7. Special Circumstances

7.1 Asthma and Pregnancy

B Some 4-7% of pregnant women suffer from asthma, which is the most common respiratory disease during pregnancy. Up to 20% of pregnant women with asthma experience exacerbations of the disease and 6% have to be admitted to the hospital because of severe attacks [310]. These figures are worse in patients with severe persistent asthma, up to 50% of whom may suffer an exacerbation [311]. The most common trigger factors are viruses. Exacerbations in pregnancy are associated with poor compliance or adherence to inhaled glucocorticoid maintenance treatment [310,312].

7.1.1 Efects of Asthma during pregnancy

C Pregnant asthma patients have a higher incidence of complications, particularly hemorrhages, eclampsia, hypertension, placental presentation, the need for caesarean delivery, low birth weight and/ or premature delivery [313]. In poorly controlled asthma, hypoxemia caused by an exacerbation is the main risk factor for premature delivery, intrauterine growth retardation and low birth weight [314]. C

The results of some recent studies suggest that in pregnant asthma patients, in whom the foetus is female, there is a deterioration of their asthma with a greater number of exacerbations and hospitalizations during gestation as a result of their disease [315].

7.1.2 Treatment of asthma during pregnancy

Practically all medications employed in the treatment of asthma cross the placental barrier; however, few have repercussions on the foetus. Poor control of maternal asthma poses a greater risk to the foetus than the possible teratogenic effects of the drugs habitually used in asthma treatment [316-318]. The drugs used to treat asthma during pregnancy are not substantially different to those employed with any other woman with asthma of a similar level of severity, including for exacerbations [318-320]. C

Table 7.1. Summary of the levels of evidence for the general and therapeutic management of pregnant women with asthma [319, 320]

Recommendations for asthma during pregnancy	Level of evidence
– The effect of asthma on pregnancy and vice versa is not a contraindication for gestation.	B
– It is safer for the patient and the fetus to receive treatment that controls asthma symptoms.	B
– Assessment must include clinical evaluations, spirometry and the occasional measurement of inflammatory parameters.	B
– To assess pulmonary function it is preferable to use spirometry rather than peak expiratory flow measurement, although the latter may be sufficient.	C
– Routine evaluation of pulmonary function (spirometry) is recommended in pregnant patients with persistent asthma, as pulmonary function and asthma severity may vary during gestation.	C
– Inhaled glucocorticoids are the first choice for control therapy in persistent asthma.	B
– Budesonide is the glucocorticoid of choice.	B
– Inhaled salbutamol is the relief therapy of choice.	B
– Salmeterol and formoterol can be used in selected cases, but considering the findings of a risk-benefit analysis.	C
– Montelukast, zafirlukast and nedocromil sodium can continue to be used in pregnant women with difficulties controlling to asthma who have previously responded to these drugs.	C
– Immunotherapy can be continued in patients who are receiving maintenance doses and who obtain a demonstrated therapeutic benefit.	B
– Breastfeeding is not contraindicated in the case of: prednisone, theophylline, antihistamines, inhaled glucocorticoids, $ß_2$ adrenergic agonists or sodium cromoglycate.	B
– The need for medication is reduced if maternal trigger factors are identified, controlled and avoided (obesity, allergens, irritants and tobacco smoke).	B
– Application of the asthma education program: monitorinf of symptoms and daily variability of lung function (peak expiratory flow meter), review of the correct inhalatory technique, implementation and regular review of the action plan.	C

C A study involving 2014 newborns, whose mothers were treated with inhaled budesonide during the period of gestation, did not identify a higher incidence of teratogenesis (3.8%) in comparison with the general population (3.5%) [321].

B Clinical studies that compared the safety of short-acting ß$_2$ adrenergic agonists (chiefly salbutamol) did not detect a greater risk of side effects [319,322]. No information is available on long-acting ß$_2$ adrenergic agonists.

B Nor did trials that evaluated the safety of theophyllines (risk category C according to the FDA) during pregnancy demonstrate a higher risk of side effects.

B With respect to the use of oral glucocorticoids (risk category B according to the FDA), although in the past they were associated with a greater risk of foetal deformities (particularly when they were taken during the last three months of pregnancy [323]), the evidence currently available is not conclusive. Our opinion is that it can be administered during pregnancy [324], as long as its use is justified.

B There are no conclusive studies about the safety of antileukotrienes in pregnancy [325].

RECOMMENDATIONS

– Given that **poor asthma control during pregnancy** entails an increase in maternal and fetal morbi-mortality because of the risk of suffering a severe asthma exacerbation, it is advisable to monitor the level of asthma control closely throughout gestation. **R2**

– The drugs usually employed (ß$_2$ adrenergic agonists and inhaled glucocorticoids) are recommended for the maintenance treatment of asthma in pregnant women. **R1**

7.2 Difficult to Control Asthma

D It is accepted that 5% of asthma patients have asthma that is difficult to control (DCA) [326]. Although a universally accepted definition is lacking, SEPAR has proposed a diagnostic approach based on major and minor criteria [327]. DCA includes all asthma patients whose disease is characterized as particularly aggressive and insufficiently or poorly controlled, although the patients follow an appropriate therapeutic strategy adjusted to their level of clinical severity [327]. Synonyms for DCA include: refractory asthma, asthma which is resistant to treatment, glucocorticoid-resistant asthma, corticoid-dependent and difficult asthma.

7.2.1 Diagnosis and associated factors

C The final diagnosis of DCA must comply with three previous conditions: confirmation that the anti-asthma treatment is appropriate and that it is being followed correctly, that other diseases resembling asthma have been ruled out (Table 7.2) and that factors that aggravate the disease are controlled (Table 7.3) (Fig. 7.1). The diagnosis is confirmed in only 55% of patients who are initially suspected of having DCA [328]. Hospital admission may be necessary to determine whether a conventional but supervised treatment achieves better results. Ten percent of DCA cases have major psychiatric problems [328,329]. Clinically, as long as there is reason to suspect DCA, all the diagnostic techniques described in Table 56 must be attempted.

7.2.2 Treatment

D Despite their side effects, oral glucocorticoids continue to be the drug of choice. Their administration must be adjusted as to deliver the minimum dose that will ensure the patient has few symptoms and exacerbations as possible. Total control of

Table 7.2. Diseases that resemble or are often associated with asthma

Oher diseases
– Chronic obstructive pulmonary disease
– Cystic fibrosis and bronchiectasis
– Bronchiolitis
– Left ventricle failure
– Bullous emphysema or emphysema due to alpha-1 antitrypsin deficiency
– Tracheal or central airway obstruction
– Hyperventilation
– Neuromuscular disease
Asthma-related Diseases
– Rhinosinusitis
– Allergic bronchopulmonary aspergillosis
– Psychiatric disorders
– Carcinoid syndrome
– Hyperthyroidism
– Gastroesophageal reflux
– Vocal cord dysfunction
– Churg-Strauss syndrome
– Eosinophillic pneumonia
– Obstructive sleep apnoea

Table 7.3. Factors that aggravate asthma

Continued exposure to allergens or irritants
- Pets
- Environmental fungi
- Inhalation of cocaine
- Domestic dust mites
- Tobacco smoke
- Occupational exposure

Drugs
- Aspirin and anti-inflammatories COX-1 inhibitor
- ß-bloquers
- Angiotensin converter enzyme inhibitors

Other factors
- Stress, anxiety, depression, panic attacks
- Premenstrual syndrome

Table 7.4. Diagnostic techniques and attitudes recommended for the evaluation of difficult to control asthma

Confirm asthma diagnosis
- Spirometry with bronchodilator test
- Bronchoconstriction test (methacholine, histamine and others agents).
- Daily variability of peak expiratory flow.

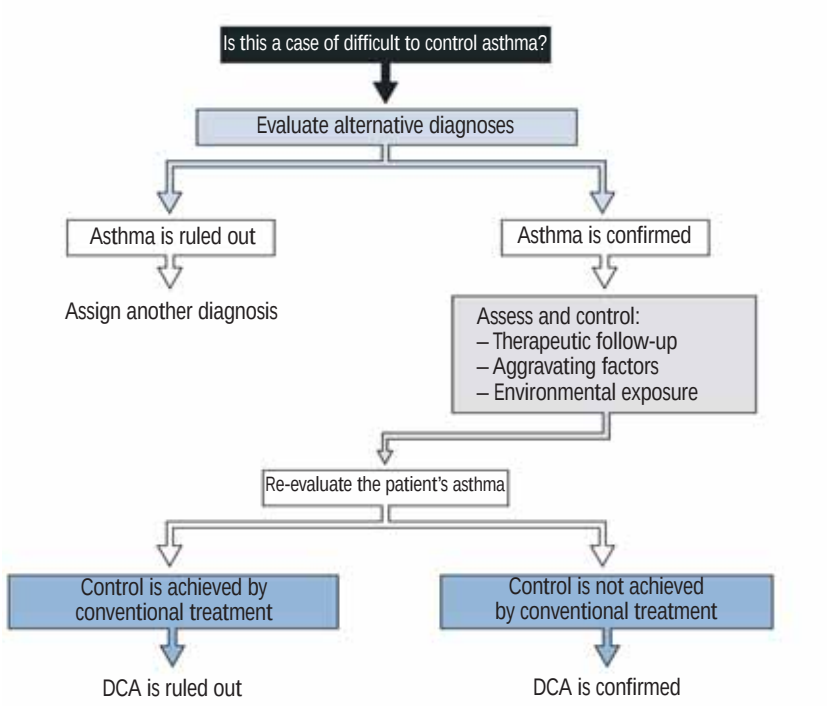
Confirm good therapeutic compliance
- Hospital admission with supervised treatment
- Morning levels of plasma cortisol (patients receiving oral glucocorticoid treatment)

Evaluation of other respiratory diseases
- Lung volumes
- CT of sinuses and upper respiratory tract
- Exhaled nitric oxide (FE_{NO}).
- Bronchoscopy
- Alveolar-capillary diffusion
- High resolution chest CT
- Laryngoscopy
- Sputum inflammatory cell count

Evaluation of aggravating factors
- Allergological assessment using prick test/IgE analysis
- Psychiatric assessment
- Oesophageal pH-metry
- Evaluation of work-related respiratory risk

Complete diagnosis with the DCA phenotype

Abbreviations: CT = computed tomography; GC = glucocorticoids; DCA: difficult to control asthma.



After an asthma diagnosis is confirmed, in just over half of cases initially suspected of being DCA, it is confirmed after three compulsory steps:
- Preparation of a detailed differential diagnosis
- Confirmation that the asthma treatment is correct and there is compliance
- Identification and control of factors that aggravate asthma and environmental exposure

Figure 7.1. Algorithm for the diagnosis of difficult to control asthma (DCA).

D the disease is not always the ultimate goal of treatment. This is why relatively frequent use of rescue medication is accepted and it is best to reach a compromise with the patient as to what level of symptoms is tolerable. A limitation in the use of oral glucocorticoids has been the main aim of a series of drugs (immunomodulators) that are specifically used for DCA. The B reduction in glucocorticoids as a result of the use of these drugs has been very modest and their role in the treatment of DCA is not entirely clear. The most recent approach is treatment using an alpha tumoral necrosis factor (TNFα) antagonist (etanercept), but, after an initially promising publication [330], its efficacy has not been confirmed in a recent clinical trial [331].

Some patients with DCA may benefit from theophylline treatment if serum levels are adjusted so that they fall within the right therapeutic range [332]. C

Recognition of the patient's phenotype may contribute therapeutic advantages [333]. Thus, in cases of asthma associated with atopia and with high levels of IgE, omalizumab B reduces the number of hospitalizations and visits to the ED [334]. In addition, in asthma associated with nasal polyposis and aspirin intolerance, antileukotriene agents may be usefu [332]. Another group of asthma patients with severe and sudden-onset crises (type II brittle asthma) may benefit from D self-administration of epinephrine using preloaded syringes (Altellus®) [326].

RECOMMENDATIONS

- Patients with difficult to control asthma (DCA) should normally be controlled at specialized hospital centers by experienced medical personnel. **R2**
- In diagnostic and therapeutic approaches to DCA it is advisable to follow a protocol framework based on decision algorithms, which establish the steps and drugs that must be used rationally, progressing in stages from less to more aggressive measures. **R2**
- Recognition of the DCA phenotype may confer therapeutic advantages. **R1**
- DCA treatment should not pursue the absolute control of symptoms, so it is advisable to reach an agreement with the patient as to what constitutes a maximum tolerable level of control of asthma symptoms. **R2**

7.3 Work-related Asthma

The inhalation of certain agents (Table 7.5) in the workplace may cause asthma or make it worse. The former is known as "occupational asthma" (OA) and the latter as "work-aggravated asthma" (WAA).

7.3.1 Occupational Asthma

OA is a disease characterized by a varying degree of airflow limitation and/or bronchial hyperresponse and/or inflammation of the respiratory tract due to causes and conditions that can be attributed to a specific work environment and not to stimuli found outside the workplace [335]. It is the most common occupational respiratory C disease and can account for as much as 25% of all cases of asthma onset in adults [337]. Depending on its mechanism of action and whether or not there is a period of latency, we can distinguish between:

7.3.1.1 Immunological occupational asthma or asthma with a latency period

C The immunological mechanism by which certain agents cause OA may or may not be mediated by IgE. In general, it is accepted that high molecular weight particles (proteins) generate an IgE-mediated response. It is possible to demonstrate sensitization to these agents by means of prick or in vitro tests, which involve determining specific IgE levels using ELISA and immunoblotting methods [68]. People who are atopic have a higher risk of developing OA [338, 339]. C

Often there is an association with rhinitis [340], and having occupational rhinitis increases the risk of suffering OA [341]. In general, when low molecular weight agents induce asthma by an immunological mechanism, they usually do so via a route that is not IgE-dependent, although sometimes some of them (isocyanates, persulfates or metals) can cause asthma by an IgE-mediated mechanism [342]. C

The diagnosis of this disease entity is based on a detailed clinical and occupational history, the demonstration of sensitization when the mechanism is IgE-mediated, confirmation of asthma and finally proof that the asthma is work-related [343]. When and how to use the different diagnostic methods at our disposal is summarized in Figure 7.2. C

The specific bronchial provocation test is considered the gold standard for confirming a diagnosis of OA [344]. C

Various studies have shown that when exposure to the

Table 7.5. Agents that cause occupational asthma [152, 336]

Type	Agent	Industry/exposure
IMMUNOLOGICAL OR WITH A LATENCY PERIOD		
High molecular weight:		
Enzymes	Alcalase, amylase, others enzymes	Soaps, breadmaking, food industry
Cereals and Flours	Wheat, barley, rye, oats, corn, sunflower seeds, soy, etc.	Baking industry, breadmaking, cakemaking milling, transport, agriculture
Animals	Rats, guinea pigs, cows, crustaceans, etc.	Laboratory personnel, vets, farmers, seafood processors
Latex	Latex	Healthcare personnel
Low molecular weight:		
Diisocyanates	Toluene diisocyanate (TDI), methylene diisocyanate (MDI) and hexamethylene diisocyante (HDI)	Polyurethane, plastic varnishes, insulation, materials, spray painting
Acid anhydrides	Phthalic, trimelthyl, hexahydrohthalic and tetrachlrophthalic acid, pyromellitic dianhydride	Plastics and resins, adhesives, chemical industry, flame retardants
Metals	Platinum salts, cobalt sulphate, chromium sulphate and other chromium salts, potassium dichromate	Platinum refineries, polishers, chrome and silver paint, tanners, ground glass
Antibiotics	Penicillin, spiramycin, tetrachycline	Pharmaceutical industry
Amines	Piperazine, ethanolamine, dimethylpropylamine, ethylenediamine, aliphatic amines, aminoethanolamine, hexamethylenetetramine	Chemical industry, aerosol paint, ski manufacturing, lacquers, photography, rubbers, soldering, cables
Woods	Red cedar, colophony	Timber, electronic welding
Miscellaneous	Glutaraldehyde, persulphate salts, cyanoacrylate, metyl methacrylate, polyethylene, chloramine	Nursing/endoscopy, hairdressing, orthopaedic, glue, paper packaging, plastic bags, sterillizing equipment
NON-IMMUNOLOGICAL OR WITH NO LATENCY PERIOD		
Bleach/hydrochloric acid	Chlorine and ammonium	Cleaning
Smoke	Smoke	Fire service, accidents, etc.
Gases	NOx, SO_2, ozone	Metallurgy, agriculture, etc.
Others	Resins, acetic acid, caustic soda, etc.	Chemical industry, healthcare personnel, etc.

C occupational agent causing OA is curtailed, there is significant clinical improvement [345].

C The symptoms and changes in pulmonary function may persist for years after the last exposure to the causal agent [346].

C The reduction of environmental levels of the causal agent minimizes the number of individuals who become sensitized and may therefore develop OA [347].

7.3.1.2 Non-immunological occupational asthma or asthma without a latency period

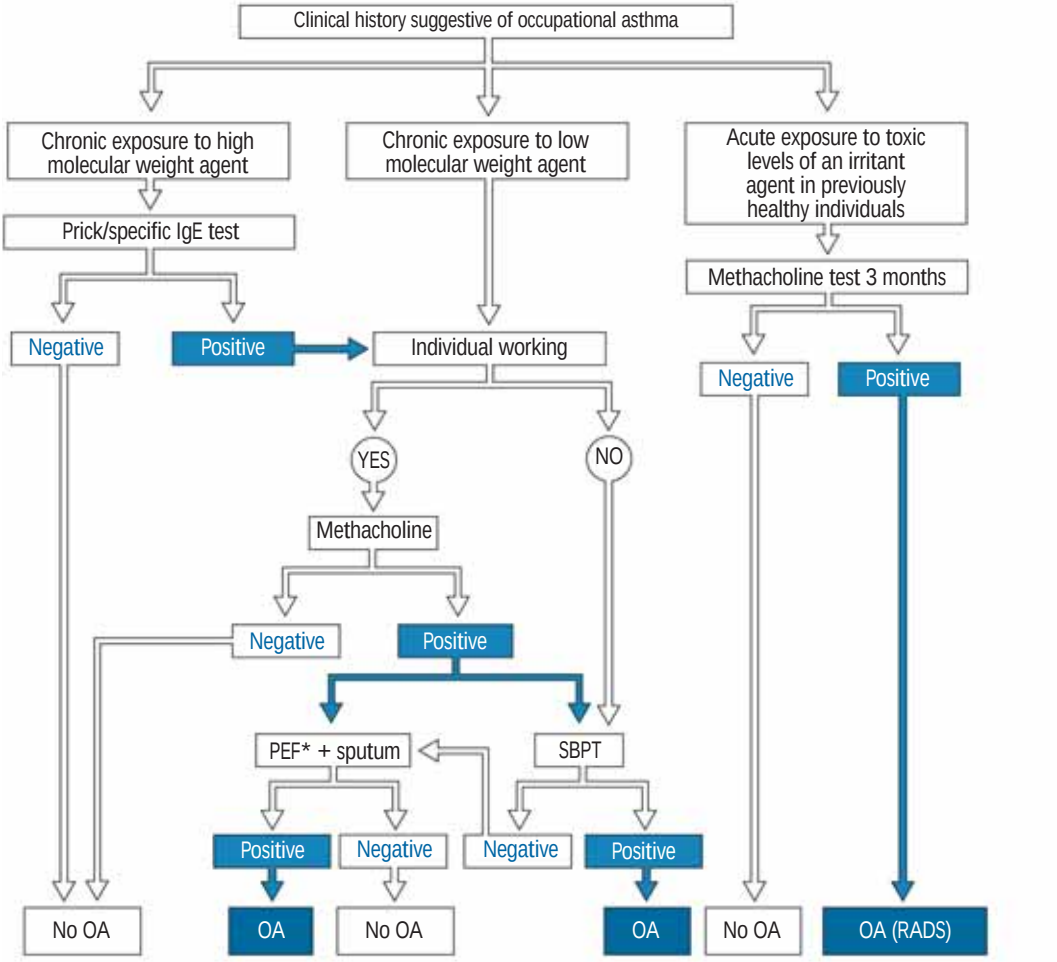
C The inhalation of high concentrations of irritant agents can cause non-immunological OA or reactive airway dysfunction syndrome (RADS) [348]. The diagnosis is made on the basis of clinical criteria [152]. If the patient recovers or his asthma is controlled by his usual treatment, a change of post is not strictly necessary [349]. It is uncertain whether chronic exposure to low doses of irritants can cause OA [350]. C

7.3.2 Work-aggravated Asthma

WAA is a situation in which the aggravation of a patient's asthma is due to circumstances that can be attributed to the workplace.

D Diagnosis is based on clinical suspicion, when the patient complains of work-related clinical deterioration of asthma that existed before he joined his post, if work-related changes in pulmonary function are demonstrated and if occupational asthma is ruled out [351].

In addition to appropriate pharmacological treatment, therapy is based on improving environmental conditions in the workplace and on the use of protection systems. The



OA: occupational asthma; RADS: reactive airway dysfunction syndrome; SBPT: specific bronchial provocation test; PEF: peak expiratory flow: *Measurements performed after a 15-day working period and 15 days on sick leave; sputum analysis of changes in the number of eosinophils.

Figure 7.2. Algorithm for the diagnosis of occupational asthma.

RECOMMENDATIONS

- In adult onset asthma occupational origin must be ruled out. **R2**
- The standard test for diagnosing immunological occupational asthma is the specific bronchial provocation test. **R2**
- For the diagnosis of WAA in a person who has previously been diagnosed with asthma the demonstration of work-related deterioration in lung function is recommended. **R2**
- In the treatment of immunological occupational asthma total cessation of exposure to the causal agent is recommended. **R2**
- In reactive airway dysfunction syndrome (RADS), if asthma control is achieved with or without medical treatment, it is not necessary for the patient to change his job. **R2**

patient will only need to abandon his post in severe cases [352].

7.4. Vocal Cord Dysfunction

B

Vocal cord dysfunction is defined as a "paradoxical adduction of the vocal cords during inspiration, which can simulate an asthma attack" [353]. It may take the form of laryngeal stridor, dyspnea, dysphonia, a dry cough, muscular retraction and/or superficial respiration, and it may be accompanied by wheezing in the upper thoracic region [354]. It is more common in adolescent women [355] and has been linked to physical exercise [356] and psychiatric factors (anxiety and personality disorders) [354]. The diagnosis is confirmed by identifying paradoxical movements and adduction of the vocal cords by fibroscopic video rhino-laryngoscopy [354]. Spirometry can show interruptions of the inspiratory loop and an increase in the forced expiratory flow/forced inspiratory flow ratio to 50% of vital capacity [357]. The proposed treatments are rehabilitation techniques based on speech therapy and relaxation, inhaled anticholinergic agents, helium inhalation or the use of a facial mask that affords inspiratory resistance [358].

D

C

RECOMMENDATIONS

– Vocal cord dysfunction must be diagnosed by fibroscopic video rhino-laryngoscopy. **R2**

– For the treatment of vocal cord dysfunction the use of speech rehabilitation and vocal cord relaxation techniques is recommended. **R2**