Working Group Report on Managing Asthma During Pregnancy: Recommendations for Pharmacologic Treatment

Update 2004
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In 1993, the National Asthma Education and Prevention Program (NAEPP) published the Report of the Working Group on Asthma and Pregnancy, which comprehensively reviewed the data to date and presented recommendations for the management of asthma during pregnancy. Since then, modification to the general asthma treatment guidelines, release of new asthma medications, revisions to the severity classification of asthma, and publication of new gestational safety data were sufficient to warrant an evidence-based update of these recommendations.

The NAEPP Working Group Report on Managing Asthma During Pregnancy: Recommendations for Pharmacologic Treatment—Update 2004 represents the ongoing effort of the NAEPP to keep recommendations for clinical practice current and based on systematic reviews of the evidence. The update was developed under the able leadership of Dr. William Busse, Working Group Chair. The National Heart, Lung, and Blood Institute (NHLBI) sincerely appreciates the work of Dr. Busse and all members of the Working Group in developing the report. Sincere appreciation also goes to the 39 organizations (professional societies, voluntary organizations, patient advocacy groups, and Federal agencies) that comprise the NAEPP Coordinating Committee for their thoughtful review and comments regarding the content of this report.

Ultimately, broad change in clinical practice depends on the influence of local physicians and other health professionals who not only provide state-of-the-art care to their patients but also communicate to their peers the importance of doing the same. We ask for the assistance of every reader in reaching our ultimate goal: improving asthma care and the quality of life for pregnant women with asthma and their families.

Publications from the NAEPP can be ordered through the NHLBI Health Information Center, P.O. Box 30105, Bethesda, MD 20824-0105. Publications are also available through the Internet at http://www.nhlbi.nih.gov.

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Asthma has been reported to affect 3.7 to 8.4 percent of pregnant women in the United States (Kwon et al. 2003), making it potentially the most common serious medical problem to complicate pregnancy. Although data have been conflicting, the largest and most recent studies (Demissie et al. 1998; Källén et al. 2000) suggest that maternal asthma increases the risk of perinatal mortality, preeclampsia, preterm birth, and low birth weight infants. More severe asthma is associated with increased risks, while better controlled asthma is associated with decreased risks (Schatz et al. 1995).

In 1993, the NAEPP published the Report of the Working Group on Asthma and Pregnancy (hereafter Asthma and Pregnancy Report 1993), which comprehensively reviewed the data to date and presented recommendations for the nonpharmacologic and pharmacologic management of asthma during pregnancy. Since then, several changes have occurred: the severity classification of asthma has been revised (NAEPP Expert Panel Report 2 [EPR-2 1997]); general pharmacologic treatment guidelines have been modified and updated (NAEPP Expert Panel Report—Update 2002 [EPR—Update 2002]); new medications have become available (e.g., budesonide, fluticasone, leukotriene receptor antagonists, long-acting beta_2-agonists); and new gestational safety data have been published for both old and new medications. The NAEPP Coordinating Committee determined that, in light of these changes, this report—an evidence-based update of the pharmacologic management of asthma during pregnancy—was warranted.

The Asthma and Pregnancy Report 1993 also addressed the three other components of asthma management: (1) objective measures for assessment and monitoring, (2) control of “triggers” or factors that contribute to asthma severity, and (3) patient education.

Although pharmacotherapy was the focus of this update, brief highlights of the three other components of asthma management were taken from the NAEPP Expert Panel Reports in 1997 and 2002 (EPR-2 1997 and EPR—Update 2002, respectively) and included in this report because they should enhance the overall success and safety of asthma management during pregnancy.

The NAEPP Working Group Report on Managing Asthma During Pregnancy: Recommendations for Pharmacologic Treatment—Update 2004 (hereafter Asthma and Pregnancy—Update 2004) represents the ongoing effort of the NAEPP to keep recommendations for clinical practice up to date and based on systematic reviews of the evidence. It was developed through the collective expertise of an expert panel on asthma and pregnancy (hereafter Working Group). The NAEPP Science Base Committee and NAEPP Coordinating Committee members provided review and comment. The recommendations made in Asthma and Pregnancy—Update 2004 are intended to assist clinical decisionmaking; the clinician and patient still need to develop individual treatment plans that are tailored to the specific needs and circumstances of the pregnant woman. The NAEPP, and all who participated in the development of this latest report, hope that
the pregnant woman with asthma and her newborn will be the beneficiaries of the recommendations in this document. This report is not an official regulatory document of any government agency.

REFERENCES


IB. Methods Used To Develop This Report

The NAEPP Science Base Committee met in December 2002 to consider the need for updating the NAEPP Report of the Working Group on Asthma and Pregnancy: Management of Asthma During Pregnancy that was published in 1993 (Asthma and Pregnancy Report 1993). The Science Base Committee conducted a preliminary scan of the scientific literature on asthma and pregnancy that had been published between 1998 and 2002. Members concluded that new information regarding pharmacologic management of asthma during pregnancy was sufficient to support a systematic review of the evidence on this topic. The Science Base Committee made its recommendation to the NAEPP Coordinating Committee, under the leadership of Claude Lenfant, M.D., Director of the National Heart, Lung, and Blood Institute (NHLBI). Dr. Lenfant convened a panel of experts (Working Group) to conduct the systematic review and to develop a position statement to bring up to date the recommendations for the pharmacologic management of asthma during pregnancy.

In March 2003, the Working Group began a series of meetings, by conference call, to carry out its task. Working Group members determined that the focus of the review should be on the safety and effectiveness of asthma medications, taken during pregnancy and lactation, for women and their fetuses/newborns. The Working Group noted that the use of antihistamines, decongestants, and inhaled nasal corticosteroids by pregnant women who have allergic rhinitis and asthma was addressed in the Asthma and Pregnancy Report 1993 and that several studies on these medications have been published since 1993. On the basis of these studies, the current Working Group offers recommendations regarding the use of allergy medications in pregnancy; however, a systematic review of the evidence on allergy medications was not included in the scope of the current evidence review.

The Working Group proceeded to conduct the systematic review of the evidence on the safety of asthma medications during pregnancy. The systematic review of the evidence included a comprehensive search of the literature; preparation of evidence tables depicting study design, research variables, and reported outcomes; and a narrative report summarizing and interpreting the literature findings.

The methods for conducting the systematic review of the evidence are summarized here.

- The literature search, designed to be as comprehensive as possible, included both animal and human studies that were published in English in peer-reviewed medical journals. The search was performed by using key text words and Medical Subject Heading (MeSH) terms to identify all relevant studies. Key words included all anti-inflammatory and bronchodilator asthma medications (systemic beta-agonists were not included because they are not recommended therapies for managing asthma in adults), teratology, fetus, fetal outcomes, congenital abnormalities, lactation, breast milk, breast feeding, and pregnancy outcomes. Publications in 1990 through May 2003 were searched in five databases: PubMed, TOXLINE (core and special), and Developmental And Reproductive Toxicology (DART; core and special).
• The search retrieved titles of 6,223 references. Of these, 100 references were identified as journal review articles and moved to a separate bibliography. References identified as letters, meeting abstracts, or book chapters were excluded. Titles of the remaining references were then screened for relevance to the topic of safety of asthma medication during pregnancy. Each title was considered by two reviewers; if both agreed the reference was relevant, it was flagged for subsequent abstract review. A difference of opinion between the reviewers also resulted in retaining a reference for abstract review.

• On the basis of the review of titles, 226 references were flagged, and abstracts for all were retrieved. Each abstract was rated independently by two Working Group members on the basis of relevance to the search question and whether the data appeared to support a change to current guidelines recommendations. A difference of opinion between two reviewers on the merits of an abstract was generally resolved by a larger group discussion. A few abstracts were rated as inconclusive, however, because information was insufficient without reviewing the full article. Abstracts rated as either relevant or inconclusive were flagged for subsequent review of the full article.

• After the review of abstracts, 55 references were flagged for review of the full article. At this point, a quality control measure also was implemented. To ensure further that no relevant studies were overlooked, this measure involved going back to the bibliography of 100 review articles and retrieving those articles with publication dates of 1998 or later. Twenty-two articles were retrieved; they were reviewed by Working Group members for the purpose of identifying possible citations missed during the basic review process. This step identified 25 potential new references; of these, 9 were deemed relevant and therefore were added to the full-article review.

• Sixty-four references underwent a full-article review by a primary and a secondary reviewer. Of these 64 references, 42 met the study selection criteria for inclusion in the systematic review of the evidence. Data from the 42 articles were abstracted to evidence tables by an outside contractor and were recorded in an electronic database. All of the evidence tables are available for online retrieval at: http://www.nhlbi.nih.gov/health/prof/lung/asthma/astpreg.htm. Subsequent to May 2003 and prior to a final draft of the report in March 2004, two additional articles that met the study selection criteria were published and included in the systematic review of the evidence. Thus, the total number of articles abstracted to evidence tables was 44. Data elements included categories such as study design and methods, patient characteristics, lung function outcomes, symptom outcomes, medication outcomes, utilization outcomes, and adverse events.

In August 2003, the Working Group met in Bethesda, M D, to discuss the systematic review of the evidence from safety studies and to interpret the implications for updating the recommendations of the Asthma and Pregnancy Report 1993 and adapting the recommendations for a stepwise approach to managing asthma presented in the EPR—Update 2002. The Working Group agreed to note the level of the evidence used to justify Working Group recommendations in parentheses following the initial recommendation for a specific medication. The level of evidence uses the categories A, B, C, or D as described below (Jadad et al. 2000).

• Evidence Category A: Randomized controlled trials, rich body of data. Evidence is from the endpoint of well-designed randomized controlled trials that provide a consistent pattern of findings in the population for which the recommendation is made. Category A requires substantial numbers of studies involving substantial numbers of participants.
• **Evidence Category B**: Randomized controlled trials, limited body of data. Evidence is from endpoints of intervention studies that include only a limited number of patients, post hoc or subgroup analysis of randomized controlled trials, or meta-analysis of randomized controlled trials. In general, Category B pertains when few randomized trials exist, they are small in size, they were undertaken in a population that differs from the target population of the recommendations, or the results are somewhat inconsistent.

• **Evidence Category C**: Nonrandomized trials and observational studies. Evidence is from outcomes of uncontrolled or non-randomized trials or from observational studies.

• **Evidence Category D**: Working Group consensus judgment. This category is used only where the provision of some guidance was deemed valuable, but the clinical literature addressing the subject was insufficient to justify placement in one of the other categories. The consensus is based on clinical experience or knowledge that does not meet the criteria for categories A through C.

Development of this report was an iterative process of drafting, reviewing, and building consensus. In the summer and fall of 2003, the Working Group writing committees drafted their respective sections of the report through electronic mail and telephone conference calls. The Working Group reviewed and revised drafts through telephone conference calls and subsequent electronic mails among the full Working Group membership. During the calls, votes were taken to ensure agreement with final recommendations. In November 2003, a draft report was mailed to the NAEPP Science Base Committee and three consultants with a specialty in maternal and fetal medicine. The Science Base Committee met by conference call to review the draft report, and the consultants mailed their comments. All comments were discussed by the Working Group in a December 2003 conference call, and agreement was reached on how to address the comments. In January 2004, a revised draft report was sent to the Science Base Committee for their final review, and in February 2004 the report was mailed to the NAEPP Coordinating Committee for its review and approval. In March 2004 conference call, the Working Group reviewed and addressed all NAEPP Coordinating Committee comments, and the report was completed.

This report was funded entirely by the NHLBI, National Institutes of Health, Department of Health and Human Services. Working Group members disclosed relevant financial interests to the NHLBI and to each other before their deliberations. Working Group members and reviewers participated as volunteers and were reimbursed only for travel expenses related to the Working Group meeting.

**REFERENCES**


IC. Executive Summary

This section presents a summary of findings from the systematic review of the evidence and key recommendations for managing asthma during pregnancy.

Systematic Review of the Evidence

A systematic review of the evidence on the safety of asthma medications during pregnancy was conducted. Of 226 abstracts retrieved in the search of literature published in peer-reviewed journals from January 1990 through May 2003, 42 met criteria for inclusion in the evidence review; 2 additional articles published after May 2003 were considered and included. A summary of the findings from the evidence, arranged by medication category, follows.

Beta2-Agonists

One experimental animal study and six human studies were included. The six human studies consisted of one case report and five clinical studies that included a total of 6,667 pregnant women, of whom 1,929 had asthma and 1,599 had taken beta2-agonists. The data were reassuring regarding the safety of beta2-agonists during pregnancy. More data were available for albuterol. Two long-acting inhaled beta2-agonists have become available since 1993—salmeterol and formoterol. Limited data are available on their use during pregnancy. The pharmacologic and toxicologic profiles of these two drugs are similar to the short-acting inhaled beta2-agonists, with the exception of their prolonged retention in the lungs.

Theophylline

Seven experimental animal studies and eight human studies were included. The experimental animal studies confirm the association of high-dose theophylline and adverse pregnancy outcome in animals. The eight human studies, consisting of two case reports and six clinical studies (of which two were randomized controlled trials), included a total of 57,163 pregnant women, of whom 3,616 had asthma and 660 had taken theophylline. Studies and clinical experience confirm the safety of theophylline at recommended doses (to serum concentration of 5–12 mcg/mL) during pregnancy. In a randomized controlled trial, there were no differences in asthma exacerbations or maternal or perinatal outcomes in the theophylline versus the beclomethasone dipropionate treatment groups. However, in the theophylline treatment group, there were higher levels of reported side effects and discontinuation of the medication and an increase in the proportion of women with forced expiratory volume in 1 second (FEV1) at less than 80 percent of that predicted.

Anticholinergics

No data on anticholinergics were available for the current evidence review.

Inhaled Corticosteroids

Three experimental animal studies and 10 human studies were included. The human studies included eight studies of pregnant women (five cohort studies, one controlled trial, and two randomized controlled trials) with a total of 21,072 pregnant women, of whom 16,900 had asthma and 6,113 had taken inhaled corticosteroids. Also included were two studies of newborns from the Swedish Birth Registry (one compared the rate of abnormalities among 2,014 newborns
whose mothers had taken budesonide to the rate of abnormalities in the total newborn population, although the number in that population was not reported; the other study compared 2,900 newborns whose mothers had taken budesonide to the 293,948 total newborn population; there may be some overlap in the populations of these two studies). There are three major conclusions from the evidence review: (1) the risk of asthma exacerbations associated with pregnancy can be reduced and lung function (FEV₁) improved with the use of inhaled corticosteroid therapy; (2) no studies to date, including studies of large birth registries, have related inhaled corticosteroid use to any increases in congenital malformations or other adverse perinatal outcomes; and (3) the preponderance of data on use of inhaled corticosteroids during pregnancy is with budesonide (few or no studies are available on use of the other inhaled corticosteroid formulations during pregnancy).

**Oral (Systemic) Corticosteroids**

Nine experimental animal studies and eight human studies were included. The animal studies do not change the previous understanding (Asthma and Pregnancy Report 1993) of the steroid-mediated clefting or decreases in fetal growth in animals. The eight human studies in the current evidence review included one report of two meta-analyses: one used six cohort studies (one of which was eligible for inclusion in the evidence review) that included 51,380 pregnant women, of whom 535 had taken oral corticosteroids (number with asthma was not reported); the other used four case-control studies (each of these was also eligible for inclusion in the evidence review) that comprised 52,038 pregnant women, of whom 25 had taken oral corticosteroids (number with asthma was not reported). The remaining human reports include one case-control study and two prospective cohort studies that included a total of 4,321 pregnant women, of whom 1,998 had asthma and 213 had taken oral corticosteroids. The findings from the current evidence review are conflicting. Oral corticosteroid use during the first trimester of pregnancy is associated with an increased risk for isolated cleft lip with or without cleft palate (the risk in the general population is 0.1 percent; the risk in women on oral corticosteroids is 0.3 percent). However, very few pregnant women who had oral steroid-dependent asthma were included in the studies, and the length, timing, and dose of exposure to the drug were not well described. Oral corticosteroid use during pregnancy in patients who have asthma is associated with an increased incidence of preeclampsia and the delivery of both preterm and low birth weight infants. However, the available data make it difficult to separate the effects of the oral corticosteroid on these outcomes from the effects of severe or uncontrolled asthma, which has been associated with maternal and/or fetal mortality.

**Cromolyn**

No experimental animal studies and two human studies were included in the current review. The two human studies consisted of prospective cohort studies that included 4,110 pregnant women, of whom 1,917 had asthma and 318 had taken cromolyn. The safety of using cromolyn during pregnancy is supported by the current review of evidence.

**Leukotriene Modifiers**

Leukotriene modifiers include two compounds available as oral tablets: leukotriene receptor antagonists (e.g., montelukast and zafirlukast) and 5-lipoxygenase pathway inhibitors (e.g., zileuton). No animal studies and one human study were available for review. The human study was an observational study of 2,205 pregnant women, of whom 873 had asthma and 9 had taken leukotriene modifiers, but the specific agent was not identified. The conclusion is that minimal data are currently available on the use of leukotriene modifiers during pregnancy.
Reassuring animal studies have been submitted to the Food and Drug Administration (FDA) for leukotriene receptor antagonists but not for the leukotriene lipooxygenase inhibitor.

**Recommendations for Managing Asthma During Pregnancy**

The Working Group recommends the following principles and stepwise approach to pharmacologic therapy (see appendix B, figures 1–6) for managing asthma during pregnancy. The principles and approach are based on the Working Group’s interpretation of the current scientific review of the evidence on the safety of asthma medications during pregnancy and consideration of previous NAEPP reports—the Asthma and Pregnancy Report 1993 and the Expert Panel Reports (EPR-2 1997 and the EPR—Update 2002).

**General Principles**

- **The treatment goal for the pregnant asthma patient is to provide optimal therapy to maintain control of asthma for maternal health and quality of life as well as for normal fetal maturation. Asthma control is defined as:**
  - Minimal or no chronic symptoms day or night
  - Minimal or no exacerbations
  - No limitations on activities
  - Maintenance of (near) normal pulmonary function
  - Minimal use of short-acting inhaled beta₂-agonist
  - Minimal or no adverse effects from medications

- **It is safer for pregnant women with asthma to be treated with asthma medications than it is for them to have asthma symptoms and exacerbations. Monitoring and making appropriate adjustments in therapy may be required to maintain lung function and, hence, blood oxygenation that ensures oxygen supply to the fetus. Inadequate control of asthma is a greater risk to the fetus than asthma medications are. Proper control of asthma should enable a woman with asthma to maintain a normal pregnancy with little or no risk to her or her fetus.**

- **The obstetrical care provider should be involved in asthma care, including monitoring of asthma status during prenatal visits. A team approach is helpful if more than one clinician is managing the asthma and the pregnancy.**

- **Asthma treatment is organized around four components of management.**

  - **Assessment and monitoring of asthma, including objective measures of pulmonary function.** In the opinion of the Working Group, women who have persistent asthma should be evaluated at least monthly during pregnancy by means of history (symptom frequency, nocturnal asthma, interference with activities, exacerbations, and medication use), lung auscultation, and pulmonary function. A major reason for this frequency of monitoring is that the course of asthma changes in approximately two-thirds of women during pregnancy. Spirometry tests are recommended at the time of initial assessment. For routine monitoring at most subsequent followup outpatient visits, spirometry is preferable, but measurement of peak expiratory flow (PEF) with a peak flow meter is generally sufficient. Patients should be instructed to be attentive to fetal activity. Serial ultrasound examinations starting at 32 weeks gestation may be considered for patients who have suboptimally controlled asthma and for women with moderate to severe persistent asthma. Ultrasound examinations are also helpful after recovery from a severe exacerbation.

  - **Control of factors contributing to asthma severity.** Identifying and controlling or avoiding such factors as allergens and
irritants, particularly tobacco smoke, that contribute to asthma severity can lead to improved maternal well-being with less need for medications (see figure 7 in appendix B).

- **Patient education.** Asthma control is enhanced by ensuring access to education about asthma and about the skills necessary to manage it—such as self-monitoring, correct use of inhalers, and following a plan for managing asthma long term and for promptly handling signs of worsening asthma. It is also important to work with patients to help identify and overcome barriers to adhering to the asthma management program.

- **A stepwise approach to pharmacologic therapy.** In this approach to achieving and maintaining asthma control, the dose and number of medications and the frequency of administration are increased as necessary, and are decreased when possible, based on the severity of the patient's asthma.

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**Recommendations for Pharmacologic Treatment of Asthma During Pregnancy**

**Stepwise Approach for Managing Asthma**

To develop recommendations for the stepwise approach to the pharmacologic treatment of asthma in pregnant women, the Working Group first considered the stepwise approach in the EPR—Update 2002, which was based on a systematic review of the evidence from medication effectiveness studies in nonpregnant adults and children. The Working Group also considered the EPR-2 1997 and the Asthma and Pregnancy Report 1993. The effectiveness of medications is assumed to be the same in pregnant women as in nonpregnant women, although there are no studies that directly test this assumption. Based on their current systematic review of evidence from safety studies of asthma medications during pregnancy, the Working Group then tailored those recommendations for stepwise therapy.

Refer to figures 1 through 6 in appendix B and to the discussion in the section of this report, Managing Asthma During Pregnancy, for recommended therapies and medication dosages in the stepwise approach to managing asthma. The differences between recommendations in this current report and those made in the Asthma and Pregnancy Report 1993 and the EPR—Update 2002 are summarized in table 1.

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<td>Step 1</td>
<td>(“Mild” in 1993.) Intermittent asthma is a new category in EPR-2 1997 and EPR—Update 2002. It is noted that patients in this category can have severe attacks. Albuterol, rather than terbutaline, is now preferred during pregnancy.</td>
<td>Albuterol is the preferred inhaled beta&lt;sub&gt;2&lt;/sub&gt;-agonist, based on safety studies during pregnancy.</td>
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<td>Step 2</td>
<td>(“Moderate” in 1993.) Inhaled corticosteroids are now the preferred treatment (starting with cromolyn is no longer recommended). Inhaled budesonide is preferred rather than beclomethasone dipropionate. Data are now available on budesonide, although clinical experience with beclomethasone dipropionate remains reassuring. (See note in next column.) New alternative treatment options: cromolyn, sustained-release theophylline, or leukotriene receptor antagonist. Dose for theophylline is to serum concentration of 5 (rather than 8)–12 mcg/mL.</td>
<td>Budesonide is the preferred inhaled corticosteroid because safety studies in pregnancy are available and are reassuring. Few or no data are available on other formulations during pregnancy, but no data indicate they are unsafe. Thus, other formulations may be continued in patients well controlled by those agents prior to pregnancy. Nedocromil is no longer available as an alternative treatment.</td>
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<tr>
<td>Step 3</td>
<td>(“Moderate with additional therapy” in 1993.) Cromolyn and oral beta&lt;sub&gt;2&lt;/sub&gt;-agonist are no longer recommended. New preferred treatment is a choice: either medium-dose inhaled corticosteroids (as in 1993) OR a combination of inhaled corticosteroids with long-acting inhaled beta&lt;sub&gt;2&lt;/sub&gt;-agonist. Theophylline is an alternative (no longer preferred) adjunctive treatment, and leukotriene receptor antagonist is a new alternative adjunctive treatment.</td>
<td>Two preferred treatment options are available rather than one: either a combination of low-dose inhaled corticosteroids and long-acting beta&lt;sub&gt;2&lt;/sub&gt;-agonist (based on effectiveness studies in EPR—Update 2002, but no safety studies in pregnancy are available) OR medium-dose inhaled corticosteroids. Budesonide is the preferred inhaled corticosteroid—see note above.</td>
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<tr>
<td>Step 4</td>
<td>(“Severe” in 1993.) Cromolyn and oral beta&lt;sub&gt;2&lt;/sub&gt;-agonist are no longer recommended. Preferred treatment is now a combination of inhaled corticosteroids and long-acting inhaled beta&lt;sub&gt;2&lt;/sub&gt;-agonists. Theophylline is now an alternative, not preferred, adjunctive therapy.</td>
<td>No differences.</td>
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REFERENCES


A. Considerations in Evaluating Medication Effects on Pregnancy Outcome

The prescribing of medication, during pregnancy or otherwise, involves consideration of risks and benefits. Benefits are usually seen as better control of a disease state and improved health of the patient. These benefits for a pregnant woman also may accrue to the embryo or fetus she is carrying, because the best environment for growing a healthy baby is a healthy mother. The question in therapeutics during pregnancy is whether adverse effects of medication on embryo or fetal development may counter the substantial potential benefit of improving the mother’s health. The estimation of possible risks on pregnancy outcome through medication exposure makes use of data from several sources, including human and experimental animal studies.

Although it is preferable to use data on humans to estimate human risk, studies in humans may not be practical or informative. The most highly valued study design for evaluating drug therapy, the randomized controlled trial, is often avoided in pregnant subjects, particularly for medications for which the effects on pregnancy are not well characterized. Often, human data are restricted to pregnancy outcome after inadvertent exposure to a medication during an unplanned pregnancy. These human reports may be limited in their interpretability. Potential problems include:

- Confounding by indication. Women exposed to medication usually have a disease or other condition. If the effects of the disease or condition on pregnancy outcome cannot be separated from the effects of the medication on pregnancy outcome, the wrong conclusion can be drawn.

- Ascertainment bias. Women who come to attention in a study because they have been exposed to a medication may differ in important ways from women with the same exposure who do not come to the same attention.

- Other exposures. Human beings are exposed to myriad chemicals (nicotine, alcohol, caffeine, other medications). These other exposures make analysis of human reports challenging.

- Misidentification of outcomes. Unless followup of pregnancy is complete and standardized, some outcomes may come to attention while others are missed. Under ideal circumstances, all babies born to women who are exposed to a medication of interest are examined by a small number of clinicians using the same protocol at the same postnatal age (because birth defects are more readily diagnosed as children get older). In many followup studies, however, outcome is evaluated on the basis of the mother’s report about what she understands her pediatrician to have said about the baby. In other studies, outcome information on the baby may be solicited from the obstetrician, who may not have evaluated the infant.

- Low power. The baseline incidence of all congenital anomalies identified at birth is about 3 percent. To identify an important increase in this incidence requires a large number of exposures, particularly if the increase is in a small fraction of total birth defects. For example, valproic acid
exposure increases the incidence of lumbar meningomyelocele from a background rate of 1/1,000 to about 1/100. Such an increase will not measurably increase the total rate of congenital malformations until hundreds of pregnancies have been exposed to that drug.

Experimental animal studies offer the availability of well-defined, genetically homogeneous populations. Single or multiple doses of a medication can be carefully controlled. Outcomes can be evaluated in detail, using standard dissection and tissue-preparation techniques. However, experimental animal studies also have important limitations:

• Interspecies extrapolation. Mechanisms of embryogenesis are highly conserved across species; however, differences in genetic programs and differences in drug handling by the mother may make extrapolation among species unreliable.

• Limited endpoints. Many experimental studies use anatomic endpoints rather than functional endpoints. Important outcome measures, such as cognitive function, may not be evaluated at all.

• Interpretation of effects at high-dose exposures. Experimental animal studies use a range of doses that typically include a high dose that causes some degree of maternal toxicity. Developmental effects that occur in relation to maternal toxicity may be difficult to interpret. Such effects might be due to the effects of the medication on embryo development or to the effects of maternal impairment on embryo development. For example, if a high dose of a drug causes a pregnant rodent not to eat, a reduction of birth weight in the offspring would not be surprising.

• Questionably relevant dosing patterns. Sometimes experimental animal studies are performed using dosing regimens based on practical considerations rather than aptness for human exposure. For example, a single daily oral bolus of a corticosteroid might be used in an experimental study to model the bid or tid use of an inhaled corticosteroid.

In spite of these limitations, human risk assessment makes use of experimental animal studies and accepts several assumptions:

• A medication exposure that causes abnormal development in humans is highly likely to do so also in experimental animals (although the converse is not true).

• In the absence of other information, an adverse outcome in any whole-animal mammalian study is taken to represent possible human developmental risk, although features of the experiment, such as the dose given to the animal, may substantially modify the level of concern.

• The endpoint of an experimental animal study that is affected by an exposure does not necessarily predict the endpoint that should be anticipated with human exposure. In other words, if a medication causes limb defects in mice, it cannot be concluded that the developing human limb is at risk. Abnormal development in an experimental study is taken as evidence that the exposure can disrupt embryonic processes, not as an indication of which processes will be disrupted.

• Nontraditional models (e.g., chick eggs, in vitro embryos, fish embryos) may be useful for evaluating mechanisms of abnormal development, but they are not used for predicting human response.

In 1979, the U.S. Food and Drug Administration (FDA) introduced a Drugs in Pregnancy category system in which one of five letter designations (A, B, C, D, X) and associated standard text is used to summarize pregnancy information on a medication. The following considerations are made regarding the FDA category system.
These categories are based on experimental animal and human gestational data submitted to the FDA (but not necessarily published in the scientific literature) as well as a consideration as to whether the benefit of the drug's use during pregnancy outweighs the risk.

No asthma medication has been placed in category A, which requires adequate and controlled human data and reassuring experimental animal studies (if animal studies have been conducted). Most asthma medications are category B (reassuring experimental animal studies) or C (absent or nonreassuring experimental animal studies), but these animal studies often are not published, and they may not be uniformly conducted or interpreted. Cromolyn, ipratropium bromide, and leukotriene receptor antagonists are labeled category B, based on experimental animal studies submitted to the FDA. Only budesonide has been labeled category B based on reassuring human data (with nonreassuring animal data based on systemic exposure). Albuterol, salmeterol, and inhaled corticosteroids other than budesonide are labeled category C. No current asthma medication is labeled category D (shown to cause problems in human pregnancy, but the benefit may outweigh the risk). Iodides are the only example of a medication for asthma with a category X (in this case, shown to cause problems in human pregnancy, and benefits for asthma do not outweigh risks).

Because these categories do not take into consideration all published human or animal gestational data, the route of administration, or the efficacy of a given drug, they have limited usefulness for clinical decision-making in pregnant patients who need medical therapy (Addis et al. 2000; Boothby and Doering 2001; Doering et al. 2002; Teratology Society Public Affairs Committee 1994). The FDA is currently revising its pregnancy labeling system to replace category designations with narrative text that more accurately and completely conveys the available information.

The Working Group recommends using the available information on pregnancy effects of a medication, rather than its category designation, in the consideration of therapeutic options in pregnant women and women of childbearing age.

REFERENCES


B. Systematic Review of the Evidence by Drug Class

Bronchodilators: Beta-Adrenergic Agonists

Evidence tables are online at: http://www.nhlbi.nih.gov/health/prof/lung/asthma/astpreg.htm

The principal action of beta_2_ agonists is to relax airway smooth muscle by stimulating beta_2 receptors, thus increasing cyclic AMP and producing functional antagonism to bronchoconstriction.

One experimental animal study and six human studies were included in the evidence tables for review. The animal study (Alexander et al. 1997) was an experiment...
to test an inhalation exposure system. Salmeterol and other beta₂-agonists have produced pharmacologic effects in experimental animal pregnancy that are similar to effects seen in human pregnancy tocolytic use of these agents. The production of adverse effects on development with sympathomimetic agents in experimental animals is believed to be associated with vasoconstrictive properties that are absent with beta₂-selective agents. Since the Asthma and Pregnancy Report 1993, no data have been found that modify this assessment. The six human studies included in the current evidence review comprised one case report and five clinical studies that included 6,667 pregnant women, of whom 1,929 had asthma and 1,599 were exposed to beta₂-agonists.

Of these studies, two reported on transient cardiovascular changes in the fetus as a result of short-acting beta₂-agonists (Baker and Flanagan 1997; Rayburn et al. 1994). Two prospective cohort studies examined the safety of asthma medications throughout pregnancy (Bracken et al. 2003; Schatz et al. 1997). A retrospective study in England examined the proportion and nature of congenital anomalies in babies born to women exposed during the first trimester to newly marketed drugs (Wilton et al. 1998). Finally, a postmarketing surveillance study of formoterol in England included a small number of women who took the drug during pregnancy (Wilton and Shakir 2002). There were no studies of pregnant patients taking the currently available oral formulation of long-acting beta₂-agonists.

Systematic Review of the Evidence: Findings

A single case report documents a transient episode of fetal atrial flutter in the 33rd week of gestation. The mother had received an overdose of albuterol over a 24-hour period. The fetal rhythm returned to normal 8 hours after albuterol was stopped, and no long-term complications occurred (Baker and Flanagan 1997). In another study, 12 women received 2 inhalations of albuterol between the 33rd and 39th weeks of gestation; after the inhalations, each woman and fetus were monitored for 2.25 hours (Rayburn et al. 1994). The mean maternal blood pressures and heart rates, systolic/diastolic flow velocity ratios of the uterine arcuate and umbilical arteries, as well as fetal heart rates and aortic flow velocities, were unaffected.

A prospective study compared outcomes in 824 pregnant women who had asthma and 678 pregnant women who did not (Schatz et al. 1997). Exposure to beta-adrenergic agonists was recorded in 488 women during the first trimester and in 667 overall. Drugs used included inhaled metaproterenol in 309, inhaled terbutaline in 316, and inhaled albuterol in 129. Fifty-one received injected epinephrine or Sushpine. No significant relationship was identified between major congenital malformations or other adverse perinatal outcomes and exposure during the first trimester or at any time to beta₂-agonists.

A second prospective study examining preterm delivery and intrauterine growth restriction (IUGR) enrolled 873 pregnant women with a history of asthma, 449 pregnant women with asthma symptoms but not with an asthma diagnosis, and 884 pregnant women with neither an asthma diagnosis nor symptoms (Bracken et al. 2003). Short-acting beta₂-agonist use was recorded in 529 women and long-acting beta₂-agonist use in 64 women. No significant effect of either class of beta₂-agonist on preterm delivery rate or IUGR was reported.

Prescription-event monitoring in England identified 65 women who took salmeterol during the first trimester of pregnancy (Wilton et al. 1998). The outcomes of 47 babies were determined. One congenital anomaly occurred—a full-term infant with Aarsgog syndrome, which is considered to have a genetic basis. Of the 47 children, 3 were premature. In a postmarketing surveillance study of formoterol, also conducted in England (Wilton and Shakir 2002), 30 women were identified who took formoterol...
during the first trimester. Of the 25 live births, 5 children were born prematurely. Two congenital anomalies occurred: one was a fetal heart rate anomaly, the other was pyloric stenosis. Although slightly more abnormalities occurred with formoterol, the data do not support a substantial difference between the two drugs because the numbers were small for each drug.

**Conclusions**

Although limited in amount, all of the additional data on short-acting beta₂-selective adrenergic bronchodilators are reassuring regarding their safety in pregnancy. No changes are required, therefore, in the previous recommendations regarding their use in pregnancy.

The Asthma and Pregnancy Report 1993 addressed only short-acting beta₂-selective and nonselective beta-adrenergic agonists. For the short-acting beta₂-selective agonists, it was concluded that animal studies were generally negative, although some of these agents produce anomalies at high doses. Experience of women with these drugs was extensive, especially as to tocolytics in the latter part of pregnancy. No evidence was found of fetal injury from the use of these drugs, either systemically or by inhalation, and no contraindication to their use during lactation was found. It was noted that concern had been raised about uterine vasoconstriction due to the alpha-adrenergic effects of epinephrine and about the effects of nonselective adrenergic agonists in experimental animals. It was concluded, however, that the occasional, episodic use of epinephrine for severe, acute exacerbations of asthma is unlikely to produce chronic hemodynamic changes such as those seen in the animal studies.

Evidence from the current review does not change these conclusions. Two long-acting, inhaled beta₂-agonists have become available since 1993—salmeterol and, just recently, formoterol—although limited data are available on their use during pregnancy. Their pharmacologic and toxicologic profiles are similar to the short-acting beta₂-agonists. Salmeterol might be chosen for asthma treatment during pregnancy because it has been available longer in the United States.

**References**


Wilton LV, Pearce GL, Martin RM, Mackay FJ, Mann RD. The outcomes of pregnancy in...


**Bronchodilator: Theophylline**

Theophylline, the principally used methylxanthine, provides mild-to-moderate bronchodilation in asthma. Although its mechanism of action has yet to be established, low serum concentrations of theophylline may be mildly anti-inflammatory (Barnes 2003; Hidi et al. 2000).

Seven experimental animal studies and eight human studies were included in the evidence tables for review. The animal studies were preclinical toxicity or teratology studies (Harris et al. 1992; Hart and Grimble 1990a, b; Lamb et al. 1997; León et al. 2002; Lindström et al. 1990; Shibata et al. 2000). Theophylline can produce abnormal effects on experimental animal development. The adverse effects of theophylline require the production of blood concentrations in the pregnant animal that are considerably higher than clinically achieved levels. Since the last report, additional experimental animal work has confirmed the association of high-dose theophylline and adverse pregnancy outcome in experimental animals. The eight human studies, consisting of two case reports (Agarwal et al. 1998; Park et al. 1990) and six clinical studies, included 57,167 pregnant women, of whom 3,616 had asthma and 660 were exposed to theophylline. Of the six clinical studies, one was a case-control study (Stenius-Aarniala et al. 1995), three were prospective cohort studies (Bracken et al. 2003; Neff and Leviton 1990; Schatz et al. 1997); and two were prospective randomized controlled trials (Dombrowski et al. 2004; Wendel et al. 1996). The Neff and Leviton study was a review of data systematically collected as part of a large standardized longitudinal study (the Collaborative Perinatal Project). Neff and Leviton reviewed data on a sample of 51,830 singleton pregnancies of women who either had or did not have a diagnosis of asthma and who were either taking or not taking theophylline during pregnancy.

**Systematic Review of the Evidence: Findings**

For many decades, theophylline has been used with no proven human teratogenic effects. In a prospective cohort study (Neff and Leviton 1990), administration of theophylline during pregnancy, for both chronic and acute care of asthma, was not associated with an increased risk of stillbirth. That study, however, had only 50 percent power because of the low incidence of stillbirth. In another study of 824 pregnant women who had asthma and 678 women who did not have asthma, theophylline was used by 429 of the women and was not associated with increased incidences of major congenital malformations, maternal preeclampsia, preterm birth, low birth weight, or being small for gestational age (Schatz et al. 1997). In a case-control study of 212 pregnant women who had asthma, use of slow-release theophylline in the first trimester was associated with an increase in preeclampsia but was not associated with prematurity or low birth weight (Stenius-Aarniala et al. 1995). The possibility of these results being confounded by oral steroid use or asthma severity was not excluded in this study. The rate of malformations did not increase, but the study did not have sufficient power to detect a difference in the rate of congenital malformations with first trimester use of theophylline.

Another case report described three infants who had complex congenital heart disease (double outlet right ventricle, hypoplastic left ventricle, and transposition of the great vessels) born to mothers who had asthma and who had taken theophylline throughout pregnancy.

Evidence tables are online at: http://www.nhlbi.nih.gov/health/prof/lung/asthma/astpreg.htm
Pregnancy is associated with hypoalbuminemia and decreased theophylline binding. The Working Group’s opinion is that when theophylline is used during pregnancy, low doses of theophylline are recommended, with maintenance of serum theophylline levels at 5–12 mcg/mL. Side effects of theophylline include insomnia, heartburn, palpitations, and nausea that may be difficult to differentiate from typical pregnancy symptoms. High doses have been observed to cause jitteriness, tachycardia, and vomiting in mothers and neonates. A case of transplacental theophylline toxicity also has been reported (Agarwal et al. 1998), with fetal theophylline levels of 8.6 mcg/mL at 1 hour of life. Other drugs can decrease theophylline clearance and result in toxicity. Two of those commonly used drugs are cimetidine, which can cause a 70 percent increase in theophylline serum levels, and erythromycin, which can cause a 35 percent increase (Hendeles et al. 1995).

The main potential advantage of theophylline is the long duration of action (10–12 hours with the use of sustained-release preparations), which may be useful in the management of nocturnal asthma. In a prospective, double-blind randomized controlled trial of pregnant women with moderate asthma, no difference was found in asthma exacerbations, treatment failures, or maternal or perinatal outcomes among the women in the beclomethasone dipropionate versus the theophylline (used as monotherapy) cohort (Dombrowski et al. 2004). Women taking theophylline, however, reported a higher frequency of side effects and discontinuation of the medication. Also, there was an increase in the proportion of women with FEV₁ at less than 80 percent of that predicted in the theophylline cohort.

Theophylline is not useful as adjunctive therapy for the treatment of acute exacerbations during pregnancy. Addition of aminophylline to inhaled albuterol and intravenous methylprednisolone during a hospitalization for an acute asthma exacerbation had no effect on length of hospitalization in a prospective, randomized study of 84 pregnant women (Wendel et al. 1996).

Conclusions

Decades of experience with theophylline have confirmed its safety during pregnancy. Serum concentrations of theophylline must be closely monitored, however, to avoid theophylline toxicity. Low-dose theophylline (to serum concentration of theophylline of 5–12 mcg/mL) is an alternative, but not preferred, therapy for mild persistent asthma. The 1993 report recommended serum concentration of theophylline ranging from 8–12 mcg/mL (Asthma and Pregnancy Report 1993); the change to 5–12 mcg/mL is based on the current Working Group’s opinion.

For moderate or severe asthma, theophylline may be considered as alternative, but not preferred, adjunctive long-acting bronchodilator therapy when inhaled corticosteroids alone do not provide adequate control of the patient’s asthma. Theophylline is not useful as adjunctive therapy for the treatment of acute exacerbations.

REFERENCES


Anticholinergics

Cholinergic innervation is an important factor in the regulation of airway smooth muscle tone. Anticholinergics are used as adjunctive therapy for acute exacerbations of asthma. Ipratropium bromide is a quaternary derivative of atropine that does not cross membranes well and therefore does not have many of atropine’s side effects. No recently published data on anticholinergics in pregnancy were available for the current evidence review.

Inhaled Corticosteroids and Pregnancy

Evidence tables are online at: http://www.nhlbi.nih.gov/health/prof/lung/asthma/astpreg.htm

Inhaled corticosteroids are currently used for the management of persistent asthma because they are the most effective anti-inflammatory medication. Their broad action on the inflammatory process may account for their efficacy as preventive therapy. Their clinical effects include reduction in severity of symptoms, improvement in peak expiratory flow and spirometry, diminished airway hyperresponsiveness, prevention of exacerbations, and possibly the prevention of airway wall remodeling. Which of these clinical effects depend on specific anti-inflammatory actions of corticosteroids is not yet clear. Corticosteroids suppress the generation of cytokines, recruitment of airway eosinophils, and release of inflammatory mediators (EPR-2 1997). Five inhaled corticosteroids are currently available in the United States: beclomethasone dipropionate, triamcinolone acetonide, flunisolide, fluticasone propionate, and budesonide.

Three experimental animal studies and 10 human studies were included in the key evidence tables for review. In all the animal studies (Rotschild et al. 1997; Sakamoto et al. 1991; Wise et al. 1991), the corticosteroids were administered by routes other than inhaled. The 10 human studies with inhaled corticosteroids included 8 studies of pregnant women as well as 2 studies of newborns from the Swedish Birth Registry. The eight studies of pregnant women enrolled a total of 21,072 pregnant women, of whom 16,900 had asthma and 6,113 had taken inhaled corticosteroids. These studies include a retrospective population-based cohort study (Alexander et al. 1998), one retrospective cohort study (Dombrowski et al. 1996), three prospective cohort studies (Bracken et al. 2003; Schatz et al. 1997; Stenius-Aarniala et al. 1996), one controlled trial (Murphy et al. 2002), and two clinical randomized controlled trials (Dombrowski et al. 2004; Wendel et al. 1996). Of the two studies using the Swedish Birth Registry, one compared rates of abnormalities among 2,014 newborns whose mothers had taken budesonide to rates of abnormalities among the total newborn population for the duration of the study, although the number in that population was not reported (Källén et al. 1999); the other study compared 2,900 newborns whose mothers had taken budesonide to the 293,948 total newborn population for the duration of the study (Norjavaara and de Verdier 2003). The populations of the two studies may overlap, and neither study reported the number of women with asthma.

Systematic Review of the Evidence: Findings

Two reports (Stenius-Aarniala et al. 1996; Wendel et al. 1996) provide data indicating that the risk of asthma exacerbations can be reduced with inhaled corticosteroid therapy during pregnancy. Stenius-Aarniala et al. (1996) reported on followup of 504 asthmatic subjects who were prospectively followed (1) to determine the effect of an asthma exacerbation during pregnancy on the course of the pregnancy or delivery, or the health of the newborn infant, and (2) to identify undertreatment as a possible cause of exacerbations. The researchers reported a higher incidence of asthma exacerbations in those who were not initially treated with inhaled corticosteroid in comparison with patients who had been on an inhaled corticosteroid from
the beginning of pregnancy. The researchers reported no differences between pregnancies with and without an exacerbation with regard to perinatal complications. The researchers concluded that patients with inadequate inhaled anti-inflammatory treatment during pregnancy run a higher risk of an acute attack of asthma than those who use an anti-inflammatory agent. If the acute attack is mild and promptly treated, however, it does not have a serious effect on the pregnancy, delivery, or health of the newborn infant. Similarly, a randomized controlled trial found that the readmission rate was decreased by 55 percent in women given inhaled beclomethasone dipropionate in addition to oral corticosteroid and beta2-agonist compared with women treated with oral corticosteroid and beta2-agonist alone (Wendel et al. 1996). A randomized controlled trial comparing the use of beclomethasone dipropionate versus theophylline during pregnancy found no differences between the treatment groups in asthma exacerbations, treatment failures, or maternal or perinatal outcomes. However, there were fewer reported side effects, less discontinuation of the medications, and a lower proportion of women with FEV1 less than 80 percent predicted in the beclomethasone dipropionate treatment group as compared to the theophylline treatment group (Dombrowski et al. 2004). Murphy et al. (2002) evaluated mechanisms for the observation that pregnancies complicated by asthma are associated with an increased risk of low birth weight. They observed a 25 percent reduction in neonatal birth weight centile in asthmatic women who did not use inhaled corticosteroid treatment. This was accompanied by both significantly reduced placental 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) activity and significantly increased fetal cortisol. The use of inhaled corticosteroid for asthma treatment was associated with outcomes similar to a nonasthmatic control group, for birth weight centile, 11β-HSD2 activity, placental CRH mRNA, and fetal cortisol and estriol concentrations. Four reports (Alexander et al. 1998; Bracken et al. 2003; Dombrowski et al. 1996; Schatz et al. 1997) were identified that addressed the effect of asthma management on neonatal outcomes. Alexander and colleagues conducted a retrospective cohort study to determine the risk of adverse effects on the mothers and infants if asthma medications are taken during pregnancy. In a comparison of women who had or did not have asthma, women who had asthma and were taking corticosteroid medication appeared to be at increased risk for pregnancy-induced hypertension, although the confidence intervals in the data and the smaller number of patients in this group do not indicate a significantly increased risk. The only significant difference in neonatal outcome was an increased risk of hyperbilirubinemia in infants of women who were taking corticosteroid medication. It was not clear whether these adverse effects were related to the corticosteroid medication or to poorly controlled asthma. In addition, the investigators did not differentiate between oral and inhaled corticosteroid use. On the basis of a prospectively monitored cohort of 824 pregnant women who had asthma and 678 pregnant women who did not have asthma, Schatz et al. (1997) concluded that there was no significant relationship between congenital malformations and exposure to corticosteroids (oral, inhaled, or intranasal) in the first trimester or at any gestational age. They also found no independent relationships between inhaled corticosteroids and preeclampsia, preterm births, infants who were small for gestational age, or low birth weight infants. In a retrospective cohort study, Dombrowski et al. (1996) reported on the use of triamcinolone acetonide during pregnancy. Although limited by a small sample size, the researchers reported no significant difference in birth weight among the groups receiving triamcinolone acetonide, beclomethasone dipropionate, or theophylline; however, the birth weight was 500 gm less in newborns of mothers receiving beclomethasone dipropionate compared to those whose mothers received triamcinolone acetonide; however, the sample size was
small and this difference was not statistically
significant. In a recent report, Bracken et al. (2003) provided reassuring information
based on a prospective study of 873 pregnant
women with asthma (778 of whom experi-
enced symptoms) and 1,333 women with
no history of asthma. In the 176 women
who received inhaled corticosteroids, the
researchers found no indication of preterm
delivery or IUGR in the newborn infants.

Two studies (Källén et al. 1999; Norjavaara
and de Verdier 2003) specifically reported on
the experience of neonatal outcomes after the
use of budesonide for asthma management
during pregnancy. Källén and colleagues
(1999) examined the potential teratogenic
risks associated with the use of an inhaled
corticosteroid, budesonide, by women in first
trimester of pregnancy. Using the Swedish
Medical Birth Registry, they found no
increase, compared to the total population, in
the overall rate of congenital malformations,
oral clefts, or cardiovascular malformations
associated with maternal use of inhaled
budesonide. Norjavaara and de Verdier
(2003) investigated whether the use of
inhaled budesonide during pregnancy
influenced birth outcome. Again, data
were obtained from the Swedish Medical
Birth Registry. The study found that inhaled
budesonide was not linked to any clinically
relevant effects on pregnancy outcome,
including fetal mortality, gestational age,
birth weight, and birth length of the
newborn.

Conclusions

The Working Group reached three major
conclusions from the systematic review of the
evidence on the use of inhaled corticosteroids
during pregnancy. (1) The risk of asthma
exacerbations associated with pregnancy can
be reduced and lung function (FEV₁)
improved with the use of inhaled cortico-
steroid therapy. (2) To date, no studies have
related inhaled corticosteroid use to any
increased congenital malformations or other
adverse perinatal outcomes. (3) In studies
using birth registries of newborns whose
mothers were exposed to budesonide, informa-
tion is reassuring regarding the use of this
medication during pregnancy.

In 1993, the Working Group on Asthma and
Pregnancy stated that corticosteroids are
among the most effective anti-inflammatory
drugs for the treatment of asthma. The
Working Group recognized three agents
available at the time in the United States for
inhalation treatment: beclomethasone dipro-
pionate, triamcinolone, and flunisolide. They
concluded that, of the three inhaled cortico-
steroids available, the most extensive experi-
ence in pregnancy was with beclomethasone
dipropionate. They indicated that the use of
triamcinolone and flunisolide during preg-
nancy had not been studied. They stated that
because of its reassuring clinical experience,
beclomethasone dipropionate is the preferred
inhaled corticosteroid during pregnancy.

They also concluded that, although systemic
absorption of inhaled corticosteroids can
occur, the low plasma concentrations
achieved by inhalation make it unlikely that
fetal effects will be seen. Neither systemic
nor inhaled corticosteroid use by the mother
is a contraindication to breast-feeding.

The data reviewed for the 1993 report indi-
cated a risk for fetal resorption and cleft
palate in experimental animal studies with
high doses of corticosteroids, including
beclomethasone dipropionate. The report
also noted that triamcinolone was 200 times
more potent than cortisone in producing
palatal clefts in mice. Triamcinolone was
10,000 times more potent a teratogen than
hydrocortisone in an avian model. The 1993
Working Group concluded that extensive
experience with humans had failed to suggest
any increase in facial clefts or other birth
defects from the use of corticosteroids
potential adverse effect reported was limited
to case reports. They concluded that, in gen-
eral, nonhalogenated corticosteroids do not
cross the placenta well, and there is no reason to believe that fetal or neonatal adrenal suppression will occur with maternal therapy.

In the 10 years since the Working Group published their conclusions, a revision (EPR-2 1997) and an update (EPR—Update 2002) to the asthma guidelines have been published. Inhaled corticosteroids are now recognized as the preferred treatment for the management of all levels of persistent asthma in adults and children of all ages. In addition, two inhaled corticosteroids (fluticasone propionate and budesonide) have been approved for use in the United States within the last 10 years.

In summary, the 1993 NAEPP Report of the Working Group on Asthma and Pregnancy recommended beclomethasone dipropionate as the preferred inhaled steroid for asthma management, primarily because the largest amount of clinical experience in pregnant women at that time was with beclomethasone dipropionate. The current evidence-based review of recent publications supports the overall safety of inhaled corticosteroid use in pregnancy and notes that the preponderance of data now available in the published literature is from studies with budesonide. Fewer published data are available with beclomethasone dipropionate, and few or no data are available for the other inhaled steroid formulations that could be used for asthma management during pregnancy.

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Oral (Systemic) Corticosteroids and Pregnancy

Nine experimental animal studies (Abbott et al. 1992a, b; Abbott et al. 1994; Abbott et al. 1999; Dodic et al. 1998; Jobe et al. 1998; Tangalakis et al. 1992; Uno et al. 1994; Watanabe et al. 1995) and eight human studies were included in the key evidence tables. In five of the nine animal studies, the corticosteroids were administered by routes other than oral. It has been known for decades that administration of corticosteroids to susceptible strains of mice and rats will increase palatal clefting. Nonhuman primates also have shown clefting with potent corticosteroid exposure during pregnancy. Since the 1993 Asthma and Pregnancy Report, there have been no studies that change our understanding of steroid-mediated clefting in experimental animals. A decrease in fetal growth that in the older literature had been associated with corticosteroid exposure in experimental animal pregnancies has been confirmed in a more recent study in sheep.

Eight human studies were identified. One report (Park-Wyllie et al. 2000) included two meta-analyses. One of these meta-analyses used six cohort studies that included 51,380 pregnant women, of whom 535 had taken oral corticosteroids (the number with asthma was not reported). Five of these cohort studies were published prior to 1990 and, therefore, were not eligible for inclusion in the current systematic review of the evidence; one study published after 1990 was included in the evidence review (Park-Wyllie et al. 2000). The other meta-analysis in the Park-Wyllie report used four case-control studies (Carmichael and Shaw 1999; Czeizel and Rockenbauer 1997; Robert et al. 1994; Rodríguez-Pinilla and Martinez-Frias 1998) that included 52,038 pregnant women, of whom 25 were exposed to oral corticosteroids (the number with asthma was not reported). These four case-control studies

Evidence tables are online at: http://www.nhlbi.nih.gov/health/prof/lung/asthma/astpreg.htm
were eligible for inclusion in the current systematic review of the evidence. The three remaining human studies in the systematic review of the evidence are a case-control study (Perlow et al. 1992) and two prospective cohort studies (Bracken et al. 2003; Schatz et al. 1997) that included a total of 4,321 pregnant women, of whom 1,998 had asthma and 213 had taken oral corticosteroid medication.

**Systematic Review of the Evidence: Findings**

The two meta-analyses study of Park-Wyllie et al. (2000) found no increased risk of major fetal malformations associated with first trimester systemic (oral) corticosteroid exposure. The two meta-analyses consisted of 10 articles (six cohort studies, four case-control studies) culled from 455 articles (1966–1999). Study sample sizes ranged from 22 to more than 50,000 neonates. The specific oral corticosteroid and dosage regimens used by the mothers were not detailed in 3 of the 10 studies. However, the meta-analysis of Park-Wyllie and colleagues that included four case-control studies—Carmichael and Shaw (1999); Czeizel and Rockenbauer (1997); Robert et al. (1994); and Rodríguez-Pinilla et al. (1998)—did show a greater than threefold increase in the risk of oral clefts, specifically, when the fetus was exposed to oral corticosteroids during the first trimester. With a background incidence of oral clefting of about 0.1 percent, the excess risk attributable to corticosteroid therapy during pregnancy would be 0.2–0.3 percent.

A case-controlled study by Perlow et al. (1992), as well as prospective studies by Schatz et al. (1997), Park-Wyllie et al. (2000), and Bracken et al. (2003), all identified an increased risk of adverse perinatal outcomes for infants born to mothers who had asthma and were exposed to oral corticosteroids during pregnancy. Both Perlow et al. and Park-Wyllie et al. identified an increased risk for low birth weight and preterm delivery. Bracken et al. identified an increased risk for preterm delivery but not for decreased IUGR. Schatz et al. identified an increased risk for preeclampsia. In the study by Perlow et al., of mothers who had asthma and were dependent on oral corticosteroids, complications also included: gestational diabetes, insulin-dependent diabetes, and an increased incidence of primary cesarean sections.

**Conclusions**

The Asthma and Pregnancy Report of 1993 stated that chronic administration of oral or parenteral (systemic) corticosteroid to women who were pregnant was associated with decreased birth weight of their infants. Experimental animal studies showed palatal clefting in species sensitive to this anomaly, but no increase in birth defects had appeared in humans. The Report cited clinical observations suggesting that prenatal exposure to systemic corticosteroid was associated with a 300- to 400-gm decrease in birth weight and a small increase in “small-for-dates” babies. The Report also stated that systemic and inhaled corticosteroid use by the mother was not a contraindication to breast-feeding.

The findings from the current review of the evidence on the safety of oral corticosteroids during pregnancy are conflicting. Oral corticosteroid use, especially during the first trimester of pregnancy, is associated with an increased risk (estimated excess risk of 0.2–0.3 percent) for isolated cleft lip with or without cleft palate. Very few pregnant women who have oral steroid-dependent asthma were included in the studies, however, and the length of exposure, the dose, and the timing of oral steroid administration were not well described in any of the studies reviewed for this evidence-based report. Oral corticosteroid use during pregnancy in patients who have asthma is associated with an increased incidence of preeclampsia and the delivery of both preterm and low birth weight infants. The available data, however, make it difficult to separate the effects of the corticosteroids on these outcomes from the
effects of severe or uncontrolled asthma. Moreover, because severe asthma has been associated with maternal and/or fetal mortality, risk-benefit considerations favor the use of oral corticosteroid medication when indicated in the long-term management of severe asthma or severe exacerbations during pregnancy.

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Cromolyn Sodium

Cromolyn sodium has anti-inflammatory properties; its mechanism appears to involve the blockade of chloride channels.

No experimental animal studies and two human studies were included in the key evidence table. Since the 1993 Asthma and Pregnancy Report, no publications have changed the conclusion in 1993 that experimental animal studies did not suggest an increase in abnormal development, except with very high doses of nedocromil (a related cromone). The two human studies were prospective cohort studies that included 4,110 pregnant women, of whom 1,917 had asthma and 318 had taken cromolyn (Bracken et al. 2003; Schatz et al. 1997).

Systematic Review of the Evidence: Findings

One prospective cohort study found no significant relationship between use of cromolyn in the first trimester or any time in the pregnancy and increased incidences of major congenital malformations, maternal preeclampsia, preterm birth, low birth weight, or being small for gestational age (Schatz et al. 1997). A recent study (Bracken et al. 2003) found no evidence of preterm delivery or fetal growth restriction among 22 pregnant women who were treated with either cromolyn or nedocromil. Both animal and human experience suggest little potential for fetal harm from cromolyn sodium.

Conclusions

Cromolyn sodium is well tolerated and has an excellent safety profile. Nevertheless, cromolyn sodium is less effective than inhaled corticosteroids in reducing objective and subjective manifestations of asthma. The 1993 report recommended that daily long-term-control therapy be initiated with cromolyn due to its safety (Asthma and Pregnancy Report 1993). The safety of using cromolyn during pregnancy is supported by the current review of the evidence, but strong evidence demonstrates that cromolyn is not as effective as inhaled corticosteroids (EPR-2 1997; EPR—Update 2002). As noted in the section on Inhaled Corticosteroids in this report, evidence supports the use of inhaled corticosteroids in pregnancy. Therefore, cromolyn is an alternative, but not preferred, treatment for mild persistent asthma.

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Bracken MB, Triche EW, Belanger K, Saftlas A, Beckett WS, Leaderer BP. Asthma symptoms,
Leukotriene Modifiers

Evidence tables are online at: http://www.nhlbi.nih.gov/health/prof/lung/asthma/astpreg.htm

Leukotriene modifiers comprise two pharmacologic classes of compounds available as oral tablets: leukotriene receptor antagonists (e.g., montelukast and zafirlukast) and 5-lipoxygenase pathway inhibitors (e.g., zileuton). No experimental animal studies were available for the key evidence tables. The one human study available was a prospective observational study of 2,205 pregnant women, of whom 873 had asthma and 9 had taken leukotriene modifiers during pregnancy. No other published data are available on the safety or efficacy of these agents during pregnancy.

Systematic Review of the Evidence: Findings

Minimal data are available on the safety of these agents during pregnancy. In the one observational study of 873 pregnant women with asthma, the 9 women who used leukotriene modifiers did not experience adverse effects, but the number of women was small and the specific agent was not identified (Bracken et al. 2003).

Conclusions

Minimal human data are currently available on the use of leukotriene modifiers during pregnancy. Data from experimental animal studies submitted to the FDA are reassuring. The two earlier reports (EPR-2 1997; EPR—Update 2002) both noted that leukotriene receptor antagonists (montelukast and zafirlukast) have been shown to be more effective than placebo in the management of mild to moderate asthma in nonpregnant adults and children, although they are less effective than inhaled corticosteroids. Reports on nonpregnant adults and children also show that these oral medications are well tolerated, with few side effects. Zileuton, a 5-lipoxygenase inhibitor, has been shown to be effective for mild persistent asthma, but data submitted to the FDA and based on animal studies are not reassuring, and thus zileuton should be avoided during pregnancy.

The opinion of the Working Group is that leukotriene receptor antagonists may be considered for use during pregnancy for patients who had a favorable response to the drug before they became pregnant. In this case, it would be preferable to maintain the therapy that successfully controlled the patient’s asthma before pregnancy. However, in the opinion of the Working Group, when initiating new treatment for asthma during pregnancy, leukotriene receptor antagonists are an alternative, not preferred, treatment option for mild persistent asthma.
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Uncontrolled maternal asthma increases the risk of perinatal mortality, preeclampsia, preterm birth, and low birth weight infants; the magnitude of risk is related to the severity of the maternal asthma. Nevertheless, most pregnant women with asthma can successfully control their asthma and have a healthy baby. Proper control of asthma should allow a woman with asthma to maintain a normal pregnancy with little or no increased risk to herself or her fetus.

This section discusses the general principles for gaining and maintaining control of asthma and presents the stepwise approach to pharmacologic treatment during pregnancy.

General Principles

- The treatment goal for the pregnant asthma patient is to provide optimal therapy to maintain control of asthma for maternal health and quality of life as well as for normal fetal maturation throughout gestation. Asthma control is defined as:
  - M inimal or no chronic symptoms day or night
  - M inimal or no exacerbations
  - No limitations on activities; no school or work missed
  - M aintenance of (near) normal pulmonary function
  - M inimal use of short-acting inhaled beta₂-agonist
  - M inimal or no adverse effects from medications

- Recommendations for pharmacologic therapy are intended to be general guidelines to assist clinical decisionmaking. They are not intended to be prescriptions for treatment or to replace individualized treatment plans. Asthma is highly variable. Specific therapy should be tailored to the needs and circumstances of individual patients. A general stepwise approach to therapy is recommended in which the number and dose of medications used are increased as necessary and decreased when possible, based on the severity of the patient’s asthma. (See appendix B, figures 1, 2, and 3 for long-term asthma management and figures 4, 5, and 6 for management of acute exacerbations.)

- Pharmacologic therapy should be accompanied at every step of severity by patient education and measures to control those factors that contribute to the severity of the asthma (EPR-2 1997; EPR—Update 2002).

- Asthma care should be integrated with obstetrics care, in the opinion of the Working Group. The obstetrical care provider should be involved in asthma care and should obtain information on asthma status during prenatal visits. Information should include day and nighttime symptoms, peak flow measures or spirometry reading, and medication usage. Consultation or comanagement with an asthma specialist is appropriate, as indicated, for evaluation of the role of allergy and irritants, complete pulmonary function studies, or evaluation of the medication plan if there are complications in achieving the goals of therapy or the patient has severe asthma. A team approach is helpful if more than one clinician is managing the asthma and the pregnancy.
Four Components of Asthma Management

Recommendations for the treatment of asthma are organized around four components of effective asthma management: assessment and monitoring of asthma, including objective measures of pulmonary function; control of factors contributing to asthma severity; patient education for a partnership in asthma care; and pharmacologic therapy using a stepwise approach (Asthma and Pregnancy Report 1993; EPR-2 1997; EPR—Update 2002). Pharmacologic therapy is the focus of this report, based on this report’s systematic review of the evidence on the safety of asthma medications during pregnancy. Brief highlights of recommendations on the remaining three components are presented in this section, however, as a reminder of their importance.

Objective Measures for Assessment and Monitoring

In the opinion of the Working Group, patients who have persistent asthma should be evaluated at least monthly during pregnancy. A major reason for this frequency of monitoring is that the course of asthma changes in approximately two-thirds of women during pregnancy (Schatz et al. 2003). Evaluation should include a history (symptom frequency, nocturnal asthma, interference with activities, exacerbations, and medication use), lung auscultation, and pulmonary function. The dyspnea in pregnancy may seem similar to the dyspnea experienced during asthma exacerbations, but the dyspnea of pregnancy is not associated with the chest tightness, wheezing, and airway obstruction characteristic of asthma. Spirometry tests are recommended at the time of the initial assessment. For routine monitoring at most subsequent followup outpatient visits, spirometry is preferable, but measurement of PEF with a peak flow meter is generally sufficient (EPR-2 1997). Patients with FEV₁ of 60–80 percent predicted are at increased risk of subsequent asthma morbidity during pregnancy, and patients with FEV₁ of less than 60 percent predicted are at even greater risk (Schatz et al. 2003). Daily peak flow monitoring should be considered for patients with moderate to severe asthma, and especially for patients who have difficulty perceiving signs of worsening asthma. The evidence is not sufficient to conclude that peak flow monitoring is any more effective than symptom monitoring, but adequate studies in patients with moderate-to-severe asthma have not been conducted. For these patients, peak flow monitoring may be a valuable tool for home monitoring of asthma and communicating asthma status to the clinician (EPR—Update 2002). Because FEV₁ and PEF do not change appreciably due to pregnancy, PEF may still be a useful monitoring tool for pregnant women with asthma.

Women who have persistent asthma during pregnancy also may benefit from additional fetal surveillance in the form of ultrasound examinations and antenatal fetal testing. Because asthma has been associated with IUGR and preterm birth, it is useful to establish pregnancy dating accurately by first trimester ultrasound where possible. In the opinion of the Working Group, the evaluation of fetal activity and growth by serial ultrasound examinations may be considered for (1) women who have suboptimally controlled asthma, (2) women with moderate to severe asthma (starting at 32 weeks), and (3) women after recovery from a severe asthma exacerbation. The intensity of antenatal surveillance of fetal well-being should be considered on the basis of the severity of the asthma as well as any other high-risk features of the pregnancy that may be present. All patients should be instructed to be attentive to fetal activity.

Avoidance of Factors Contributing to Asthma Severity

Identifying and avoiding factors that can contribute to asthma severity (“asthma triggers”) can lead to improved maternal well-being with less need for medications. (Refer to appendix B, figure 7, Summary of Control
Measures for Environmental Factors That Can Make Asthma Worse.) In previously untested patients, either prick skin tests or in vitro (radioallergosorbent test [RAST] or enzyme-linked immunosorbent assay [ELISA]) tests may be performed to identify relevant allergens (e.g., mites, animal dander, mold, cockroaches) for which specific environmental control instructions can be given (EPR-2 1997). If the patient is using allergen immunotherapy for the control of allergies, it can be continued during pregnancy. However, benefit-risk considerations do not generally favor beginning immunotherapy during pregnancy because the initiation of immunotherapy can be associated with anaphylaxis, which can be fatal to the mother and fetus (Asthma and Pregnancy Report 1993).

Smokers must be encouraged to discontinue smoking, and all patients should try to avoid, as much as possible, exposure to environmental tobacco smoke and other potential irritants. Morbidity during pregnancy due to smoking may be independent of and additive to morbidity due to asthma (Schatz et al. 1990). Furthermore, maternal smoking may be associated with increased risk for wheezing and development of asthma in her child (Arshad and Hide 1992; Martinez et al. 1995).

Patient Education

It is recommended that the clinical team members help to ensure that the pregnant woman has access to education about asthma so that she can understand the potential interrelationships between asthma and pregnancy. Controlling asthma during pregnancy is important for the well-being of the fetus. The woman should understand that it is safer to be treated with asthma medications than it is to have asthma symptoms and exacerbations. To prevent maternal and fetal hypoxia, she should be able to recognize and promptly treat signs of worsening asthma. She should have a basic understanding of medical management during pregnancy, including self-monitoring and the correct use of inhalers. The pregnant patient should be given an individualized action plan that is based on a joint agreement between the patient and the clinician about the goals of therapy and treatment. The patient should have prompt access to her clinician for uncontrolled symptoms. The patient should also understand how she can reduce her exposure to or control those factors (“asthma triggers”) that contribute to her asthma’s severity.

Pharmacologic Therapy

It is safer for pregnant women with asthma to be treated with asthma medications than to have asthma symptoms or exacerbations and reduced lung function that may potentially impair oxygenation for the fetus. The type and amount of medication necessary to meet the goals of therapy are dictated by the severity of the patient’s asthma. (See appendix B, figure 1 for classification of asthma severity and recommended treatment at each step.) Medications are categorized in two general classes: (1) long-term-control medications to achieve and maintain control of persistent asthma; especially important is daily medication to suppress the inflammation that is considered an early and persistent component in the pathogenesis of asthma; and (2) quick-relief medications that are taken as needed to treat symptoms and exacerbations. See the following section for recommendations about pharmacologic therapy during pregnancy at each step of asthma severity.

The Stepwise Approach to Gaining and Maintaining Control of Asthma

The stepwise approach to therapy, in which the dose and number of medications and frequency of administration are increased as necessary and decreased when possible, is used to achieve and maintain asthma control. To develop the following recommendations for the stepwise approach to pharmacologic treatment for pregnant women, the Working Group first considered the stepwise approach
in the EPR—Update 2002, which was based on a systematic review of evidence from medication effectiveness studies in nonpregnant adults and children. The Working Group also considered the EPR-2 1997 and the Asthma and Pregnancy Report 1993. The effectiveness of medications is assumed to be the same in pregnant women as in nonpregnant women, although there are no studies that directly test this assumption for inhaled corticosteroids. The Working Group tailored a recommendation for stepwise therapy on the basis of their current systematic review of evidence from safety studies during pregnancy. In the following discussion, the level of evidence from safety studies during pregnancy is indicated parenthetically after the initial recommendation of a specific medication. Refer to appendix B, figures 1 through 3, for a summary of the recommended therapies and medication dosages in the stepwise approach to long-term management of asthma during pregnancy and lactation.

Gaining Control of Asthma

The pregnant patient with asthma poses unique challenges for the clinician. The clinician judges individual patient needs and circumstances to determine at what treatment step to initiate therapy, while focusing on the health and well-being of both the mother and the fetus. Assessment of the patient’s asthma history, current symptoms, and objective measures are all important in making this determination. For example, pregnant women with asthma may have minimal symptoms but still have abnormal pulmonary function tests and potentially impaired oxygenation.

Continual monitoring is useful to ensure that asthma control is achieved. Asthma control is best indicated by patient history (i.e., symptom frequency, amount of medication used) and by repeated pulmonary function measures (PEF or spirometry). If control is not achieved with initial therapy (e.g., within 1 month) or sufficient symptom reduction within 5–7 days of initiating or changing the therapeutic plan, then the plan, patient adherence, and possibly the diagnosis should be reevaluated.

Maintaining Control of Asthma

Maintain the Treatment

Once control is achieved and sustained for several months, a step down to less intensive therapy is encouraged for nonpregnant patients to identify the minimum therapy for maintaining control. A similar step-down approach should be considered for pregnant patients; however, such a step down should be undertaken cautiously and gradually to avoid compromising the stability of the patient’s asthma control. For some patients, it may be prudent to postpone, until after the infant’s birth, attempts at reducing therapy that is effectively controlling the patient’s asthma.

Regular Followup Visits (at 1- to 2-Month Intervals) Are Important

Clinicians need to assess whether control of asthma has been maintained and whether an alteration in the patient’s therapy is appropriate. Clinicians also need to monitor and review the action plan for daily self-management and response to worsening signs of asthma, the medications, and the patient’s self-management behaviors (e.g., inhaler and peak flow monitoring techniques as well as actions for controlling factors that aggravate one’s asthma). More frequent clinician-patient visits will depend on the patient’s response to the prescribed treatment regimen(s) and the time of gestation. Depending on the severity of the underlying maternal asthma, it is reasonable to expect that the patient’s asthma may require closer monitoring and possibly more frequent medication dose adjustment as the pregnancy progresses. Furthermore, the varying stages of gestation...
may introduce additional physiologic changes in the patient that may indicate the need to adjust her medications.

If optimal control of asthma is not achieved and sustained at any step of care (as indicated by nocturnal symptoms, urgent care visits, or an increased need for short-acting beta₂-agonists), several actions may be considered.

- **Review the plans for long-term asthma management and for responding to signs of worsening asthma** to ensure that the clinician and patient are in agreement with the recommended actions. Assess patient adherence, and address those issues that may be affecting it.

- **Assess the patient’s technique in using medications correctly.**

- **Increase anti-inflammatory therapy temporarily if needed to reestablish control.** A deterioration of asthma control may be characterized by gradual reduction in PEF or FEV₁, failure of inhaled beta₂-agonist therapy to produce a sustained response, reduced tolerance to activities, or increasing nocturnal symptoms. To regain control of asthma, a short course of oral prednisone may be warranted.

- **Other factors that diminish control may need to be identified and addressed.** Reassessment of specific asthma triggers or the identification of previously uninvolved triggers should be undertaken. Evaluate possible allergens, environmental pollution or smoking, patient or family barriers to adequate self-management behaviors, psychosocial problems, or newly prescribed or over-the-counter or herbal medications that might influence patient response.

- **A step up to the next higher step of care may be necessary.**

- **Consultation with an asthma specialist may be indicated.**

### Intermittent Asthma

**Step 1: Mild Intermittent Asthma.**

- **A short-acting inhaled beta₂-agonist is used as needed to treat symptoms and is usually sufficient therapy for mild intermittent asthma (Level C evidence from safety studies in pregnancy).** If effective in relieving symptoms and normalizing pulmonary function, intermittent use of short-acting inhaled beta₂-agonist can be continued on an as-needed basis. If significant symptoms recur or short-acting inhaled beta₂-agonist is required for quick-relief treatment more than two times a week (with the exception of using inhaled beta₂-agonist to prevent exercise-induced bronchospasm), the patient should be moved to Step 2 of care.

- **Albuterol is the preferred short-acting, short-duration beta₂-agonist for use during pregnancy (Level C evidence from safety studies in pregnancy).** This drug is very selective for the beta₂-receptor and possesses an excellent safety profile for both pregnant and nonpregnant women with asthma. Although evaluations of drugs during pregnancy are limited, the greatest amount of efficacy and safety data during pregnancy exists with albuterol.

- **Patients with intermittent asthma who experience exercise-induced bronchospasm benefit from using a short-acting inhaled beta₂-agonist shortly before exercise.** During pregnancy, albuterol is also the preferred agent for treating exercise-induced bronchospasm.

### Persistent Asthma

The Working Group recommends that patients with persistent asthma, whether mild, moderate, or severe, receive daily long-term-control medication. The most effective long-term-control medications are the inhaled corticosteroids, which diminish chronic airway inflammation and airway hyper-
responsiveness. Strong evidence from clinical effectiveness trials supports the use of inhaled corticosteroids in nonpregnant adults with asthma. Reassuring efficacy and safety data from prospective cohort studies support using inhaled corticosteroids in pregnant women with asthma (Level C evidence from safety studies in pregnancy).

Quick-relief medication should be available to all patients with persistent asthma. Short-acting inhaled beta₂-agonist (albuterol is preferred for pregnant women) is used as needed to relieve symptoms (Level C evidence from safety studies in pregnancy). The intensity of treatment will depend on the severity of the exacerbation. (See section below on Managing Acute Exacerbations of Asthma During Pregnancy.) Use of short-acting inhaled beta₂-agonist on a daily basis, or increasing use, indicates the need for additional long-term-control therapy.

Step 2: Mild Persistent Asthma.

• The preferred treatment for long-term-control medication in Step 2 is daily low-dose inhaled corticosteroid (Level C evidence from safety studies in pregnancy). Proper technique is essential for the effective use of and optimal response from inhaled corticosteroid therapy. Budesonide is the preferred inhaled corticosteroid, both because more data are available on using budesonide in pregnant women than are available on other inhaled corticosteroids and because the data are reassuring. The Asthma and Pregnancy Report 1993 listed beclomethasone dipropionate as the preferred inhaled corticosteroid because, although there were few published studies on asthma medication in pregnant women, clinical experience with beclomethasone dipropionate during pregnancy was substantial—more so than with other inhaled corticosteroids. The clinical experience for beclomethasone dipropionate remains reassuring. However, published studies are now available on the use of inhaled cortico-

costeroids, and the study data are preponderantly on budesonide. Thus, budesonide is the preferred inhaled corticosteroid for use during pregnancy because there are more data on budesonide, not because budesonide is demonstrably safer than other corticosteroid preparations. It is important to note that no data indicate that the other preparations are unsafe. Therefore, inhaled corticosteroids other than budesonide may be continued in patients who were well-controlled by these agents prior to pregnancy, especially if it is thought that changing formulations may jeopardize asthma control.

• Alternative but not preferred treatment options are presented below in alphabetical order because data are not available to allow rankings of alternative treatments relative to each other. It is important to recognize that none of these alternative treatments, either alone or together, has been demonstrated to be as effective as the therapeutic benefit of inhaled corticosteroids.

- Cromolyn is an alternative but not preferred long-term-control medication (Level C evidence from safety studies in pregnancy) that has been used for decades as a medication for the chronic treatment of asthma and exercise-induced bronchospasm. Although the drug has limited effectiveness compared to inhaled corticosteroids, the advantage of cromolyn is its high degree of tolerance by patients and its exceptional safety profile. The safety data for use of cromolyn during pregnancy are reassuring. The Asthma and Pregnancy Report 1993 recommended initiating daily long-term-control therapy in pregnant women with cromolyn because of its excellent safety profile. Data published since 1993 on the safety and effectiveness of inhaled corticosteroids in nonpregnant patients, combined with recent reassuring safety data on the use of inhaled corticosteroids in pregnant women, warrant removing
the recommendation for cromolyn and supporting the use of inhaled corticosteroid as the preferred Step 2 therapy.

- **Leukotriene receptor antagonists**, including zafirlukast and montelukast, may also be considered as alternative but not preferred long-term-control medication (Level D evidence from safety studies in pregnancy). Although minimal published data exist assessing the safety of leukotriene receptor antagonists in pregnancy, and no published data assess their efficacy during pregnancy, data in animal studies submitted to the FDA suggest the safety of leukotriene receptor antagonists for use during pregnancy. Similar reassurance is not available for the leukotriene synthesis inhibitor zileuton. Leukotriene receptor antagonists have been demonstrated to provide statistically significant but modest improvements when used as monotherapy in both children and nonpregnant adults. When comparing overall efficacy of leukotriene receptor antagonists to that of inhaled corticosteroids, however, most outcome measures clearly favored inhaled corticosteroids. In the opinion of the Working Group, leukotriene receptor antagonists may be considered for use during pregnancy for patients who had a favorable response to the drug before they became pregnant. In this case, it would be preferable to maintain the therapy that successfully controlled the patient’s asthma before pregnancy. However, in the opinion of the Working Group, when initiating new treatment for asthma during pregnancy, leukotriene receptor antagonists are an alternative but not preferred treatment option for mild persistent asthma.

- **Sustained release theophylline** preparations represent another alternative but not preferred treatment option (Levels B and C evidence from safety studies in pregnancy). Theophylline therapy has demonstrated clinical effectiveness in some studies and has been used for years in pregnant women with asthma. Theophylline is primarily a bronchodilator, and its anti-inflammatory activity demonstrated thus far is modest. However, it also has the potential for serious toxicity (nausea, vomiting, tachycardia, tachydysrhythmia, seizures) resulting from excessive dosing and/or select drug–drug interactions (e.g., with erythromycin). Thus, using theophylline during pregnancy requires careful titration of the dose and regular monitoring of serum theophylline concentrations. Timed-release preparations permit easier dosing with less fluctuation in serum theophylline concentrations. The opinion of the Working Group is that theophylline dosing should be selected to maintain serum theophylline concentrations between 5–12 mcg/mL.

Step 3: **Moderate Persistent Asthma.**

- The two preferred treatment options for initiating Step 3 therapy are either a combination of a low-dose inhaled corticosteroid and a long-acting inhaled beta₂-agonist or increasing the dose of inhaled corticosteroid to the medium-dose range. No data from studies during pregnancy clearly delineate that one option is recommended over another. On the one hand, strong evidence from clinical randomized controlled trials in nonpregnant adults favors combination therapy over increasing the dose of inhaled corticosteroid. On the other hand, only limited observational data are available on long-acting inhaled beta₂-agonist during pregnancy. Thus, some clinicians may prefer increasing the dose of inhaled corticosteroid, for which data on use during pregnancy exist, rather than adding a second medication.

Preferred Step 3 treatment is:

**Either:**

- Maintain a low-dose inhaled corticosteroid and add a long-acting inhaled
beta₂-agonist (Level C evidence from safety studies of inhaled corticosteroids in pregnancy; Level C evidence from safety studies of long-acting inhaled beta₂-agonists; Level D evidence from safety studies of combination therapy in pregnancy). Limited data describe the efficacy and/or safety of the use of combination therapies during pregnancy, but strong, Level A evidence from effectiveness studies is found in nonpregnant adults that adding long-acting inhaled beta₂-agonist to a low dose of inhaled corticosteroid provides greater asthma control than only increasing the dose of corticosteroid (EPR—Update 2002). Although only limited observational data are available on long-acting inhaled beta₂-agonists in pregnancy, there is justification for expecting long-acting inhaled beta₂-agonists to have a safety profile similar to that of albuterol, for which data exist on safety during pregnancy. There are no data on which to base selection of a preferred long-acting inhaled beta₂-agonist, but salmeterol has been available longer than others in this class of medications. When using a long-acting inhaled beta₂-agonist, it is important to inform the patient that this medication should not be used for the treatment of acute asthma exacerbations, should only be used in combination with an inhaled corticosteroid, and should be used at no more than the recommended dose.

Or:

• Increase inhaled corticosteroid to medium dose (Level C evidence from safety studies in pregnancy). This strategy will benefit many patients. Adverse effects, although infrequent, may arise. For example, with an increased dose, some patients may experience oral candidiasis or dysphonia, especially if they use improper inhaler technique. Inhaler technique should be reviewed regularly and whenever doses are adjusted.

If the patient’s asthma is not optimally controlled with initial Step 3 therapy, and medications are used correctly, additional therapy is recommended, particularly for patients with recurring severe exacerbations. A combination of a medium-dose inhaled corticosteroid and a long-acting inhaled beta₂-agonist is recommended. Referral of the patient to an asthma specialist is appropriate if there is difficulty achieving control at this step of asthma severity.

• Alternative but not preferred treatments for Step 3 care include low-dose inhaled corticosteroid and the addition of either theophylline or a leukotriene receptor antagonist (Level D evidence on safety of combination therapy in pregnancy). If necessary, increase the inhaled corticosteroid dose to within the medium-dose range. Favorable to the selection of theophylline as adjunctive therapy is the consideration that more extensive clinical experience and observational data are available and are reassuring concerning the use of theophylline during pregnancy. In the opinion of the Working Group, if theophylline is selected, serum concentrations should be maintained between 5–12 mcg/mL.

Step 4: Severe Persistent Asthma.

• Patients whose asthma is not controlled on medium dose inhaled corticosteroid along with the addition of a long-acting inhaled beta₂-agonist may also require oral systemic corticosteroid on a regularly scheduled, long-term basis (Level C evidence from safety studies in pregnancy). It is preferable to avoid the use of systemic corticosteroids if possible. Before additional medication is considered, both the patient’s inhaled corticosteroid, long-acting inhaled beta₂-agonist dose and the patient’s technique for aerosol administration should be critically reevaluated. If additional therapy is required, the inhaled corticosteroid dose should be increased to within the high-dose range and the use of budesonide is preferred. Referral
of the patient to an asthma specialist is recommended for assistance in the care of patients requiring Step 4. If the appropriate use of high-dose inhaled corticosteroid and long-acting inhaled beta2-agonist is insufficient in managing symptoms, the addition of systemic corticosteroid therapy is warranted. Aggressive doses should be employed on a short-term basis, e.g., 2 mg/kg/day to a maximum daily dose of 60 mg of prednisone equivalent. For patients who require long-term systemic corticosteroid:

- Use the lowest possible dose (single dose daily or on alternate days).

- Monitor patients closely for adverse side effects of corticosteroids.

- When control of asthma is achieved, make persistent attempts to reduce the dose of or discontinue systemic corticosteroid. High-dose inhaled corticosteroid is preferable to systemic corticosteroid administration. Depending on the duration of systemic corticosteroid administration, care must be exercised in their withdrawal to avoid disease exacerbation and/or serious hypothalamic-pituitary-adrenal (HPA) crisis.

- Consultation with an asthma specialist is recommended.

**Pharmacologic Management of Allergic Rhinitis**

Rhinitis, sinusitis, or gastroesophageal reflux disease (GERD) are conditions that are often associated with asthma and are frequently more troublesome during pregnancy. These conditions may exacerbate coexisting asthma. If these conditions are present, appropriate treatment is an integral part of asthma management. These topics were outside the scope of the current evidence-based review, but relevant studies on the safety of rhinitis medications during pregnancy were reviewed in order to present the following recommendations. The availability of newer medications for rhinitis and newer data regarding use of rhinitis medications during pregnancy deserve comment for several reasons. Asthma and rhinitis frequently coexist (Bousquet et al. 2001); the courses of gestational rhinitis and gestational asthma are usually concordant (Kircher et al. 2002); and the treatment of rhinitis may improve coexistent asthma (Bousquet et al. 2001). The following summary is based on studies deemed relevant by the Working Group, but the studies and conclusions are not the result of a systematic review of the evidence.

Safety data regarding use of currently available second-generation antihistamines during human gestation are summarized in table 2 (Diav-Citrin et al. 2003; Einarson et al. 1997; Källén 2002; Mørte et al. 2003). No data on human gestation have been published for azelastine or desloratadine, data are minimal for fexofenadine, and experimental animal studies are not reassuring for these medications. Desloratadine is a major metabolite of loratadine. The different results from experimental animal studies on these two drugs may be due to different study designs and conditions. Because it is a derivative of loratadine, desloratadine may replicate the human safety study results of loratadine. However, there are no specific data on desloratadine during pregnancy.

**Pharmacologic Management of Asthma During Lactation**

Prednisone, theophylline, antihistamine, inhaled corticosteroid, beta2-agonist, and cromolyn are not contraindications to breastfeeding (American Academy of Pediatrics Committee on Drugs 1989; Asthma and Pregnancy Report 1993). However, maternal use of theophylline may cause irritability, feeding difficulties, or jitteriness in sensitive nursing infants. Recommendations for managing asthma during lactation are the same as those for managing asthma during pregnancy.
Based on the available data for humans as well as reassuring animal studies, loratadine or cetirizine are the current second-generation antihistamines of choice for use during pregnancy. Data on the excretion of loratadine in breast milk suggest that the amount of loratadine received by the nursing infant would not present a hazard (Hilbert et al. 1988).

Intranasal corticosteroids are the most effective medications for the management of allergic rhinitis (Bousquet et al. 2001) and have a low risk of systemic effect when used at recommended doses (Allen 2000). Although no specific safety studies of intranasal corticosteroids during pregnancy were identified, when need is indicated, their use during pregnancy is recommended, on the basis of reassuring data from studies of the oral inhaled corticosteroids. (See section above on Inhaled Corticosteroids.) Montelukast, a leukotriene receptor antagonist, can be used for the treatment of allergic rhinitis, but minimal data are available on the use of this drug during pregnancy.

Finally, three studies suggest that oral decongestant exposure in the first trimester may increase the risk of a rare birth defect, gastroschisis (Torfs et al. 1996; Werler et al. 1992; Werler et al. 2002), but the absolute risk of gastroschisis in exposed fetuses is still extremely small. If nasal decongestion treatment is indicated in early pregnancy, an external nasal dilator, short-term topical oxymetazoline, or intranasal corticosteroid can be considered before use of oral decongestant.

### Table 2

**Data Regarding the Safety of Currently Available Second-Generation Antihistamines During Pregnancy**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Animal Studies*</th>
<th>Human Studies: Reference</th>
<th>Human Studies: Number of Exposures</th>
<th>Human Studies: Incidence of Major Malformations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Exposed</td>
</tr>
<tr>
<td>Loratadine</td>
<td>Reassuring</td>
<td>Källén 2002</td>
<td>1,769</td>
<td>3.4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Morretti 2003</td>
<td>161</td>
<td>3.1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diav-Citrin 2003</td>
<td>175</td>
<td>2.3%</td>
</tr>
<tr>
<td>Cetirizine</td>
<td>Reassuring</td>
<td>Källén 2002</td>
<td>917</td>
<td>4.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Einarson 1997</td>
<td>33</td>
<td>0.0%</td>
</tr>
<tr>
<td>Fexofenadine</td>
<td>Not reassuring</td>
<td>Källén 2002</td>
<td>16</td>
<td>Not reported</td>
</tr>
<tr>
<td>Desloratadine</td>
<td>Not reassuring</td>
<td></td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Azelastine</td>
<td>Not reassuring</td>
<td></td>
<td></td>
<td>—</td>
</tr>
</tbody>
</table>

* Reported to the FDA by the manufacturer.

a 403,545 total infants born in the Swedish general population concurrently followed.

b 161 unexposed controls concurrently followed.

* 844 nonteratogenic controls concurrently followed.

Management of Acute Exacerbations of Asthma During Pregnancy

Recommendations for managing acute exacerbation of asthma during pregnancy are presented in this section. The recommendations are based on Working Group review and adaptation of the 1993 Asthma and Pregnancy Report and the EPR-2 (1997).

Home Management of Asthma Exacerbations

Asthma exacerbations have the potential to lead to severe problems for the fetus (Gelber et al. 1984; Gordon et al. 1970; Warrell and Taylor 1968). A maternal pO₂ <60 mmHg or hemoglobin saturation <90 percent may be associated with fetal hypoxia. Therefore, asthma exacerbations in pregnancy should be managed aggressively.

Pregnant women with asthma should be taught to recognize signs and symptoms of early asthma exacerbations, such as coughing, chest tightness, dyspnea, wheezing, or a 20 percent decrease in their PEF rate. A decrease in fetal movement may be an early manifestation of an asthma exacerbation. Early recognition of worsening asthma is important so that prompt home rescue treatment may be instituted to avoid maternal and fetal hypoxia. Patients should be given an individualized guide for decisionmaking and rescue management. In general, home treatment begins with inhaled albuterol (2–4 puffs every 20 minutes for up to 1 hour). A good response is characterized by symptoms that are resolved or become subjectively mild, the ability to resume normal activities, and PEF rate >80 percent of personal best. The patient should seek further medical attention promptly if the response is incomplete or if fetal activity is decreased. (See appendix B, figure 4.)

Hospital and Clinic Management

Recommendations for assessment and treatment of exacerbations in the hospital and clinic setting are presented in appendix B, figure 5, and usual drug dosages for asthma exacerbations are presented in figure 6. The prevention of maternal and fetal hypoxia is the principal goal. Continuous electronic fetal monitoring should be considered when the fetus is potentially viable. Albuterol delivered by nebulizer (2.5 mg = 0.5 mL albuterol in 2.5 mL normal saline driven with oxygen) is recommended; treatments should be given every 20 minutes in the first hour (EPR-2 1997). Oral systemic corticosteroids should be given to patients with FEV₁ or PEF above 50 percent predicted if there is no immediate response to albuterol or if the patient recently took oral corticosteroids; corticosteroids should be given orally for patients with lower FEV₁ or PEF and intravenously for those with impending respiratory arrest. In addition to albuterol, oxygen to achieve oxygen saturation ≥95 percent is recommended for all patients.

Ipratropium bromide, an anticholinergic, is recommended as additional therapy in severe exacerbations (EPR-2 1997; Rodrigo and Rodrigo 2002). No published data on anticholinergics in pregnancy were available for the current evidence review. However, studies show minimal absorption of quaternary amines from the lung (Pakes et al. 1980). Considering the inhalation route of administration and reassuring experimental animal studies submitted to the FDA, ipratropium bromide can be recommended for use during pregnancy.

In the opinion of the Working Group, the patient should be assessed for pulse rate, use of accessory muscles, wheezing, and FEV₁ and/or PEF rate before and after each bronchodilator treatment. Measurement of oxygenation via pulse oximeter or arterial blood gases is essential. Arterial blood gas measurements should be obtained if the patient is in severe distress. Chest x-rays should not be routinely obtained. Repeat assessment of patients with severe exacerbations is recommended after the initial dose of inhaled beta₂-
agonist, and repeat assessments of all patients are recommended after three doses (60–90 minutes after initiating the treatment). Inhaled corticosteroid should be continued if the patient was already taking inhaled corticosteroid, or an inhaled corticosteroid should be initiated at discharge from the emergency department or hospital (e.g., as part of discharge planning during hospitalization). The rationale for introducing an inhaled corticosteroid is that this treatment reduces recurrent exacerbations in pregnant women with asthma (Wendel et al. 1996).

Management of Asthma During Labor and Delivery

Asthma medications should be continued during labor and delivery. Although asthma is usually quiescent during labor, consideration should be given to assessing PEF rates on admission and at intervals during labor. If systemic corticosteroid has been used in the previous 4 weeks, then stress-dose steroid (e.g., hydrocortisone 100 mg q 8 hours, iv) should be administered during labor and for the 24-hour period after delivery to prevent maternal adrenal crisis (Asthma and Pregnancy Report 1993).

Rarely, if ever, is it necessary to deliver a fetus via cesarean due to an acute exacerbation of asthma. Usually, maternal and fetal hypoxia can be managed by optimal medical management. Occasionally, delivery may improve the respiratory status of a patient who has unstable asthma and is near term. Prostaglandin (PG) E₂ or E₁ can be used for cervical ripening, the management of spontaneous or induced abortions, or postpartum hemorrhage. However, 15-methyl PGF₂α and methylergonovine can cause bronchospasm. Magnesium sulfate, which is a bronchodilator, and beta-adrenergic agents such as terbutaline can be used to treat preterm labor. Indomethacin, however, can induce bronchospasm in the aspirin-sensitive patient. No reports were found of the use of calcium channel blockers for tocolysis among patients with asthma.

Epidural analgesia has the benefit of reducing oxygen consumption and minute ventilation during labor (Hagerdal et al. 1983). Meperidine causes histamine release but rarely causes bronchospasm during labor. A 2 percent incidence of bronchospasm has been reported with regional anesthesia (Fung 1985). Communication between the obstetric, anesthetic, and pediatric caregivers is recommended.

REFERENCES


Appendix A: Review of Selected Experimental Animal Studies From the Current Systematic Review of the Evidence

**Beta-Agonists**

A study by Alexander et al. (1997) described a snout-only exposure technique for rabbit teratology studies. The test agent was salbutamol. The study used four pregnant animals per dose group (much smaller than the conventional study group size) and did not describe methods of fetal evaluation. The results stated that fetal weight and development were not affected by treatment, but no data were shown. This study is not adequate for assessing possible developmental effects of salbutamol.

**Theophylline**

Using a standard protocol, the National Toxicology Program evaluated theophylline in commonly used strains of rats and mice (Lindström et al. 1990). Rats were exposed to theophylline in their feed, and mice were exposed to theophylline in their drinking water. Treatment began on gestation day 6, which is just after the expected day of implantation, and continued through gestation day 15, which encompasses the so-called organogenesis period. Rats were exposed to estimated theophylline doses of 0, 124, 218, or 259 mg/kg/day, and mice were exposed to estimated theophylline doses of 0, 282, 372, or 396 mg/kg/day. In rats, maternal feed consumption and weight gain decreased at the highest dose of theophylline, and water consumption increased at all doses of theophylline. The number of live fetuses per litter decreased at the highest theophylline dose, and fetal weight decreased at the top two theophylline doses. In mice, maternal water consumption and weight gain decreased at the top two doses. At the top two doses, resorptions (analogous to miscarriage) increased and fetal weight decreased. It is not possible to say whether the theophylline treatment had a direct effect on embryo development or whether the adverse effects on the offspring were due to maternal food or water deprivation (both of these conditions can adversely affect development on their own). No increase in malformation occurred at any dose in either rats or mice. There were no adverse effects in either dams or offspring at 10 times the human dose (on a weight basis) in rats or at 20–25 times the human dose (on a weight basis) in mice. On the basis of this study, exposure to therapeutic doses of theophylline during human pregnancy would not be expected to increase the risk of abnormal development.

A short-term test using theophylline, among other chemicals, was published by Harris et al. (1992). This design involved treating mice for 1 week before pregnancy and during the first 2 weeks of pregnancy. Endpoints evaluated included number of implantation sites, live offspring, weight of the live offspring, survival of offspring to postnatal day 4, and external malformations. Theophylline at up to 200 mg/kg/day by mouth did not increase the incidence of adverse outcome. This result is consistent with Lindström et al. (1990) in not showing adverse developmental effects of theophylline in this dose range.

A continuous breeding study from the National Toxicology Program was published in summary form (Lamb et al. 1997). Male and female mice were given theophylline in their diet during continuous housing as mating pairs. The number of pups per litter and pup weight were decreased at all exposure levels, the lowest of which was 0.075 percent weight per volume in food. The report did
not give the amount of theophylline represented by this dietary concentration, but assuming a pregnant mouse eats 200 g/kg/day, the lowest dose in this study would be 150 mg/kg/day. No adverse effects occurred in a second generation exposed to the same levels of theophylline. These effects were averaged over the total number of litters produced during the study (this report does not state the number, but it is usually about five and may represent cumulative effects of prolonged exposure to high doses of theophylline). Exposure to clinical doses would not be expected to produce these effects; however, because all doses used in this study were active (i.e., produced toxicity), a “no effect” dose cannot be determined.

A study (Shibata et al. 2000) using intravenous theophylline in pregnant rabbits reported an increase in cleft palate and supernumerary ribs (a common variation in rabbits) at 60 mg/kg/day but not at 30 mg/kg/day. Feed intake and maternal weight gain were reduced at the 60 mg/kg/day dose as well, raising the possibility that maternal stress was a cause of or contributor to the adverse developmental outcomes. The peak plasma concentrations of theophylline in the groups receiving 60 and 30 mg/kg/day were, respectively, 105 and 57 mcg/mL. The top dose produced peak plasma concentrations in rabbits that were about 9–10 times the therapeutic concentration in humans, thus suggesting that therapeutic concentrations of theophylline in humans would not be associated with adverse developmental effects.

Two reports by Hart and Grimble (1990a, b), which may represent the same experiments, did not identify adverse effects of theophylline in drinking water at 1 mg/kg/day in lactating rats. Milk production and offspring weight gain were the endpoints of interest. The use of a single, low dose of theophylline makes this study of little value, however, in assessing the potential lactational toxicity of theophylline.

Corticosteroids

Four papers from the same laboratory used hydrocortisone and dioxin (2,3,7,8-TCDD; an environmental pollutant) to investigate mechanisms of cleft palate production in rodents (Abbott et al. 1992a, b; Abbott et al. 1994; Abbott et al. 1999). These studies made use of the known activity of hydrocortisone in production of cleft palate in rodents and used this agent to explore mechanisms not related to human risk assessment.

Another paper (Watanabe et al. 1995) on palate defects in the offspring of corticosteroid-treated rats compared the relative potencies of prednisolone, triamcinolone acetonide, and hydrocortisone given subcutaneously on gestation days 14–15 (the time of palate closure in the rat). The dose of prednisolone and triamcinolone acetonide producing a 50 percent incidence of palate defect was estimated from a probit model at 70 and 1 mg/kg/day, respectively, demonstrating much greater potency of triamcinolone in the production of this abnormality. Hydrocortisone was given at only one dose (100 mg/kg/day) and did not produce palate defects at this dose. Fetal weight reduction was seen at all doses of all corticosteroids, beginning at 12.5 mg/kg/day for prednisolone and 0.25 mg/kg/day for triamcinolone acetonide. This study is limited by the analysis of adverse outcome on a per fetus rather than a per litter basis. The results are consistent, however, with previous studies that suggest an increase in cleft palate risk and a decrease in fetal growth associated with sufficient exposure to corticosteroids in a number of experimental animal models. The dose of these agents at which growth retardation in human pregnancy might be seen cannot be estimated from this study. In addition, the route of administration (single subcutaneous administration) cannot be assumed to model the clinical use of inhaled corticosteroids.

A decrease in fetal growth was also shown in pregnant sheep given betamethasone (0.5 mg/kg) as a single dose or as three doses
evenly spaced over 2 weeks (Jobe et al. 1998). A dose-related decrease in fetal body weight occurred in animals delivered at term (145 days) and preterm (125 days). The average size of the weight decrement in term lambs was 14 and 19 percent after one and three doses, respectively. In preterm lambs, the weight decrements were 11 and 25 percent after one and three doses, respectively. This study used both a species that is similar to humans during late pregnancy and a medication dose that is reasonably close to human clinical doses, thus increasing the likelihood that the reduction in fetal weight will also be observed in human fetuses exposed to maternal corticosteroid therapy in sufficient doses.

Another study in pregnant sheep evaluated the possible effects of antenatal corticosteroid exposure on the programming of cardiovascular function in later life (Dodic et al. 1998). Pregnant sheep were transported from a farm to a research institute and given intravenous dexamethasone, 0.28 mg/kg/day as a 48-hour infusion; then they were transported back to the farm. One group of animals underwent the treatment at the end of the first month of gestation; a second group of animals underwent the treatment at the end of the second month of gestation. A control group had neither dexamethasone exposure nor transport to and from the institute. Female offspring were oophorectomized (to remove estrous cycle effects) and then evaluated at 3 time points over the first 19 months of age. Animals that had been exposed at the end of the first month of pregnancy showed an increase of 6–8 mmHg in mean arterial blood pressure compared to the control animals. Mean arterial blood pressure did not increase in the group exposed at the end of the second month of pregnancy. No difference was found among the groups in the blood pressure response to infused pressors or to adrenocorticotropic hormone (ACTH). The clinical significance of these results is not clear, except to suggest that cardiovascular programming can occur during early pregnancy.

Rhesus monkeys exposed during the third trimester of pregnancy to dexamethasone (5 mg/kg/day but not 0.5 mg/kg/day) were reported to have a decrease in number and differentiation of hippocampal and cortical neurons (Uno et al. 1994). This study is difficult to interpret because of the lack of presentation of quantitative methods and the very high dose of dexamethasone that was shown to be active.

REFERENCES


Abbott BD, Harris MW, Birnbaum LS. Comparisons of the effects of TCDD and hydrocortisone on growth factor expression provide insight into their interaction in the embryonic mouse palate. Teratology 1992b;45(1):35–53.


## Appendix B: Figures

### Figure 1: Stepwise Approach for Managing Asthma During Pregnancy and Lactation: Treatment

<table>
<thead>
<tr>
<th>Classify Severity: Clinical Features Before Treatment or Adequate Control</th>
<th>Medications Required To Maintain Long-Term Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Daily Medications</td>
</tr>
<tr>
<td><strong>Step 1</strong></td>
<td><strong>Mild Intermittent</strong></td>
</tr>
<tr>
<td>≤2 days/week</td>
<td>≥80%</td>
</tr>
<tr>
<td>≤2 nights/month</td>
<td>20–30%</td>
</tr>
<tr>
<td></td>
<td>• No daily medication needed.</td>
</tr>
<tr>
<td></td>
<td>• Severe exacerbations may occur, separated by long periods of normal lung function and no symptoms. A course of systemic corticosteroid is recommended.</td>
</tr>
<tr>
<td><strong>Quick Relief</strong></td>
<td><strong>All Patients</strong></td>
</tr>
<tr>
<td></td>
<td>• Short-acting bronchodilator: 2–4 puffs of <strong>short-acting inhaled beta₂-agonist</strong> as needed for symptoms.</td>
</tr>
<tr>
<td></td>
<td>• Intensity of treatment will depend on severity of exacerbation; up to 3 treatments at 20-minute intervals or a single nebulizer treatment as needed. Course of systemic corticosteroid may be needed.</td>
</tr>
<tr>
<td></td>
<td>• Use of short-acting inhaled beta₂-agonist &gt;2 times a week in intermittent asthma (daily, or increasing use in persistent asthma) may indicate the need to initiate (increase) long-term-control therapy.</td>
</tr>
</tbody>
</table>

### Goals of Therapy: Asthma Control

- Minimal or no chronic symptoms day or night
- Minimal or no exacerbations
- No limitations on activities; no school/work missed
- Maintain (near) normal pulmonary function
- Minimal use of short-acting inhaled beta₂-agonist
- Minimal or no adverse effects from medications

### Notes

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- Classify severity: assign patient to most severe step in which any feature occurs (PEF is percent of personal best; FEV₁ is percent predicted).
- Gain control as quickly as possible (consider a short course of systemic corticosteroid), then step down to the least medication necessary to maintain control.
- Minimize use of short-acting inhaled beta₂-agonist (e.g., use of approximately one canister a month even if not using it every day indicates inadequate control of asthma and the need to initiate or intensify long-term-control therapy).
- Provide education on self-management and controlling environmental factors that make asthma worse (e.g., allergens, irritants).
- Refer to an asthma specialist if there are difficulties controlling asthma or if Step 4 care is required. Referral may be considered if Step 3 care is required.

* There are more data on using budesonide during pregnancy than on using other inhaled corticosteroids.
† There are minimal data on using leukotriene receptor antagonists in humans during pregnancy, although there are reassuring animal data submitted to FDA.
‡ There are more data on using albuterol during pregnancy than on using other short-acting inhaled beta₂-agonists.
Table 2: Usual Dosages for Long-Term-Control Medications During Pregnancy and Lactation*

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage Form</th>
<th>Adult Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inhaled Corticosteroids</strong> (See Estimated Comparative Daily Dosages for Inhaled Corticosteroids [Figure 3].)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>2, 4, 8, 16, 32 mg tablets</td>
<td>• 7.5–60 mg daily in a single dose in a.m. or qod as needed for control</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>5 mg tablets, 5 mg/5 cc, 15 mg/5 cc</td>
<td>• Short-course “burst” to achieve control: 40–60 mg per day as single dose or 2 divided doses for 3–10 days</td>
</tr>
<tr>
<td>Prednisone</td>
<td>1, 2.5, 5, 10, 20, 50 mg tablets, 5 mg/cc, 5 mg/5 cc</td>
<td></td>
</tr>
<tr>
<td><strong>Long-Acting Inhaled Beta2-Agonists (Should not be used for symptom relief or for exacerbations. Use with inhaled corticosteroids.)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salmeterol</td>
<td>MDI 21 mcg/puff, DPI 50 mcg/blister, DPI 12 mcg/single-use capsule</td>
<td>2 puffs q 12 hours, 1 blister q 12 hours, 1 capsule q 12 hours</td>
</tr>
<tr>
<td>Formoterol</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Combined Medication</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluticasone/Salmeterol</td>
<td>DPI 100, 250, or 500 mcg mcg</td>
<td>1 inhalation bid; dose depends on severity of asthma</td>
</tr>
<tr>
<td><strong>Cromolyn</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cromolyn</td>
<td>MDI 1 mg/puff, Nebulizer 20 mcg/ampule</td>
<td>2–4 puffs tid-qid, 1 ampule tid-qid</td>
</tr>
<tr>
<td><strong>Leukotriene Receptor Antagonists</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Montelukast</td>
<td>10 mg tablet</td>
<td>10 mg qhs</td>
</tr>
<tr>
<td>Zafirlukast</td>
<td>10 or 20 mg tablet</td>
<td>40 mg daily (20 mg tablet bid)</td>
</tr>
<tr>
<td><strong>Methylxanthines (Serum monitoring is important [serum concentration of 5–12 mcg/mL at steady state].)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Theophylline</td>
<td>Liquids, sustained-release tablets, and capsules</td>
<td>Starting dose 10 mg/kg/day up to 300 mg max; usual max 800 mg/day</td>
</tr>
</tbody>
</table>

DPI, dry powder inhaler; MDI, metered-dose inhaler.
*Adapted from EPR—Update 2002.
**Notes:** • The most important determinant of appropriate dosing is the clinician’s judgment of the patient’s response to therapy.
• Some doses may be outside package labeling, especially in the high-dose range.

Figure 3: Estimated Comparative Daily Dosages for Inhaled Corticosteroids*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adult Low Daily Dose</th>
<th>Adult Medium Daily Dose</th>
<th>Adult High Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone CFC</td>
<td>168–504 mcg</td>
<td>504–840 mcg</td>
<td>&gt;840 mcg</td>
</tr>
<tr>
<td>Beclomethasone HFA</td>
<td>80–240 mcg</td>
<td>240–480 mcg</td>
<td>&gt;480 mcg</td>
</tr>
<tr>
<td>Budesonide DPI</td>
<td>200 mcg/inhalation</td>
<td>600–1,200 mcg</td>
<td>&gt;1,200 mcg</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>500–1,000 mcg</td>
<td>1,000–2,000 mcg</td>
<td>&gt;2,000 mcg</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>88–264 mcg</td>
<td>264–660 mcg</td>
<td>&gt;660 mcg</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>400–1,000 mcg</td>
<td>1,000–2,000 mcg</td>
<td>&gt;2,000 mcg</td>
</tr>
</tbody>
</table>

DPI, dry powder inhaler; MDI, metered-dose inhaler.
*Adapted from EPR—Update 2002.
Management of Asthma Exacerbations During Pregnancy and Lactation: Home Treatment

Assess Severity

Measure PEF: Value <50% personal best or predicted suggests severe exacerbation

Note signs and symptoms: Degrees of cough, breathlessness, wheeze, and chest tightness correlate imperfectly with severity of exacerbation

Accessory muscle use and suprasternal retractions suggest severe exacerbation

Note presence of fetal activity*

Initial Treatment

Short-acting inhaled beta2-agonist: up to 3 treatments of 2–4 puffs by MDI at 20-minute intervals or single nebulizer treatment

Good Response

Mild Exacerbation
PEF >80% predicted or personal best. No wheezing or shortness of breath. Response to short-acting inhaled beta2-agonist sustained for 4 hours. Appropriate fetal activity.*

Treatment:
• May continue short-acting inhaled beta2-agonist every 3–4 hours for 24–48 hours.
• For patients on inhaled corticosteroid, double dose for 7–10 days.

Contact clinician for followup instructions.

Incomplete Response

Moderate Exacerbation
PEF 50%–80% predicted or personal best.
Persistent wheezing and shortness of breath.

Decreased fetal activity.*

Treatment:
• Add oral corticosteroid.
• Continue short-acting inhaled beta2-agonist.

Contact clinician urgently (this day) for instructions.

Poor Response

Severe Exacerbation
PEF <50% predicted or personal best. Marked wheezing and shortness of breath. Decreased fetal activity.*

Treatment:
• Add oral corticosteroid.
• Repeat short-acting inhaled beta2-agonist immediately.
• If distress is severe and nonresponsive, call your clinician immediately and proceed to emergency department; consider calling ambulance or 911.

Proceed to emergency department.

MDI, metered-dose inhaler; PEF, peak expiratory flow.
*Fetal activity is monitored by observing whether fetal kick counts decrease over time.
Management of Asthma Exacerbations During Pregnancy and Lactation: Emergency Department and Hospital-Based Care

**Initial Assessment**
- History, physical examination (auscultation, use of accessory muscles, heart rate, respiratory rate), PEF or FEV₁, oxygen saturation, and other tests as indicated
- Initiate fetal assessment (consider continuous electronic fetal monitoring and/or biophysical profile if pregnancy has reached fetal viability)

**FEV₁ or PEF >50%**
- Short-acting inhaled β₂-agonist by MDI or nebulizer, up to three doses in first hour
- Oxygen to achieve O₂ saturation ≥95%
- Oral systemic corticosteroid if no immediate response or if patient recently took oral systemic corticosteroid

**FEV₁ or PEF <50% (Severe Exacerbation)**
- High-dose short-acting inhaled β₂-agonist by nebulization every 20 minutes or continuously for 1 hour plus inhaled ipratropium bromide
- Oxygen to achieve O₂ saturation >95%
- Oral systemic corticosteroid

**Impending or Actual Respiratory Arrest**
- Intubation and mechanical ventilation with 100% O₂
- Nebulized short-acting inhaled β₂-agonist plus inhaled ipratropium bromide
- Intravenous corticosteroid

**Moderate Exacerbation**
- FEV₁ or PEF 50%–80% predicted/personal best
  - Physical exam: moderate symptoms
  - Short-acting inhaled β₂-agonist every 60 minutes
  - Systemic corticosteroid
  - Oxygen to maintain O₂ saturation >95%
  - Continue treatment 1–3 hours, provided there is improvement

**Severe Exacerbation**
- FEV₁ or PEF <50% predicted/personal best
  - Physical exam: severe symptoms at rest, accessory muscle use, chest retraction
  - History: high-risk patient
  - No improvement after initial treatment
  - Short-acting inhaled β₂-agonist hourly or continuously plus inhaled ipratropium bromide
  - Oxygen
  - Systemic corticosteroid

**Repeat Assessment**
- Symptoms, physical examination, PEF, O₂ saturation, other tests as needed
- Continue fetal assessment

**Admit to Hospital Intensive Care (see box below)**

**Good Response**
- FEV₁ or PEF ≥70%
- Response sustained 60 minutes after last treatment
- No distress
- Physical exam: normal
- Reassuring fetal status

**Incomplete Response**
- FEV₁ or PEF <50% but >70%
- Mild or moderate symptoms
- Continue fetal assessment

**Poor Response**
- FEV₁ or PEF <50%
- PCO₂ >42 mmHg
- Physical exam: symptoms severe, drowsiness, confusion
- Continue fetal assessment

**Individualized Decision re: Hospitalization**

**Discharge Home**
- Continue treatment with short-acting inhaled β₂-agonist
- Continue course of oral systemic corticosteroid
- Initiate or continue inhaled corticosteroid until review at medical followup
- Patient education:
  - Review medicine use
  - Review/initiate action plan
  - Recommend close medical followup

**Admit to Hospital Ward**
- Short-acting inhaled β₂-agonist plus inhaled ipratropium bromide
- Systemic (oral or intravenous) corticosteroid
- Oxygen
- Monitor FEV₁ or PEF, O₂ saturation, pulse
- Continue fetal assessment until patient stabilized

**Admit to Hospital Intensive Care**
- Short-acting inhaled β₂-agonist hourly or continuously plus inhaled ipratropium bromide
- Intravenous corticosteroid
- Oxygen
- Possible intubation and mechanical ventilation
- Continue fetal assessment until patient stabilized

**Improve**
- Continue treatment with short-acting inhaled β₂-agonist
- Continue course of oral systemic corticosteroid
- Initiate or continue inhaled corticosteroid until review at medical followup
- Patient education:
  - Review medicine use
  - Review/initiate action plan
  - Recommend close medical followup

**Discharge Home**

FEV₁, forced expiratory volume in 1 second; MDI, metered-dose inhaler; PCO₂, carbon dioxide partial pressure; PEF, peak expiratory flow.

*Adapted from EPR-2 1997.
### Medications and Dosages for Asthma Exacerbations During Pregnancy and Lactation*

#### Short-Acting Inhaled Beta₂-Agonists

<table>
<thead>
<tr>
<th>Medications</th>
<th>Adult Dose</th>
<th>Child Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albuterol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nebulizer solution</td>
<td>2.5–5 mg every 20 minutes for 3 doses, then 2.5–10 mg every 1–4 hours as needed, or 10–15 mg/hour continuously</td>
<td>0.15 mg/kg (minimum dose 2.5 mg) every 20 minutes for 3 doses, then 0.15–0.3 mg/kg up to 10 mg every 1–4 hours as needed, or 0.5 mg/kg/hour by continuous nebulization</td>
<td>Only selective beta₂-agonists are recommended. For optimal delivery, dilute aerosols to minimum of 3 mL at gas flow of 6–8 L/min. As effective as nebulized therapy if patient is able to coordinate.</td>
</tr>
<tr>
<td>MDI (90 mcg/puff)</td>
<td>4–8 puffs every 20 minutes up to 4 hours, then every 1–4 hours as needed</td>
<td>4–8 puffs every 20 minutes for 3 doses, then every 1–4 hours inhalation maneuver; use spacer/holding chamber</td>
<td></td>
</tr>
<tr>
<td>Bitolterol</td>
<td>See albuterol dose.</td>
<td>See albuterol dose.</td>
<td>H as not been studied in severe asthma exacerbations. Do not mix with other drugs.</td>
</tr>
<tr>
<td>Nebulizer solution (2 mg/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDI (370 mcg/puff)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levalbuterol (R-albuterol)</td>
<td>1.25–2.5 mg every 20 minutes for 3 doses, then 1.25–5 mg every 1–4 hours as needed, or 5–7.5 mg/hour continuously</td>
<td>0.075 mg/kg (minimum dose 1.25 mg) every 20 minutes for 3 doses, then 0.075–0.15 mg/kg up to 5 mg every 1–4 hours as needed, or 0.25 mg/kg/hour by continuous nebulization</td>
<td>0.63 mg of levalbuterol is equivalent to 1.25 mg of racemic albuterol for both efficacy and side effects.</td>
</tr>
<tr>
<td>MDI (0.63 mg/mL, 1.25 mg/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pirbuterol</td>
<td>See albuterol dose.</td>
<td>See albuterol dose; thought to be half as potent as albuterol on a mg basis.</td>
<td>H as not been studied in severe asthma exacerbations.</td>
</tr>
<tr>
<td>MDI (200 mcg/puff)</td>
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<td></td>
<td></td>
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</tbody>
</table>

#### Systemic (Injected) Beta₂-Agonists

<table>
<thead>
<tr>
<th>Medications</th>
<th>Adult Dose</th>
<th>Child Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>0.3–0.5 mg every 20 minutes for 3 doses sq</td>
<td>0.01 mg/kg up to 0.3–0.5 mg every 20 minutes for 3 doses sq</td>
<td>No proven advantage of systemic therapy over aerosol.</td>
</tr>
<tr>
<td>Terbutaline</td>
<td>0.25 mg every 20 minutes for 3 doses sq</td>
<td>0.01 mg/kg every 20 minutes for 3 doses, then every 2–6 hours as needed sq</td>
<td>No proven advantage of systemic therapy over aerosol.</td>
</tr>
</tbody>
</table>

#### Anticholinergics

<table>
<thead>
<tr>
<th>Medications</th>
<th>Adult Dose</th>
<th>Child Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipratropium bromide</td>
<td>0.5 mg every 30 minutes for 3 doses, then every 2–4 hours as needed</td>
<td>0.25 mg every 20 minutes for 3 doses, then every 2 to 4 hours</td>
<td>May mix in same nebulizer with albuterol. Should not be used as first-line therapy; should be added to beta₂-agonist therapy. Dose delivered from M DI is low and has not been studied in asthma exacerbations.</td>
</tr>
<tr>
<td>Nebulizer solution (0.25 mg/mL)</td>
<td>4–8 puffs as needed</td>
<td>4–8 puffs as needed</td>
<td></td>
</tr>
<tr>
<td>M DI (18 mcg/puff)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipratropium with albuterol</td>
<td>3 mL every 30 minutes for 3 doses, then every 2–4 hours as needed</td>
<td>1.5 mL every 20 minutes for 3 doses, then every 2–4 hours</td>
<td>Contains EDTA to prevent discoloration. This additive does not induce bronchospasm.</td>
</tr>
<tr>
<td>Nebulizer solution (Each 3 mL vial contains 0.5 mg ipratropium bromide and 2.5 mg albuterol)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M DI (Each puff contains 18 mcg ipratropium bromide and 90 mcg albuterol)</td>
<td>4–8 puffs as needed</td>
<td>4–8 puffs as needed</td>
<td></td>
</tr>
</tbody>
</table>

#### Systemic Corticosteroids

<table>
<thead>
<tr>
<th>Medications</th>
<th>Adult Dose</th>
<th>Child Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone</td>
<td>120–180 mg/day in 3 or 4 divided doses for 48 hours, then 60–80 mg/day until PEF reaches 70% of predicted or personal best</td>
<td>1 mg/kg every 6 hours for 48 hours, then 1–2 mg/kg/day (maximum = 60 mg/day) in 2 divided doses until PEF is 70% of predicted or personal best</td>
<td>For outpatient “burst” use 40–60 mg in single or 2 divided doses for adults (children: 1–2 mg/kg/day, maximum 60 mg/day) for 3–10 days.</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisolone</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Adapted from EPR—Update 2002.

Notes:
- The most important determinant of appropriate dosing is the clinician’s judgment of the patient’s response to therapy.
- No advantage has been found for higher dose corticosteroids in severe asthma exacerbations, nor is there any advantage for intravenous administration over oral therapy.
- The most important determinant of appropriate dosing is the clinician’s judgment of the patient’s response to therapy.
- An emergency department visit may last from 3 to 10 days. If patients are then started on inhaled corticosteroids, studies indicate there is no need to taper the systemic corticosteroid dose. If the followup systemic corticosteroid therapy is to be given once daily, one study indicates that it may be more clinically effective to give the dose in the afternoon at 3 p.m., with no increase in adrenal suppression (Beam et al. 1992).

Appendix B: Figures
Summary of Control Measures for Environmental Factors That Can Make Asthma Worse

**Allergens:**
Reduce or eliminate exposure to the allergen(s) the patient is sensitive to, including:

- **Animal dander:** Remove animal from house, or, at a minimum, keep animal out of patient’s bedroom and seal or cover with a filter the air ducts that lead to the bedroom.

- **House-dust mites:**
  - Essential: Encase mattress in an allergen-impermeable cover; encase pillow in an allergen-impermeable cover or wash it weekly; wash sheets and blankets on the patient’s bed in hot water weekly (water temperature of >130°F is necessary for killing mites).
  - Desirable: Reduce indoor humidity to less than 50 percent; remove carpets from the bedroom; avoid sleeping or lying on upholstered furniture; remove carpets that are laid on concrete.

- **Cockroaches:** Use poison bait or traps to control. Do not leave food or garbage exposed.

- **Pollen** (from trees, grass, or weeds) and outdoor molds: To avoid exposure, adults should stay indoors—especially during the afternoon—with the windows closed during the season in which they have problems with outdoor allergens.

- **Indoor mold:** Fix all leaks and eliminate water sources associated with mold growth; clean moldy surfaces. Consider reducing indoor humidity to less than 50 percent.

**Tobacco Smoke:**
Advising patients and others in the home who smoke to stop smoking or to smoke outside the home. Discuss ways to reduce exposure to other sources of tobacco smoke, such as from daycare providers and the workplace.

**Indoor/Outdoor Pollutants and Irritants:**
Discuss ways to reduce exposures to the following:

- Wood-burning stoves or fireplaces
- Unvented stoves or heaters
- Other irritants (e.g., perfumes, cleaning agents, sprays)

*Adapted from EPR-2 1997.

**References**


Appendix C: Acronyms and Abbreviations

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH</td>
<td>Adrenocorticotropic hormone</td>
</tr>
<tr>
<td>DPI</td>
<td>Dry powder inhaler</td>
</tr>
<tr>
<td>ELISA</td>
<td>Enzyme-linked immunosorbent assay</td>
</tr>
<tr>
<td>EPR</td>
<td>Expert Panel Report</td>
</tr>
<tr>
<td>FDA</td>
<td>U.S. Food and Drug Administration</td>
</tr>
<tr>
<td>FEV₁</td>
<td>Forced expiratory volume in 1 second</td>
</tr>
<tr>
<td>HFA</td>
<td>Hydrofluoroalkane</td>
</tr>
<tr>
<td>HPA</td>
<td>Hypothalamic-pituitary-adrenal</td>
</tr>
<tr>
<td>IUGR</td>
<td>Intrauterine growth rate</td>
</tr>
<tr>
<td>MDI</td>
<td>Metered-dose inhaler</td>
</tr>
<tr>
<td>MeSH</td>
<td>Medical subject heading</td>
</tr>
<tr>
<td>NAEPP</td>
<td>National Asthma Education and Prevention Program</td>
</tr>
<tr>
<td>NHLBI</td>
<td>National Heart, Lung, and Blood Institute</td>
</tr>
<tr>
<td>PEF</td>
<td>Peak expiratory flow</td>
</tr>
<tr>
<td>RAST</td>
<td>Radioallergosorbent test</td>
</tr>
</tbody>
</table>
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