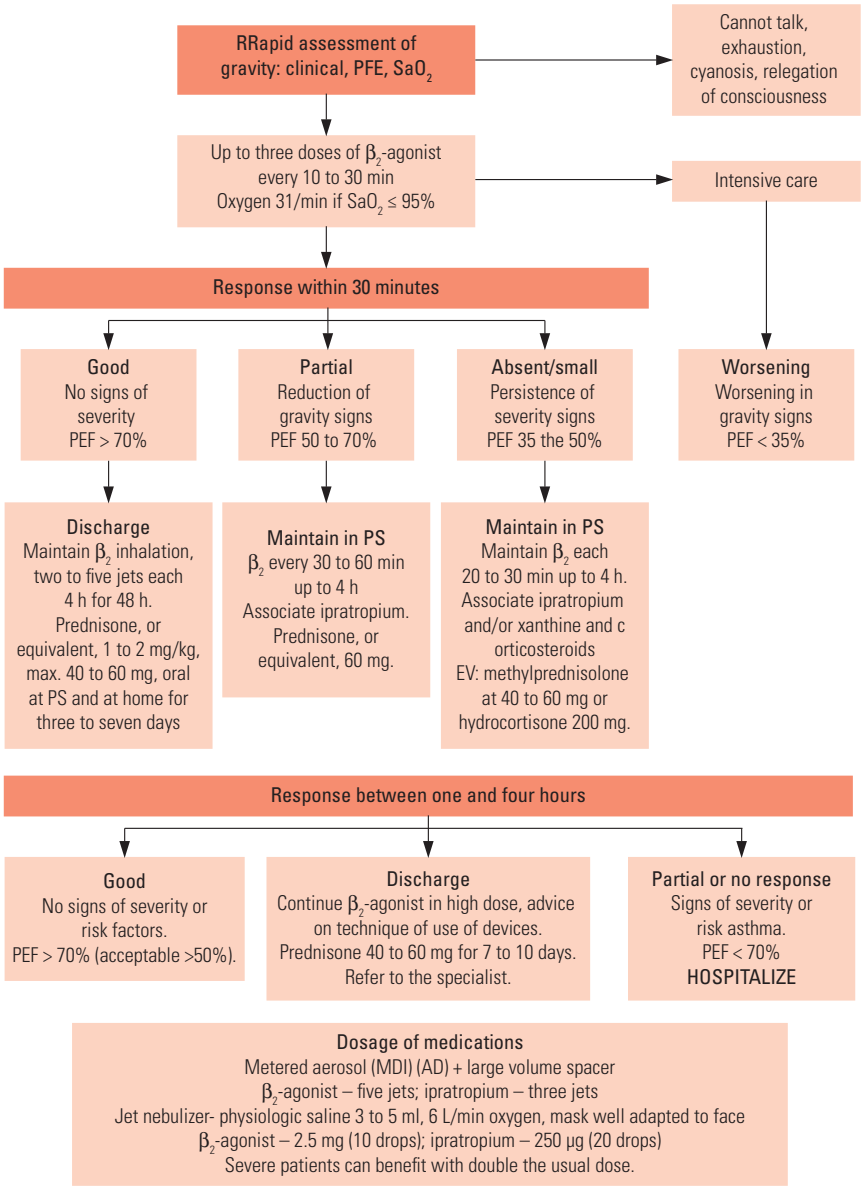

Figure 1 - Treatment algorithm of asthma crises – III Brazilian Consensus for Asthma Management 2002.

In the case of bleeding, opt for oxytocin as the first choice and, if necessary, misoprostol (E1prostaglandin does not trigger bronchospasm).[20]

MAINTENANCE TREATMENT

Mild persistent asthma

- **inhaled corticosteroid –** beclomethasone dipropionate (400-800 mcg/day).

Options: other inhaled corticosteroid, anti-leukotrienes, cromones.

MODERATE PERSISTENT ASTHMA

- inhaled corticosteroid + β 2-agonist of long duration or double the dose of inhaled corticosteroid (beclomethasone > 800 mcg/day).

If symptoms persist, associate anti-leukotrienes or slow-release theophylline or β 2-agonist of long duration.

SEVERE PERSISTENT ASTHMA

- keep medications from the previous step + oral systemic corticosteroid – 40-60 mg/day 3-10 days.

Inhaled corticosteroid may be used during pregnancy; beclomethasone is the most studied in pregnancy and considered safe. The FDA recently approved budesonide as category B, being the only inhaled corticosteroid in that category, constituting the best therapeutic option for an early treatment.[1,21,22,23]

There is a preference for prednisone and prednisolone during pregnancy. Dexamethasone and betamethasone should be avoided due to crossing the placenta in high concentrations, which can induce adrenal suppression in the fetus.[1]

Although not routinely recommended in pregnancy, theophylline is not associated with fetal malformation. However, it is associated with worsening of digestive symptoms (nausea, vomiting, and gastro esophageal reflux).[1]

If the patient remains stable for a period of three months, dose reduction can be considered.

Medicines for asthma in pregnancy, sorted into categories by the FDA are shown.[1,2] (Table 4)

FETAL MONITORING

The ultrasound should be performed early for adequate pregnancy dating allowing the appropriate monitoring of fetal growth. Serial exams on the 2nd and 3rd trimesters are essential if the pregnant woman has moderate or severe asthma or if there is suspicion of fetal growth restriction.

Cardiotocography and evaluation of the fetal biophysical profile should be performed routinely after 32 weeks in moderate and severe asthma.

In the case of asthma exacerbation, ultrasound is always recommended after recovery.

Breastfeeding in the postpartum should be encouraged. There is no contraindication to the use of corticosteroid, β2-agonist, and theophylline during breastfeeding. Occasionally, theophyllines can cause irritability in children.[24]

Table 4 - Categories of Anti-asthma Medicines in Pregnancy

Category	Interpretation	
A	Controlled studies show absent risk	
B	No evidence of risk in humans	
C	Risk not excluded (potential benefits justify potential risk)	
D	Positive evidence of risk (research data show risk for fetus but potential benefits can outweigh risk)	
X	Contraindicated in pregnancy (fetal risk clearly greater than potential benefits)	
Class	**Specific Drug**	**FDA Category**
β_2-agonist	Salbutamol	C
	Terbutaline	B
	Salmeterol	C
Methylxanthines	Theophylline	C
Anticholinergics	Ipratropium	B
Corticosteroids	Budesonide	B
	Beclomethasone	C
	Triamcinolona	C
	Flunisolide	C
	Fluticasone	C
Cromones	Cromolyn sodium	B
	Nedocromil	B
Anti-leukotrienes	Montelukast	B
	Zafirlukast	B

REFERENCES

1. III Consenso Brasileiro no Manejo da Asma. Rev AMRIGS. 2002; 46(3,4):151-72.
2. Hardy-Fairbanks JA, Baker RE. Asthma in pregnancy: pathophysiology, diagnosis and management. Obstet Gynecol Clin N Am. 2010; 37:159-72.
3. Nelson HS, Weber RW. Endocrine aspects of allergic diseases.In Bierman CW, Pearlman DS, eds. Allergic Diseases from Infancy and Adulthood. Philadelphia:WB Saunders; 1988.
4. Stenius-Aarniala R, Pirila P, Teramo K. Asthma and pregnancy: a prospective study of 198 pregnancies. Thorax. 1988; 43(1):12-8.
5. Enriquez R, Griffin MR, Carroll KN, Wu P, Cooper WO, Gebretsadik T, *et al*. Effect of maternal asthma and asthma control on pregnancy and perinatal outcomes. J Allergy Clin Immunol. 2007; 120(3):625-30.
6. Schatz M, Hoffman E, Zeiger RS. The course and management of asthma and allergic diseases during pregnancy. In Middleton E, Reed CE, Ellis EF,eds. Allergy: Principles and Practice. St Loouis: Mosby Year Book Inc; 1988.
7. Schatz M, Dombrowski MP, Wise R, Thom EA, Landon M, Mabie W, *et al*. Asthma morbidity during pregnancy can be predicted by severity classification. J Allergy Clin Immunol. 2003; 112(2):283-8.
8. Kumar R. Understanding airway wall remodeling in asthma: a basis for improvements in therapy. Pharmacol Ther. 2001; 91:93-104.
9. Liccardi M, D'Amato M, D'Amato G. Asthma in pregnant patients: pathophysiology and management. Monaldi Arch Chest Dis. 1998; 53(1):151-2.
10. Scatz M. Asthma during pregnancy: interrelationships and management. Ann Allergy. 1992; 68(1):123-5.
11. Busse W, Lemanske R. Asthma. N Eng J Med. 2001; 344:350-62.
12. National Asthma Education Program Report of the Working Group on Asthma and Pregnancy. Bethesda: NTH Publication; 1993, p.1-47.
13. Drombrowski M, Schatz M. Asthma in pregnancy. Clin Obstet Gynecol. 2010; 53(2):301-10.
14. National Institute of Health and National Heart, Lung and Blood Institute. Practical guide for diagnosis and management of asthma. NIH Publ. 1997; 97:1-8.
15. Orsida B, Ward C, Li X, Bish R, Wilson JW, *et al*. Effect of a long-acting beta 2-agonist over three months on airway wall-vascular remodeling in asthma. Am J Respir Crit Care Med. 2001; 164(1):117-21.
16. Suissa S, Ernst P. Inhaled corticosteroid: impact on asthma morbidy and mortality. J Alergy Clin Immunol. 2001; 107:937-44.
17. Andersson F, Kjellman M, Forsberg G, Möller C, Arheden L. Comparison of the cost-effectiveness of budesonid and sodium cromoglycate in the management of childhood asthma in everyday clinical practice. Ann Allergy Asthma Immunol. 2001; 86(5):537-44.
18. The use of newer asthma and allergy medications during pregnancy. Ann Allergy Asthma Immunoll. 2000; 84(5):475-80.
19. Crawford J. Bronchospam following ergometrine. Anaesthesia. 1980; 35(4):397-8.
20. Towers C, Briggs G, Rojas J. The use of prostaglandin E2 in pregnant patients with asthma. Am J Obst Gynecol. 2004; 190(6):1777-80.
21. Dombrowski M. Asthma and pregnancy. Obstet Gynecol. 2006; 108(3):667-81.
22. Blais L, Beauchesne M, Rey E, Malo JL, Forget A. Use of inhaled corticosteroids during the first trimester of pregnancy and the risk of congenital malformations among womem with asthma. Thorax 2007; 62(4):320-8.
23. Kallen B, Rydhstroem H, Aberg A. Congenital malformations after the use of inhaled budesonide in early pregnancy. Obst Gynecol. 1999; 93(3):392-5.
24. National Asthma Education and Prevention Program expert panel report. Managing asthma during pregnancy: recommendations for pharmacologic treatment. J Allergy Clin Immunol. 2005; 115(1):34-46.