



General strategy for the management of bronchial asthma in pregnancy

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KEYWORDS

Airway inflammation;
Bronchial asthma;
Pregnancy;
Management;
Side effects

Summary Epidemiological studies showed that bronchial asthma is one of the most common diseases which can complicate pregnancy (1–7%). In about 0.05–2% of the cases, asthma occurs as a life-threatening event. In the common medical practice a waiting strategy or, even, the complete refusal for drug therapies are frequently observed. This is justified by the fear of the possible adverse effects of drugs on developing fetus. On the contrary, several studies have demonstrated that severe and uncontrolled asthma may produce serious maternal and fetal complications, such as gestational hypertension and eclampsia, fetal hypoxemia and an increased risk of perinatal death. Therefore, all pregnant women suffering from bronchial asthma should be considered as potentially at high risk of complications and adequately treated. Since asthma is a chronic disease with acute exacerbations, a continuous treatment is mandatory to control symptoms, to prevent acute episodes and to reduce the degree of airway inflammation. The global strategy for asthma management in pregnancy includes five main topics: (1) objective evaluation of maternal/fetal clinical conditions; (2) avoidance/control of triggering factors; (3) pharmacological treatment; (4) educational support; (5) psychological support. As far as drug therapy is concerned, the International Guidelines and Recommendations suggest that the general strategy does not differ significantly from management outside pregnancy. We herein review and discuss the available data and the criteria for the management of asthma in pregnant patients.

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Introduction

The recently published large population-based epidemiological studies have shown that the prevalence of asthma is high and constantly increasing. This finding is mainly evident in industrialized countries, but consistent data from developing and low-income countries are also available.^{1–3} In particular, bronchial asthma represents one of the most frequent diseases that may complicate

pregnancy (about 1–7% of all pregnancies).^{4,5} In about 0.05–2% of cases, asthma is a life-threatening event.⁶ Unfortunately, it is likely that these figures may be underestimated, since many patients suffering from bronchial asthma do not inform their physicians about the disease.

Uncontrolled asthma can lead to nocturnal troublesome respiratory symptoms, emergency department visits, hospitalizations, intubation, and even death. Similarly, uncontrolled asthma in pregnancy can have adverse effects on both the mother and fetus.^{7,8} In fact, it may result in serious complications such as fetal hypoxemia and

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reported increased risk of perinatal death,^{4,9} pregnancy-induced hypertension and preeclampsia,⁹⁻¹¹ preterm birth,^{9,11,12} and low birth weight.^{9,11} Furthermore, asthma may worsen gestative hypertension and eclampsia.^{8,9} However, Schatz and coworkers,¹³ who have compared pregnant patients with actively managed asthma with healthy control obstetric patients in a prospective case-controlled study, were unable to document such a finding. They found no difference in preeclampsia, preterm birth, low birth weight, IUGR, congenital malformation, and perinatal mortality.

It must be remarked that the outcome of pregnancy in optimally treated asthmatic women does not significantly differ from that of healthy women.¹⁴ Therefore, all pregnant women suffering from bronchial asthma should be considered as potentially at high risk of complications¹⁵ and adequately treated. Because prior observations suggest that severe asthma itself may be associated with maternal and/or fetal mortality risk, risk/benefit considerations favor the use of medication, when indicated, for the treatment of asthma during pregnancy. However, medical-legal considerations on the responsibility of physicians and/or specialists (gynaecologist, pulmonologist, etc.) who manages asthma, suggest the need for an adequate knowledge of the management strategies during pregnancy, in order to avoid the possibility of litigation on the respective therapeutic objectives. Although the presently available experimental data provide reasonable suggestions and recommendations, several aspects of the management of asthma during pregnancy are still a matter of debate.¹⁴

In this review we will outline and discuss the available data and the criteria for the pharmacological management of asthma in pregnant patients.

General aspects of the management strategy

Bronchial asthma is, in the majority of cases, a chronic disease sustained by an inflammatory process. Many triggering factors can intervene at different levels and time points on the underlying inflammation (e.g. allergen exposure, emotional stress, viral infections etc.) thus leading to the well-known clinical variability of the disease itself. This means that the onset of asthmatic attacks is largely unpredictable and it can be controlled only by a continuous preventive strategy associated to the control of inflammation. Therefore, the man-

agement strategy is complex and it should be carried out for long periods.^{16,17}

The objectives of asthma management during pregnancy are shown in Table 1. The prevention of asthma exacerbations is essential to avoid recurrent episodes of hypoxemia, hypocapnia, alkalosis and dehydration. The achievement and maintenance of an optimal respiratory function is mandatory to avoid the chronic hypoxemia, which may be responsible for fetal distress and growth retardation. Finally, a correct and optimal management, by avoiding exacerbations, would exclude the need for acute pharmacological treatments (high dosages of drugs) and even for intensive care.

The global strategy of asthma management in pregnancy includes five essential aspects.¹⁸

- (1) Objective evaluation of maternal/fetal clinical conditions.
- (2) Avoidance/control of triggering factors.
- (3) Pharmacological treatment (immunotherapy when indicated).
- (4) Educational support.
- (5) Psychological support.

The management of bronchial asthma during pregnancy should be carried out by a trained team of health care professionals such as obstetricians, midwives, physicians and nurse specialists, plus the pregnant woman herself, which should manage together the ongoing problems starting from the conception until delivery.^{19,20} A close contact among different specialists is the ideal way to optimize asthma management and, in some cases, to newly diagnose asthma in otherwise unaware women.^{18,20}

Assessment of the Maternal and Fetal Status

When evaluating the clinical conditions of a fetus carried by a woman suffering from moderate to severe asthma, we should consider it at high risk of complications.²¹ Although epidemiological studies supporting this hypothesis are often not comparable each other due to methodological reasons, we should perform the fetal evaluation keeping into account these possible complications. An accurate calculation of the date of onset of pregnancy represents the first correct approach. In pregnant patients suffering from bronchial asthma a sonographic evaluation should be performed between the 16th and 18th weeks, with particular regard to the location of placenta and the amount of amniotic fluid.

Table 1 Goals of asthma management during pregnancy.

Optimal control of respiratory symptoms, including nocturnal exacerbations
Achieving a normal (or close to normal) respiratory function
Allowing to perform usual activities of every day's life and slight exercise
Avoiding or minimizing asthma exacerbations
Preventing or avoiding side effects due to antiasthma medications for the mother and the fetus

In well-controlled asthmatic women with a regular embryonal growth, usually it is not necessary to perform subsequent unscheduled sonographic assessments. In contrast, in severe or uncontrolled asthma, the risk of complications is higher.^{7,8} Therefore repeated sonographic evaluations should be performed for monitoring fetal growth. The daily count of fetal movements or "kicks" is a useful marker of fetal vitality.²² In the case of less than ten movements/hour, other evaluations, such as external spontaneous monitoring of fetal beats or external monitoring of fetal beats during spontaneously or induced uterine contractions are needed.^{23,24}

Every pregnant woman suffering from bronchial asthma should be evaluated by a detailed clinical examination and with a routine pulmonary function test, in order to assess asthma severity. These clinical and functional evaluations are necessary in order to exclude possible discrepancies between physician's and patient's perception of the disease and to differentiate asthmatic symptoms from other causes of dyspnoea during pregnancy.¹⁸ A daily evaluation of peak expiratory flow rate (PEFR) may also be a useful way to obtain objective informations about the degree of bronchial obstruction throughout the day.

Avoid-Control Triggers for Asthma Exacerbations

Since bronchial asthma is often associated with atopy, particularly in young women, an adequate program of environmental intervention for removing common indoor allergens such as those produced by mites, cockroaches and pets must be always recommended to all pregnant asthmatics²⁵⁻²⁹ sensitized to those allergens. Despite the results from meta-analysis of mite-avoidance trials, indicating only a marginal effect on asthma symptoms,³⁰ any attempt to reduce environmental exposure should be made.³¹ Some essential environmental care measures are always feasible and affordable. These include: encasing mattresses and pillows with impermeable coats, removing carpets

and curtains, vacuum cleaning beds and furniture with HEPA filters, and hot-washing bed linen and blankets once a week. Concerning domestic animals, the only effective measure is to remove the pet and to carefully vacuuming the environment. Frequently washing of cats can reduce allergens, but the overall clinical benefit achieved is modest.³² When they are recognized to be responsible of symptoms, food additives (such as sulphites), drugs and ASA should be avoided as well. β -Blockers are in general contraindicated in asthmatics, but when they are required for controlling gestational hypertension, the relative risk/benefit evaluation should be taken in account.

A particular care should be paid to control possible viral and bacterial infections, which have been suggested, to be more frequent in pregnant than in non-pregnant women.³³ For this reason the contact with people suffering from upper and lower airways viral and/ or bacterial infections should be avoided.

General Aspects of Pharmacological Treatment

In theory, pregnant women should not receive drugs, especially during the first 3 months of gestation. In reality, however, asthma in pregnancy needs to be treated and drugs are necessary, since uncontrolled asthma represents a risk factor to both the mother and the fetus.¹⁸

The potential teratogenic effects of drugs represent the main fear for both physician or patients. However congenital malformations, including those that are minor or major, are relatively common (about 3-5% of all living newborns in the United States).³⁴ Two to 3% will have a major malformation, which is defined as one that is incompatible with survival or one requiring major surgery for correction or one producing major dysfunction, that may be confidently attributed, at least in part (<1%) to drugs administration (teratogenic effect).³⁴ These malformations may be also induced by maternal or environmental factors, genetic factors, although in the majority of the cases the

causes remain unknown. The embryo is most susceptible during organ formation, from 4 to 10 weeks following the last menstrual period.

Only few drugs really increase teratogenic risk in humans (Table 2). Nevertheless physicians should be cautious in prescribing antiasthmatic drugs, since the possible risks are not completely known. Consequently, they should provide some simple and clear information on this topic to their pregnant patients (Table 3).

Few drugs are reported to be relatively contra-indicated during lactation (Table 4). In any case, there are no particular problems for the newborn by drugs regularly taken by the mother during pregnancy because the fraction of drugs passing into breast milk is lower than that passed through the placenta during gestation.³⁵

The choice of a given drug for treating bronchial asthma during pregnancy should be carried out according to some general criteria that are indicated in Table 5.

Unfortunately, the available data on the safety of antiasthmatic drugs have many limits, mainly due to the objective (and ethical) problems in assessing the safety in pregnant women in vivo.³⁶

The US Food and Drug Administration (FDA) subdivides drugs into five safety categories, based on the available experimental data. Noteworthy, none of the drugs usually prescribed for the treatment of asthma belongs to Pregnancy Risk Category A, which is characterized by the highest level of safety (Table 6).³⁷ The other risk categories report data regarding studies carried out in experimental animals with few (or any) studies in

humans. Only 0.7% of drugs carry a Pregnancy Risk Category A classification³⁸ and the vast majority are in B and C. In particular, 66% of all medications with a pregnancy category are now in Pregnancy Risk Category C.³⁹ This classification may not be considered completely reassuring since the negative association between drug intake during pregnancy and the onset of malformations, per se, did not guarantee the safety. In fact, no currently approved asthma medications carry a FDA label of Pregnancy Risk Category A, which stipulates “adequate and well controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy and there is no evidence of risk in later trimester.” This uncertainty reflects the sparsity of data on the effects of asthma medications during pregnancy.

Recently, some studies have been carried out on the outcome of a large cohort of pregnancies during which any drug administration has been carefully registered. The objectives of these studies were to evaluate the occurrence, at birth, of “major disorders” associated with the intake of a given drug during pregnancy.^{40,41} In Table 7 are shown the drugs which did not exhibit a “strong association” with the onset of fetal malformations.

Treatment of Chronic Asthma

The recommendations from the National Asthma Education Program Report of the Working Groups on

Table 2 Drugs with ascertained theratogenic effect (35).

Talidomide	Alkilant agents
Diethylstilbestrol	Alchool
Androgens	Antiepileptic agents
Antifolate agents	Lythium
Tetraciclins	Warfarin
	Aminoglucosides

Table 4 Drugs contraindicated during lactation (36).

Immunosuppressors—antineoplastics
Metimazole/thiouracyle
Phenindione
Ergotamine
Gold salts
Potassium iodide
Diuretics can potentially reduce milk production

Table 3 Essential informations to be provided to asthmatic pregnant women.

Although only few drugs can be really noxious or harmful during pregnancy, none of the available antiasthmatic drugs can be considered completely safe, since few controlled studies have been performed in pregnancy
Uncontrolled bronchial asthma have ascertained deleterious effects on the course of pregnancy and represents a risk factor for the newborn's health
The risk/benefit ratio in pregnancy of many of antiasthmatic drugs is overall favourable
The choice of the drug(s) to be given is made by the physician according to the clinical situation (severity and duration of symptoms)

Table 5 Criteria for selecting drugs to be administered during pregnancy.

Consult literature databases for potential/described side effects
Give preference to drugs with ascertained efficacy
Give preference to drugs with reassuring human gestational safety data
Use the inhalatory route, when possible
Give preference to drugs available since the most long time period

Table 6 FDA Classification for drugs in pregnancy.

Category	Risk based on either animal testing or from information in humans	Interpretation
A	Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester, and the possibility of fetal harm appears remote	This means that there is no evidence of increased risk in animals or humans
B	Animal studies do not indicate a risk to the fetus, and there are no controlled human studies. Or animal studies show an adverse effect on the fetus, but well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus	This usually means there is no evidence in animal studies that risk exists, but no adequate human data exist
C	Studies have shown that the drug exerts animal teratogenic or embryocidal effects, but there are no controlled studies in women or no studies are available in either animals or women	This usually means there is evidence in animal studies of a risk of loss of pregnancy or birth defects, but no adequate human data exist
D	Positive evidence of human fetal risk exists, but benefits in certain situations (for example, life-threatening situations or serious diseases for which safer drugs cannot be used or are ineffective) may make use of the drug acceptable despite its risks	This means there is evidence of a risk of loss of pregnancy or birth defects in human pregnancy that must be balanced against the value of treatment
X	Studies in animals or humans have demonstrated fetal abnormalities or evidence of fetal risk, and the risk clearly outweighs any possible benefit	This means there is evidence of a risk of loss of pregnancy or birth defects in human pregnancy without any overriding benefit

Asthma and Pregnancy¹⁸ are applicable in most cases. However, they should be adapted to each single patient and must be modified when new data become available in literature.

β_2 agonists

Schatz and coworkers⁴² demonstrated the safety of inhaled β_2 -agonist bronchodilators in a prospective study of 259 pregnant asthmatics who were using β_2 agonists compared with 101 pregnant asthmatics not using bronchodilators and with 295 pregnant control subjects. Overall, as drug class, the inhaled β_2 agonists are not associated with an increased frequency of malformation or other unwanted effects in newborn⁴². There are no solid data in literature indicating that one specific β_2 agonist

should be considered preferable. Nevertheless, salbutamol, terbutaline and metaproterenol are considered short-acting β_2 agonists of first choice, because they have been used for decades without any reported significant side effect in humans.^{41,42} The inhalatory route is generally well tolerated and the use of a spacer can improve the delivery of the drug to the lungs.⁴³ Oral/parenteral administration of β_2 agonists to asthmatic pregnant women is not recommended for some important causes, such as the lack of safety data in the first trimester, the potential inhibitory effect on the delivery, the higher rate of side effects (tachycardia and/or tremors) when compared with the inhalatory route.¹⁸

The use of short-acting β_2 agonists should be limited when asthma is well controlled. However,

Table 7 Drugs that apparently are not associated with congenital malformations.

Group health cooperative study (40)	
Pseudoephedrine	Brompheniramine+phenylephrine
Phenylephrine	Chlorpheniramine
Tripolidine+pseudoephedrine	Chlorpheniramine+phenylpropanolamine
Dyphenidramine	Beta-lactams
Oxymetazoline	Erythromycin
	Tetracyclins
Surveillance study of Michigan (41)	
Albuterol	Isoproterenol
Atropine	Metaproterenol
Beclometasone	Methylprednisolone
Chlorpheniramine	Prednisone
Cimetidine	Pseudoephedrine
Cromolin sodium	Terbutaline
Epinephrine	Terfenadine (withdrawn)
Hydroxyzine	

when the need for their use increases, inhaled steroids must start or be increased.¹⁸

Only few data are available on the safety during pregnancy of salmeterol and formoterol, due to their recent commercial availability. Animal studies with salmeterol administered parenterally are not reassuring.⁴⁴ However the experience with chemically similar drugs such as salbutamol (animal but not human studies reporting adverse effects) suggests that animal studies cannot be entirely transposed to humans.⁴⁵ At present, in principle, the newest agents should not replace salbutamol and terbutaline, which are proved safe. However, a post-marketing surveillance study of formoterol in general practice in England did not show any important side effect in 33 patients who took formoterol during pregnancy.⁴⁶ In any case, it is important to outline that when asthma symptoms are not controlled by inhaled corticosteroids, the addition of salmeterol is more effective than doubling the dose of steroids.⁴⁷ Moreover, Pollart and coworkers⁴⁸ demonstrated that salmeterol is more effective and induces fewer side effects than theophylline. Consequently, long-acting β_2 agonists can be prescribed to pregnant patients, at least after an in depth evaluation of the risk/benefit ratio, if they have been successfully treated with these agents before pregnancy or are suffering from recurrent nocturnal asthma.

Theophylline

Theophylline carries a Pregnancy Risk Category C. Although there are no studies on birth defects in humans, some studies in animals have shown that theophylline can cause birth defects when given in

doses many times the human dose⁴⁹. Unfortunately, the ability to clear theophylline from body may decrease later in pregnancy;⁵⁰ therefore dosages of theophylline may need to be adjusted due to the changing pharmacokinetics as pregnancy progresses. Theophylline readily crosses the placenta. Use of this medicine during pregnancy may cause unwanted effects, such as fast heartbeat, irritability, jitteriness, or vomiting, in the newborn infant if the amount of medicine in mother's blood is too high.⁵¹ In any case, theophylline may induce several side effects in pregnancy such as nausea/gastroesophageal reflux exacerbations, hypertension, delivery inhibition, etc.

Cromones

Cromolyn sodium is considered safe in pregnancy because of its virtually complete absence of systemic side effects.⁵² Further studies are necessary to confirm the equivalent safety of the newer cromone sodium nedocromil, although there is no pharmacological reason to expect a different safety profile. However, nedocromil has an FDA pregnancy category B rating, meaning that although human data are not available, teratogenic events were not demonstrated in animal studies.

Inhaled corticosteroids (ICS)

ICS are the cornerstones of long-term therapy of bronchial asthma because they effectively control inflammation, and reduce asthma exacerbations and the need for on-demand bronchodilators.^{53,54} Some controlled studies on the safety profile of these drugs in pregnancy, which are in any case

reassuring, are presently available in the literature.⁵⁵ Unfortunately, they are few and for this reason, all inhaled corticosteroids, except budesonide, remain at Pregnancy Risk Category C. The FDA has upgraded inhaled budesonide to Pregnancy Risk Category B based on data from three Swedish registries covering over 2000 births from 1995–1997 (i.e. Swedish Medical Birth Registry; Registry of Congenital Malformations; Child Cardiology Registry). The studies showed no increased risk of congenital malformations when pregnant women used budesonide.⁵⁶ The new, upgraded rating for budesonide may make it the drug of choice for pregnant women who need an inhaled corticosteroid to control their asthma. However, despite the upgraded rating, this drug—like all drugs—should be used during pregnancy only when clearly needed and when the benefit to the mother outweighs the risk to the fetus.

Adequate and well-controlled studies regarding the use of fluticasone during pregnancy have not been done. Its use during pregnancy should be avoided unless the potential benefit justifies the potential but unknown risk to the fetus, also considering that in animal studies, fluticasone given by injection was shown to cause birth defects.⁵⁷ However, considering the route of administration it is unlikely it can induce serious side effects on developing fetus. Recently, Ellegard and coworkers⁵⁸ have evaluated the effect of 8 weeks of treatment with fluticasone propionate aqueous nasal spray in 53 women with pregnancy rhinitis. There was no detectable influence on maternal cortisol as measured by morning serum-cortisol and overnight 12-h-urine-cortisol, or any difference in ultrasound measures of fetal growth or pregnancy outcome.

Ipratropium bromide

Ipratropium bromide is an anticholinergic agent which is considered safe and which is largely used for the treatment of chronic obstructive pulmonary diseases,⁴⁴ but no data concerning its use in pregnancy are available, although studies in rats, mice and rabbits showed no birth defects when this medication is used. Since it does not offer significant advantages over β_2 agonists, it cannot be considered as first choice drugs, and adrenergic bronchodilators are preferred.

Leukotriene modifiers

Montelukast and zafirlukast are now widely commercialized. Animal studies on zafirlukast and on

montelukast have not detected problems during pregnancy; however, no human gestational data are available for any of these drugs. For this reason, both zafirlukast and montelukast carry FDA Pregnancy Risk Category B classification, whereas zileuton carries Pregnancy Risk Category C classification because of adverse effects in animal studies.⁵⁹ A Pregnancy Risk Category B or C rating does not imply that the medication cannot be prescribed during gestation. The physician is advised to weigh the benefit to the patient versus the risks, which, if any exist, are usually not known at the time.⁶⁰ Therefore, these drugs should be used only in pregnant women with resistant asthma who has previously responded successfully.⁴⁵

Systemic corticosteroids

Systemic corticosteroids may be needed in pregnant women requiring steroid therapy for severe asthma. In such cases, the lowest effective dosage must be used, possibly on alternate days. Corticosteroid therapy in pregnancy is also appropriate to treat an in utero infant suffering from neonatal lupus-associated carditis, in stress doses (in corticosteroid-treated patients) for labor and delivery, and, pre-delivery, to induce fetal lung maturation.⁶¹ Chronic use of oral corticosteroids, or even assumption of high-dose systemic steroid during pregnancy does carry some risk. Perlow and coworkers reported an increased incidence of diabetes mellitus, preterm labor, premature rupture of membranes, preterm delivery, and low-birth-weight infants in 31 steroid-dependent pregnant asthmatics.⁶² An association with preeclampsia has been noted.^{63,64} Also an increased incidence of pregnancy-induced hypertension in pregnant asthmatic women taking corticosteroids in comparison to nonsteroid-treated asthmatics has been described.⁵ In animals, systemic corticosteroids have been associated with cleft palate, placental insufficiency, spontaneous abortion, and growth retardation.⁶⁵ In humans, data derived from the Spanish Collaborative Study of Congenital Malformations have shown a relationship between exposure to corticosteroids during the first trimester of pregnancy and an increased risk of cleft lip (with or without cleft palate) in the newborn infants.⁶⁶ However, this study suffers from several deficiencies.⁶⁷ First, the histories of first trimester drug exposures were obtained retrospectively from the mothers after delivery and diagnosis of the congenital abnormality, possibly leading to recall bias. Second, only four of 1184 infants with oral clefts had a history of corticosteroid exposure. Third, the

period of corticosteroid exposure was highly variable, with one exposure of only two doses of 40 mg of prednisolone. Finally, the logistic regression model in this study did not include confounding variables of maternal illness or degree of smoking. Even if this association of corticosteroids and malformations is confirmed, the incidence of oral clefts in children of women receiving corticosteroids in the first trimester was only 0.4%,⁶⁶ substantially less than the incidence of untoward perinatal outcome in poorly controlled asthma. Two other case-control studies have associated first trimester maternal use of systemic corticosteroids with an increased risk of oral clefts.^{68,69} However, a population-based case control study of teratogenic potential of corticosteroids has demonstrated that there has been no association with cleft palate or other congenital anomalies.⁷⁰ Many normal infants have been born to mothers who have received systemic corticosteroids throughout pregnancy, but there have been reports of low birth-weight⁷¹ and an increased risk of hyperbilirubinemia.⁷²

Asthma exacerbations during pregnancy

Pregnancy should be an indication for maximizing therapy during an asthma exacerbation, rather than withholding therapy, because neonatal outcomes are clearly superior when maternal symptoms are controlled, and oxygenation and pulmonary function are optimized.⁷¹ Potential harm to the fetus is more likely to result from severe uncontrolled asthma rather than from the medications used to treat it.⁷³ Nevertheless, during asthma exacerbations, both subjective and objective parameters must be carefully evaluated. For instance, heart rate is usually higher in pregnancy. If heart rate is higher than 120 beats/min in the absence of other causes of tachycardia such as fever, use of β_2 agonists, anxiety, anaemia, etc. the negative prognostic value may be significant. A similar attention should be devoted to a paradox pulse >12 mmHg.

The peak expiratory flow rate (PEFR) measurement is easy to perform and provides a useful additional clinical datum. A diurnal variability of PEFR $>30\%$ must be considered as an alert signal,⁷⁴ as well as the decrease below 92% of the arterial oxygen saturation (SpO_2) as measured by pulse oximetry.⁷⁵

Treatment is no different from the emergency management of acute severe asthma outside pregnancy. Oxygen, nebulized β_2 agonists, nebu-

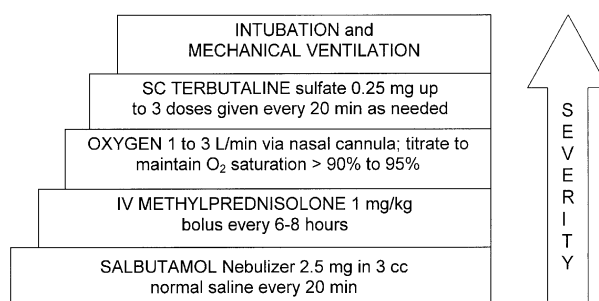


Fig. 1 A suggested protocol for the treatment of asthma exacerbations according to the degree of asthma severity.

lised ipratropium, oral or intravenous steroids and, in severe cases, intravenous aminophylline or parenteral β_2 agonists should be used as indicated. A suggested protocol for the treatment of asthma exacerbations, according to the degree of severity is shown in Fig. 1.

It has been suggested that theophylline added to adequate β_2 agonist and systemic corticosteroid therapy does not increase benefit for acute asthma exacerbations, particularly in first four hours of treatment.^{18,54}

As previously reported, physicians should evaluate the risk/benefit ratio in prescribing systemic corticosteroids in pregnancy, but they must always prescribe these agents when they are essential as in the case of severe acute exacerbations of asthma. Recently Cydulka and coworkers⁷³ studied the modality of asthma treatment in pregnant and non-pregnant women referred to emergency departments. They demonstrated that both groups received comparable amounts of nebulised β_2 agonist treatment in the first hour, but the pregnant women were significantly less likely to be given systemic steroids (44% versus 66%). The pregnant women were equally likely to be admitted (24% versus 21%), but were less likely to be prescribed steroids if sent home (38% versus 64%). At the 2 week follow up interview the pregnant women were three times more likely to report an ongoing exacerbation of their asthma.

A number of case reports indicate magnesium is beneficial for treating acute severe asthma.⁷⁶ The suggested mechanism of action is smooth-muscle relaxation secondary to inhibition of Ca^{++} influx by blocking the voltage-dependent calcium channels.⁷⁷ Thus, it could be classified as a pure bronchodilator and theoretically would work best in situations when airway edema is not the most prominent feature of status asthmaticus.⁷⁸ Some reports indicate that it is useful and safe in the treatment of status asthmaticus even in pregnancy.⁷⁹

Asthma During Delivery

Although the risk of asthma exacerbation during delivery is relatively low, pregnant patient should not discontinue their inhalation therapy, if any. If bronchial symptoms are not adequately controlled by β_2 agonists an additional administration of intravenous methylprednisolone may be necessary. If a pregnant asthmatic patient has been treated for long periods with oral steroids, she should receive parenteral steroids (hydrocortisone 100 mg 6–8 h) during labor, and until she is able to restart her oral medication to prevent the possible onset of adrenal failure.⁸⁰

The use of oxytocic drugs such as prostaglandin (PG)F_{2 α} , methilergonovine or ergonovine should be avoided in asthmatic women during delivery, because these agents may determine bronchial obstruction.⁸¹ Oxytocine represents a good alternative to the use of methilergonovine or ergonovine.¹⁴ The use of steroids is recommended when presumably oxytocin is not effective. On the contrary, high doses of β_2 agonists and/or theophylline may determine a retardation of the onset of delivery.

Oxygen administration may be necessary, after the evaluation of blood gases, to maintain an adequate oxemia. When possible, local (peridural) anesthesia should be preferred to a general anaesthesia because of the increased risk of chest infection and associated atelectasis. When a general anesthesia is required (caesarean section), propofol is considered to be the agent of choice for induction of anesthesia in asthmatics.⁸² Non-steroidal antiinflammatory drugs (NSAIDs) are commonly used for pain relief following a caesarean section. Women with asthma should be asked about any known sensitivity to aspirin or NSAIDs before using these drugs.²⁰

Other Treatments

Specific immunotherapy is generally well tolerated during pregnancy and its use is not associated with fetal malformations or complications of pregnancy and/or of delivery.⁸³ Nevertheless, the risk of severe or life-threatening reactions must be taken in account although it seems to be a remote possibility. It is generally believed that an ongoing and well-tolerated immunotherapy does not need to be discontinued during pregnancy. In this condition, a significant reduction of usual dosage of allergenic extract may be necessary to avoid the risk of systemic reactions.⁸⁴ On the other hand,

based on risk/benefit considerations, it is not recommended to start a new immunotherapy course once pregnancy has begun.

The use of epinephrine during pregnancy is strictly indicated only in the case of anaphylaxis^{85,86} or status asthmaticus because it may induce a contraction of uterine blood vessels and consequently a reduction of blood flow.⁸⁷

H₁ receptor blockers are not per se an antiasthmatic treatment; however they are frequently used when rhinitis symptoms are present.^{88,89} Most H₁ receptor blockers did not cause birth defects in animal studies. These include diphenhydramine and chlorpheniramine, as well as dimenhydrinate, dexchlorpheniramine, brompheniramine, cetirizine, loratadine, azatadine, doxylamine, tripelemine, cyproheptadine, clemastine, and ebastine. However, animal studies indicated that if taken in extremely high doses (far above the recommended dosage), certain antihistamines could cause birth defects in animal offspring.⁹⁰ Since data on the safety of H₁ blockers during pregnancy are not conclusive they should be, in general, avoided,⁸⁸ although some reassuring human data have been published for several agents.^{91,92} For instance, the use of terfenadine in the first trimester has not been associated with congenital malformation, although some data have shown an association between maternal exposure to terfenadine and a lower infant birth weight.⁹³ It is important to outline that few studies addressing small samples of patients may not exclude the risk of congenital malformations or other complications. In any case, the older H₁ blockers diphenhydramine and dexchlorpheniramine and the newer non-sedating cetirizine and loratadine carry FDA Pregnancy Risk Category B classification, whereas hydroxyzine, terfenadine, astemizole, and fexofenadine carry FDA Pregnancy Risk Category C classification.⁹⁴

Education and Psychological Aspects

The patients' education is mandatory to optimize the outcomes of therapy in asthmatic patients. However, in the case of pregnant women, strict and repeated reassurance on the significance and safety of a regular therapy for controlling airway inflammation is definitely essential to ensure adequate compliance.²⁰ The physician in charge of asthma should identify the degree of asthma severity and the possible triggering factors such as allergens and pollutants, supply with psychological support and warrant his/her availability in the case of asthma exacerbations.

It seems of primary importance that the patient can have regular and frequent contacts with physicians who are in charge of both pregnancy and asthma. This simple fact may reassure the patient and reduce her emotional stress. A clear and simple explanation of the nature of the disease, its risks and possible treatments should be able to make the patient more confident towards medications and diagnostic procedures. Only in the case of severe mood/behavior disturbances, the help of a psychiatric consultant should be asked.

Conclusions

The problem of asthma management in pregnancy has received during the last ten years an increasing attention and, in parallel, our knowledge has rapidly improved. This improvement is due to several factors, including: (a) the detailed information on the mechanisms underlying bronchial inflammation; (b) the data provided by large epidemiological studies; (c) the introduction in clinical practice of new drugs and their molecular mechanisms. On the other hand, since pharmacological studies in pregnant women are usually unethical and difficult to perform, recommendations must necessarily be based on the available clinical experience.⁹⁵

Several guidelines and recommendations have been published. They agree on the fact that the general strategy of management of asthma in pregnancy does not differ significantly from management outside pregnancy. The complete control of symptoms and the prevention of exacerbations are the primary objectives, since it is ascertained that poorly controlled asthma is responsible for the potential small risk of harm to the fetus. These goals can be reached by using a little number of drugs which are in use since decades, whereas the prescription of the newest treatment should be carefully evaluated case by case.

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