

PREGNANCY AND ATOPIC DISEASES

Dominick A. Minotti, MD, MPH

Atopic diseases affect between 15% and 20% of the normal population, and this proportion holds true for women of child-bearing age as well. Asthma, one of the most common of the respiratory diseases encountered during pregnancy, affects about 4% of pregnant women.⁷ This article details the normal physiologic changes that occur with pregnancy and discusses the concerns regarding the use of medications in pregnancy. It reviews the effects of pregnancy on asthma and the effects of asthma on pregnancy. Guidelines for the treatment of asthma and other allergic diseases are presented.

PHYSIOLOGIC CHANGES OF PREGNANCY

There are many physiologic changes that occur during pregnancy. In the cardiovascular system there are increases in total body weight, total body water, sodium and blood volume, as well as plasma volume and cardiac output. These changes support the growing uteroplacental circulation. Increased blood flow to the kidneys also accounts for decreased creatinine, blood urea nitrogen, and increased creatinine clearance, promoting optimal renal function in the pregnant woman.⁷

For the respiratory system, airway mechanics are generally unchanged. There is a decrease in pulmonary resistance, probably caused by elevated progesterone, which is balanced by an increase in resistance caused by hypocapnia. In early pregnancy, sleep dyspnea may occur in

From Northwest Asthma and Allergy Center, Seattle, Washington

75% of pregnant women without wheezing or cough. In late pregnancy, decreases in expiratory reserve volume (ERV) and residual volume (RV) lead to a decrease in functional residual capacity (FRC).¹⁶ When FRC approaches closing volume, relative underventilation of some areas of the lungs may occur, potentially worsening asthma.⁷

Gestational diabetes is common and, often, increased insulin resistance is seen. Increases in maternal prolactin, parathyroid hormone, calcitonin and 1,25 vitamin D promote a positive calcium balance permitting calcium deposition to the fetal skeleton in the second half of pregnancy. The importance of these changes to allergic disease and asthma is unknown.

Serum levels of inflammatory mediators such as prostaglandins are increased. Prostaglandin E acts as a bronchodilator, whereas prostaglandin $F_{2\alpha}$ (PGF_{2 α}) is a bronchoconstrictor. Histamine levels appear to decrease, whereas increased levels of histaminase are noted. Histaminase is produced by the fetus in levels 1000 times normal.⁸ No difference has been found, however, in women whose asthma worsened compared with women whose asthma improved or remained the same. The placenta also produces major basic protein independent of local factors or maternal eosinophilia, which may also exacerbate maternal asthma.

In general, steroids, especially cortisol and cortisol-binding globulin, rise during pregnancy, particularly during the last month with an additional increase during labor and delivery; this generally portends a salutary effect on maternal asthma. End organs are more refractory to cortisol during pregnancy, however. In addition, progesterone, deoxycortisol (DOC), and aldosterone compete with cortisol for receptor sites. The final effect of steroids is mixed, depending on which agent holds sway.

FETAL OXYGENATION

The fetus functions completely by aerobic metabolism and has substantial reserve. Fetal blood PO₂ can never exceed maternal venous partial pressure of oxygen (PO₂) because of simple concurrent exchange circulation in the placenta. The arterial PO₂ of the fetus is one third to one quarter that of the arterial PO₂ of the mother.¹⁶

This inefficiency in oxygenation is compensated by a number of adaptive mechanisms that allow adequate oxygenation to permit the fetus to thrive. First, uterine blood flow is twice the umbilical cord flow, allowing an increased perfusion rate. Fetal hemoglobin also has a higher affinity for oxygen than adult hemoglobin, resulting in higher saturation of fetal hemoglobin and red blood cells (shift to the left of the oxygen dissociation curve).¹⁶ This higher saturation allows fetal hemoglobin to deliver more oxygen under conditions of lowered oxygen saturation. In addition, fetal hemoglobin levels are 15% to 20% higher than adult levels, increasing the oxygen-carrying capacity of fetal blood. The perfusion of fetal organs is high, 2.5 times greater to fetal tissues relative to

adult tissues. Vascular flow in the fetus is preferentially distributed to the vital organs of liver, heart, and brain.

Abnormalities in pulmonary function in the pregnant woman may have effects on the fetus. For example, maternal hyperventilation can lead to fetal hypoxia. Maternal hyperventilation at room air leads to a PCO_2 of 14 and a fetal scalp blood PO_2 of 19, a significant decrease; this occurs through a direct effect of alkalosis or hypocapnia on uterine vessels resulting in decreased blood flow. In addition, the mechanical effects of hyperventilation in the mother may decrease venous return and elicit reflex maternal vascular constriction.

Hypoxemia in the mother can be caused by either pulmonary or cardiac disease. In these situations, the fetus responds by increasing oxygen extraction and redistributing blood to the heart, brain, and adrenal glands, deferring growth needs for the short term (resulting in small for age fetus). Labor and external pressure upon the abdomen may also impair umbilical cord blood flow. If placental exchange is cut off completely, it has been estimated that the fetal store of oxygen in circulating blood would suffice for less than 2 minutes.

In studies of pregnant women where oxygen deprivation may have occurred, it has been noted that twins grew significantly larger when the mother was placed at bedrest after 28 weeks. Newborns of women who worked throughout the third trimester were found to weigh less than those of nonworking mothers. Pregnancies at high elevation such as Colorado were found to result in lower birth weights. Women with congenital heart disease have also been found to have lower live-born rates, higher rates of prematurity, and lower birth weight infants.

Maternal hemoglobin is a good indicator of fetal survival. If the maternal hemoglobin is greater than 18 grams/100 mL, no fetus will survive. If the hemoglobin is between 15 and 18, there is a 44% survival rate, and a hemoglobin less than 15 gives a 85% survival rate.

THE EFFECT OF PREGNANCY ON ASTHMA

The overall effect of pregnancy on asthma is variable. Numerous studies demonstrate that one third of women will have worsening of their asthma, one third will have improvement, and one third will remain the same.¹³ Of the women whose asthma worsens, most will have asthma-related problems during weeks 29 to 36.^{13, 38} This increase in symptoms of asthma during weeks 29 and 36 may reflect a decrease in progesterone at that time. Respiratory infections of the mother also peak between 24 and 36 weeks, exacerbating asthma. In some studies, there appears to be an increase of up to 1.5 times normal of bacterial sinusitis, which may also complicate asthma. Changes in gastrointestinal physiology and upward pressure from the womb contribute to gastro-esophageal reflux which can make asthma worse. Last, psychologic issues such as body image, stress, or fears of pregnancy can make asthma worse.

An improvement in asthma during pregnancy is likely to correlate with improved nasal symptoms, as well as an increased gestational time, and pregnancy hypertension. This improvement may reflect a rise in cortisol levels during pregnancy, especially in the last month of pregnancy, and during labor and delivery. In fact, during weeks 36 to 40 the asthma of most women improves, even of those whose asthma may have worsened earlier, and 90% of pregnant women have improved asthma during labor and delivery.^{13, 17, 36, 38}

Within 3 months of delivery, nearly 75% of women revert to their prepregnancy status. For successive pregnancies, 75% will also follow the same pattern.³⁸

THE EFFECTS OF ASTHMA ON PREGNANCY

In early retrospective studies there appeared to be an increase in preterm births, low birth weight infants, neonatal fatality, neonatal hypoxia, antepartum bleeding, toxemia of pregnancy, hyperemesis gravidarum, induced labor, and labor complications in asthmatic women compared with controls.⁴⁹ Some studies also showed an increased incidence of neurologic abnormalities in the offspring at age 1 year and a doubled rate of perinatal fatality, most prominent in asthmatic black women.

A more detailed, prospective study (Schatz)³⁶ evaluated pregnant women with asthma comparing variables of forced expiratory volume at 1 second (FEV_1), age, smoking, parity, prepregnancy weight, weight gain during pregnancy, asthma medication use, overall asthma severity, and acute asthma episodes. These variables were correlated with outcome measures such as the dependent variables of birth weight, ponderal index (a proxy for intrauterine growth retardation), preterm birth less than 38 weeks, chronic gestational hypertension, and preeclampsia. No differences regarding age, parity, corticosteroid use, other medication use, or asthma severity in the mother were noted. In addition, there were no differences between mothers who required emergency therapy and those who did not. Women who smoked during pregnancy had newborns with lower mean birth weights; however, no relationship between maternal smoking and ponderal indices was seen.

Lower maternal FEV_1 was associated with low birth weight and low ponderal index. In fact, an FEV_1 of 90% (of predicted normal) appeared to be quite discriminating. Pregnant women with an FEV_1 of less than 90% were 2.5 times more likely to deliver an infant with low birth weight and a low ponderal index than women with an FEV_1 of more than 90%.

Other studies have shown that pregnant women with asthma who are closely monitored and the asthma well controlled have a lower rate of perinatal deaths. Their newborns also have higher birth weights, better Apgar scores, decreased rates of hyperbilirubinemia, and fewer malformations. These outcomes lend support to the goal of close supervision and maximal therapeutic intervention in pregnant women with asthma.

CONGENITAL ANOMALIES AND TERATOGENESIS

Spontaneous abortion occurs in 50% of early pregnancies (up to 8 weeks), mostly caused by abnormal chromosomal makeup. From weeks 8 to 16, about 15% to 20% of pregnancies abort. This rate decreases to 2% by 20 weeks, remaining there until term.²⁸ Congenital anomalies and birth defects may occur in 3.5% to 5.0% of infants, and of these, 65% to 70% have an unknown cause.²⁸ Drugs may be responsible for 1% of such anomalies affecting at least 1 out of 400 infants, but many children may not have these abnormalities detected until age 5. Therefore, the percentage may be underestimated. Birth defects are higher among stillbirths and miscarriages, especially during the first trimester. Morphology is established during the embryonic period, that is, the first 8 weeks after conception. After the embryonic phase, the fetal period is characterized by growth from 8 weeks until delivery. Most human teratogens have been discovered only after numerous children have been affected. In animal studies, more than half of 2000 various drugs and chemicals studied have shown teratogenic effects.²⁸ Unfortunately, most animal studies have a statistical sensitivity and specificity of more than 60% when interpreted for humans. Studies in nonhuman primates have a sensitivity and specificity of more than 90% but are much more expensive to conduct. Medications that have known human teratogenicity are listed in Table 1.

Although maternal ingestion of drugs may account for less than 1% of all congenital anomalies, there is an appropriate concern regarding the use of any drug in a pregnant woman. Three critical time periods during pregnancy may allow maternal drugs to affect the fetus.²⁸

For the first week after conception, there is no interface between the blastocyst and the mother. Therefore, there is no passage of drugs or medications from the mother to the fetus. The embryonic period extends from implantation to 8 weeks after conception. Malformations occurring during this period may lead to spontaneous abortions if they are lethal or to congenital anomalies if they are not lethal. During the period of fetal development, that is from 8 weeks after conception to delivery, drugs continue to cross the placenta freely.

Table 1. MEDICATIONS WITH PROVEN HUMAN TERATOGENICITY

Aminopterin and methylaminopterin	Lithium
Androgenic hormones	Methimazole
Busulfan	Penicillamine
Coumarin anticoagulants	Phenytoin
Cyclophosphamide	Tetracyclines
Diethylstilbestrol	Thalidomide
Etretinate	Trimethadione
Isotretinoin	Valproic acid

From Little BB, Gilstrap LC III: Human teratology principles. In Gilstrap LC III, Little BB (eds): *Drugs and Pregnancy*. New York, Elsevier, 1992, p 9; with permission.

Most drugs cross the placenta by simple diffusion (99% of them), especially those of a molecular weight less than 1000, unless there is an active transport system involved. Highly polar drugs pass poorly, as do those tightly bound to maternal serum proteins. Lipid-soluble drugs cross easily both ways, however, and water-soluble drugs tend to accumulate in the amniotic fluid.²⁸

Fetal effects are summarized into four categories: (1) damage during embryogenesis, (2) damage during histiogenesis in the fetal period, (3) growth retardation, and (4) fetal death or still birth.²⁸ Neonatal and postnatal effects have also been demonstrated: (1) growth and developmental delays or withdrawal (e.g., in the infant of a pregnant woman using heroin), (2) floppy infant syndrome (e.g., when the mother has used benzodiazepines near term), (3) patent ductus arteriosus, from maternal use of prostaglandin inhibitors (aspirin, indomethacin), and (4) gray baby syndrome when the mother has used chloramphenicol near term.

MEDICATION USE IN PREGNANCY

Up to 97% of pregnant women may take prescribed prescription drugs. Almost two thirds may take self-administered drugs, and almost half may take some medication other than iron or vitamin supplements.²⁹ The first trimester use of prescription drugs among pregnant mothers is summarized in Table 2.²⁹

Because the majority of pregnant women do not present for prenatal care until embryogenesis is complete (8 weeks after conception), the effects of drugs may have already occurred. In addition, 10% to 20% of pregnant women use other substances, such as alcohol or cocaine, that

Table 2. FIRST TRIMESTER USE OF PRESCRIPTION DRUGS AMONG MORE THAN 18,000 GRAVIDAS

Drug Class*	Percentage
Antibiotics	35.3
Antihistamines and cold remedies	27.3
Miscellaneous gastrointestinal	14.7
Hormonal agents	11.4
Nonnarcotic analgesics	10.8
Narcotic analgesics	8.1
Anticholinergics	4.0
Topical dermatologic agents	1.6
Stimulants	1.3
Diuretics	1.2
Anticonvulsants	1.1
Antiasthma agents	0.6
Tranquilizers	0.6

From Little BB, Gilstrap LC III: Human teratology principles. In Gilstrap LC III, Little BB (eds): Drugs and Pregnancy. New York, Elsevier, 1992, p 3; with permission.

can adversely impact the fetus. The average atopic pregnant woman takes 12 medications compared with 8 medications taken by nonatopic pregnant women, one quarter of which are over-the-counter drugs. Many allergy drugs contain other substances such as alcohol, aspirin, acetaminophen, iodine, and caffeine which are potentially harmful to the fetus.

LEGAL CONSIDERATIONS

Three out of four obstetric and gynecology physicians have been sued at least once (one in four have been sued more than 3 times!), and over half of the suits are obstetric cases.¹¹ Although drug exposure ranks last as a cause of birth defects, it ranks high on the list as reasons for litigation. Criminal law requires strict proof of cause and effect (beyond a reasonable doubt), but civil law is based on probabilities (jury needs to be only more than 50% sure).¹¹

Drugs may be declared as legal "teratogens," although that may not be validated by scientific evidence. It is more accurate to describe them as "litogens" (i.e., implicated as a cause for litigation).¹¹ One of the best examples is Bendectin, which was removed from the market despite the fact that numerous studies showed no increase in birth defects.

Food and Drug Administration Classification and Informed Consent

Until 1979, the wording by the FDA was "safe use in pregnancy has not been established" and "should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards."

In 1979, the FDA developed five risk categories (Display Box 1), but these have been shown to have little correlation to teratogenic risk as determined by the Teratogen Information Service (TERIS) computerized database.¹¹

Display Box 1. FDA Pregnancy Risk Categories (1979)

- A** Controlled human studies indicate no risk
- B** No evidence of risk in humans, but there are no controlled human studies
- C** Risk to humans has not been ruled out
- D** Positive evidence of risk to humans from human or animal studies
- X** Use during pregnancy is contraindicated

The following alternative wordings for drug labeling or counseling have been suggested.¹¹

- "The risk of spontaneous malformation is much greater than any risk of the drug that could be hypothesized from available information."^{3a}
- "The embryotoxic risks of (methotrexate, for example) have been evaluated by human and animal teratologic studies. An inadvertent or therapeutic exposure during pregnancy imposes an increased risk substantially greater than the spontaneous risk."^{3a}
- "Although this agent may be associated with an increased risk of malformation when utilized in the first 8 to 10 (menstrual) weeks of pregnancy, it would legally not be expected to be associated with significant risk when given in the latter half of pregnancy."¹¹
- "It is logical to conclude that [tetracycline, for example] would not be expected to cause yellow-brown discoloration of the teeth when given during the first 16 to 20 weeks of pregnancy."¹¹
- "Although the actual teratogenic risk of this agent is unknown, given the dose and route of administration, the fetal risk of this preparation is negligible to nonexistent since little to none of it reaches the fetus."¹¹

The key differentiation among the categories depends on the documentation of use during pregnancy by reliable studies and on the estimated risk versus benefit ratio. No drug should be administered during pregnancy unless the potential benefits outweigh potential risks to the fetus. Category X denotes drugs that may have teratogenic potential and are clearly contraindicated during pregnancy. The current FDA risk categories are summarized in Display Box 2.

Display Box 2. FDA Pregnancy Risk Categories (1998)

- A** Adequate studies in pregnant women have not demonstrated a risk to the fetus in the first trimester of pregnancy and there is no evidence of risk in later trimesters.
- B** Animal studies have not demonstrated a risk to the fetus, but there are no adequate studies in pregnant women.
or
Animal studies have shown an adverse effect, but adequate studies in pregnant women have not demonstrated a risk to the fetus in the first trimester of pregnancy, and there is no evidence of risk in later trimesters.
- C** Animal studies have shown an adverse effect on the fetus, but there are no adequate studies in humans; the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.

or

There are no animal reproduction studies and no adequate studies in humans.

- D** There is evidence of human fetal risk, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.
- X** Studies in animals or humans demonstrate fetal abnormalities, or, adverse reaction reports indicate evidence of fetal risk. The risk of use in a pregnant woman clearly outweighs any possible benefit.

PATIENT COUNSELING

Counseling should focus on the patient's understanding of the differences between embryo and fetus, and of course, on the patient's understanding of the disease to be treated. Preconception counseling is very useful, but many patients present late for care. If the patient has been exposed to a drug, the provider must do a careful assessment of the known characteristics of the drug, its route of administration, timing of use during pregnancy, duration of use, as well as of the patient's current health history and status and genetic pedigree. In addition, reproductive history, occupational exposure, and social/illicit substance use should be reviewed and documented.²⁷

For more than 60% of medications, there is insufficient teratogenic information.²⁷ Information may be obtained from the sources outlined in Table 3.

A summary of drugs mentioned in this article and their current FDA risk ratings is presented in the appendix at the end of the article.

Table 3. SOURCES OF INFORMATION ON POTENTIAL TERATOGENS FOR COUNSELING

Computerized data bases

ReproTox, Columbia Women's Hospital, Washington, DC (202) 293-5138
 TERIS-Department of Pediatrics, University of Washington, Seattle (206) 543-3180
 National Library of Medicine, Bethesda, MD 301-496-6095

Published volumes

Berkowitz RL, Coustan DR, Mochizuki TK: Handbook for Prescribing During Pregnancy. Boston, Little, Brown, & Co., 1981
 Briggs GC, Freeman RK, Yaffe SJ: Drugs in Pregnancy and Lactation. Baltimore, Williams & Wilkins, 1990
 Niebyl JR: Drug Use in Pregnancy. Philadelphia, Lea & Febiger, 1988
 Rubin PC: Prescribing in Pregnancy. BMJ 1987
 Schardein JL: Chemically Induced Birth Defects. New York, Marcel Dekker, 1985
 Shepard TH: Catalog of Teratogenic Agents. Baltimore, Johns Hopkins University Press, 1989

From Little BB, Gilstrap LC III: Counseling and evaluation of the drug-exposed pregnant patient. In Gilstrap LC III, Little BB (eds): Drugs and Pregnancy. New York, Elsevier, 1992, p 26; with permission.

SPECIFIC OBSTETRIC MEDICATIONS AND EFFECTS ON ASTHMA

For pregnant women with asthma, standard medications used by the obstetrician may affect the asthma. Ergonovine, a medication used to stimulate myometrial contraction and to reduce postpartum blood loss, has been shown to exacerbate asthma. It is thought that ergonovine increases contraction of tracheal smooth muscle. Prostaglandins used to induce therapeutic abortion (PGF_{2α}) can cause bronchospasm. On the other hand, terbutaline, often used to slow labor, is a bronchodilator.

AGENTS USED TO TREAT ASTHMA

In the late 1990s, there is a wide variety of medications that the physician can use to treat asthma. The Collaborative Perinatal Project (CPP) is a helpful resource when evaluating the potential effects of these medications on pregnancy.

Theophyllines

The use of theophyllines in asthma has decreased considerably in recent years, although they are still considered quite useful for nocturnal asthma. Therapeutic levels are often close to toxic levels, and the metabolism of theophylline can be affected by age, weight, food intake and types of food, concomitant use of other drugs, infection, and fever. Most of these effects prolong the half life of theophylline and decrease its clearance, making toxicity all the more likely. It is often difficult to manage dosing schedules to achieve benefit without side effects. Theophylline may decrease the frequency of preeclampsia and at higher-than-therapeutic doses has been shown to decrease uterine activity (although not effective for premature labor).³⁵ Theophyllines cross the placenta easily and can have direct toxic effects on the fetus which include jitteriness, vomiting, tachycardia and withdrawal apnea.³⁵ At three times the therapeutic dose, it is teratogenic in mice and rats. However, the Collaborative Perinatal Project (CPP) found no increase of congenital abnormalities in 200 women. During pregnancy, maternal serum levels should be maintained at less than 12 mg/mL to avoid toxic effects in the fetus.²⁴

β-Adrenergic Agonists

Twenty years ago, researchers reported that epinephrine caused fetal malformations if used in the first trimester.²² In animal studies, high-dose epinephrine caused limb defects, cleft palate, and fetal loss. The dose of epinephrine was thousands of times greater than usual

doses.³⁵ Epinephrine, used to alleviate bronchospasm and severe allergic reactions, can be given intramuscularly in doses of 0.3 to 0.5 mL of a 1:1000 dilution. It is rapidly metabolized and crosses the placenta easily. Although it may have direct effects, albeit transient, on the fetus, it is not believed to cause fetal malformations when used in the usual manner and doses.²⁴

Isoproterenol is teratogenic in some animals, but not in others, at high doses, and there are no reports of congenital malformations in the CPP.²²

Resorcinol agents include albuterol, metaproterenol, salmeterol, and terbutaline, all widely used in asthma. Human experience with inhaled β_2 adrenergic drugs has been quite extensive, especially during the last half of pregnancy, and provides no evidence of fetal injury from either systemic or inhaled use.²⁴ Most of these are category C.

Terbutaline is also used to treat premature labor. In some animal studies albuterol and metaproterenol have been associated with an increase in cleft palates. All β_2 adrenergic drugs can have direct, but reversible, effects on the fetus, such as tachycardia, hypoglycemia, and tremor in neonates.²⁴ In human studies of pregnant women with asthma using metaproterenol and theophylline, no increase in congenital malformations was noted.

Cromolyn Sodium, Nedocromil

Although no controlled studies in pregnant women with asthma have been done, cromolyn appears to be a very safe, albeit mild, anti-inflammatory medication. Animal studies show little potential for fetal damage.^{24, 35} Both drugs are classified Category B.

Methotrexate

Methotrexate is associated with malformations such as skeletal defects, hypertelorism, and craniosynostosis if given in first trimester.¹² This effect may be dose related. It appears that methotrexate does not cause malformations when given *before* conception.

Leukotriene Antagonists

Recently introduced oral leukotriene modifiers (montelukast, zafirlukast, and zileuton) have proven to be effective in the treatment of asthma. Montelukast has shown no teratogenicity in animal studies at doses 300 to 500 times the usual human dose. There are no adequate and well-controlled studies in pregnant humans, and the drug is classified Category B.³⁴ In animal studies, zafirlukast has shown increased maternal toxicity, deaths, fetal reabsorption, and spontaneous abortions but

only at doses 400 to 500 times the normal human dose. There are no adequate and well-controlled studies in pregnant humans, and the drug is classified Category B.³⁴ Zileuton studies have shown an association with reduced body weight, skeletal variations, and cleft palates in animal offspring. There are no adequate and well-controlled studies in pregnant humans, and the drug is classified Category C.³⁴

Anticholinergics

Atropine crosses the placenta easily and can cause vagal blockade and tachycardia in the fetus.³⁵ Although no increase in congenital defects has been seen in the offspring of women exposed to atropine in early pregnancy (CPP), the systemic effects of these drugs have generally limited their use. Ipratropium bromide does not cross the placenta easily and has fewer systemic effects on the mother. Animal teratology studies are negative, but there have been no human studies.²⁴ Ipratropium bromide is classified Category B, whereas atropine is classified Category C.

Glucocorticoids

Prednisone is metabolized to prednisolone in the maternal liver. Prednisolone can be oxidized by the placenta to prednisone or inactive cortisone. The transfer of steroids to the fetus is minimal; maternal-to-fetal gradient of the steroid is 10:1, so the fetus is exposed to only 10% to 13% of the maternal dose.³⁵

Elevated frequencies of perinatal death and placental insufficiency were seen in 34 pregnancies in which prednisone was used.³⁵ An increased incidence of fetal growth retardation was seen in 119 term infants whose mothers were treated with 10 mg of prednisone daily for infertility but results were not confirmed in two other studies.³⁵ Infants born to prednisone-treated mothers were *not* found to have symptoms of adrenal suppression and had normal reserves.³⁵

Both prednisone and prednisolone in larger doses have been found to cause malformations in animal models. Other animal studies have demonstrated a decrease in fetal weight and survival with steroid use.³⁵

In a study examining the use of inhaled beclomethasone in 45 pregnancies (40 women), 43 live births resulted. One infant had congenital heart malformation. (The mother also had diabetes and schizophrenia and was on insulin and fluphenazine.)¹⁸

Beclomethasone, cortisone, dexamethasone and betametasone generally have not been reported to have any teratogenic effects in humans. Betamethasone and dexamethasone are used to accelerate fetal lung maturation in premature labor and betamethasone showed no adverse effects in offspring in a 6-year follow-up.³⁵

Triamcinolone, flunisolide, fluticasone, and budesonide have not

been studied in pregnancy. Because beclomethasone has been on the market for so long, it has had the greatest use in pregnancy, and this clinical experience has made it the preferred inhaled steroid.

In general, the vast experience of using corticosteroids in humans, whether oral, parenteral or inhaled, has failed to show any increase in facial clefts or other birth defects, and they remain the most effective anti-inflammatory agents for the treatment of asthma. They are ranked as Category C.

OTHER ATOPIC DISEASES

Anaphylaxis is extremely uncommon in pregnancy.^{6, 40} The fetus may be protected by the placenta, which has high histaminase activity. IgE does *not* cross the placenta; however, maternal hypotension or hypoxia can affect the fetus. The most common agents that cause anaphylaxis in pregnancy are penicillin and procaine. Treatment of anaphylaxis follows the usual guidelines: turn patient on left side and give intravenous epinephrine (despite decreased uteroplacental blood flow). Ephedrine may also be used for hypotension because it has less effect on uterine blood flow than epinephrine.⁶

Urticaria may be associated with all the usual causes. In addition, the urticaria of pregnancy may be seen, which may be caused by an "autoimmune progesterone dermatitis."⁴⁰ The symptoms may be triggered by intramuscular progesterone and can be treated by estrogen.

A polymorphic eruption of pregnancy may be seen consisting of pruritic striae on the abdomen. This eruption usually occurs in primigravidas and begins in the last 5 weeks of pregnancy, rarely persisting for more than a few weeks. Immunofluorescence studies are negative, and the condition is easily treated with topical steroids.⁴⁰

Many other pruritic dermatoses of pregnancy may be seen. The treatment usually is tripeleminamine, tripeleminamine plus ephedrine, or both plus hydroxyzine. Rarely are steroids required.

With hereditary angioneurotic edema (HAE), abdominal pain may occur, and the differential diagnoses of obstetric or surgical emergencies must be considered. Most HAE patients seem to do better during pregnancy (because of a steroid effect?). The trauma of normal delivery does *not* precipitate attacks but a cesarean section *may* do so. It may be important, therefore, to pretransfuse the patient with 2 units of plasma to provide missing components of complement. Regional anesthesia is preferred to avoid endotracheal intubation and possible laryngeal edema. Danazol should be avoided because of its virilizing effects on fetus. During the postpartum period, attacks may increase.⁴⁰

Atopic Dermatitis

In a 20-year study of 117 pregnant women, 3% with mild or severe atopic dermatitis noted improvement, whereas 1% noted worsening

during the course of pregnancy. This result is in marked contrast to normal menses in which 9% of patients with mild dermatitis and 19% of patients with severe dermatitis noted worsening. Other studies have shown that about half of pregnant women with atopic dermatitis worsen, whereas one fourth improve and one fourth remain the same. Treatment should focus on avoidance of allergens, including suspected foods, and avoidance of irritating agents such as wools, chemicals, and cosmetics. The patient should avoid excessive heat, perspiration, stress, occlusive clothing, and other known irritants. Skin care should minimize soaps and include moisturizers, lubricants, and possibly Burow's solution or baking soda to relieve pruritic symptoms. Antihistamines should be used at the lowest possible dose (e.g., chlorpheniramine or tripeleonnamine, or after the first trimester, hydroxyzine, cetirizine, or loratadine). Topical corticosteroids are safe to use; lower potency preparations are preferred. Secondary infections may be treated with synthetic penicillins or erythromycin.^{12, 40}

Drug Allergy

For routine infection in penicillin-allergic patients, use erythromycin (tetracycline and sulfa are not recommended). If the patient has had positive penicillin skin tests, and erythro-sulfa (early) is not adequate, consider clindamycin or chloramphenicol. Desensitization can also be done. A recent study⁵³ described 15 women with serious infections and penicillin allergy with positive skin tests. Oral desensitization achieved good results. Long-acting penicillin preparations apparently sustain desensitization for up to 3 weeks.

Because of the occurrence of diabetes in pregnancy and avoidance of oral agents, some women who need insulin may develop a reaction to it. Insulin from a different species may be tried or desensitization may be necessary. Human-derived insulin stimulates IgE antibodies less frequently than animal-derived insulin. In subsequent pregnancies, patients may show an increased sensitivity to insulin.⁴⁰

Rhinitis

Thirty percent of pregnant patients have some form of rhinitis, compared with 15% to 20% of the normal population. This increase may be caused by pregnancy-associated hormones or vasomotor mechanisms. Vasomotor rhinitis of pregnancy is usually seen in the second half of pregnancy and disappears within 5 days postpartum.⁴²

In general, 34% of patients with allergic rhinitis worsen, 15% improve, and 45% remain unchanged. Five percent of pregnant patients may have sinusitis (a rate that is six times that seen in the normal population).⁴⁰ Superimposed rhinitis medicamentosa is also common as patients attempt to deal with their symptoms.⁴²

Ear congestion is common from otitis media, eustachian tube dysfunction, or patulous eustachian tubes. Patulous eustachian tubes are more common in pregnant women and may be a reflection of increased estrogen levels.

Treatment of rhinitis may include oxymetazoline at the lowest dose and frequency and pseudoephedrine.⁴³ The need for antibiotics for infectious rhinitis or sinusitis prompts a careful evaluation of those drugs and their effects on mother and fetus. Amoxicillin is the initial drug of choice, but other antibiotics may also be used such as cefaclor, cefuroxime, and others. For rhinitis medicamentosa, treat one nostril only and allow the other to clear. For allergic rhinitis, some antihistamines appear to be safe. Tripelemamine or chlorpheniramine may be used. Topical cromolyn or topical steroids are believed to be safe (similar to pulmonary cromolyn and beclomethasone).⁴⁴ And, as always, for allergic rhinitis, environmental controls and avoidance of allergens are primary to any treatment plan. Saline irrigation is safe and provides good relief of symptoms of rhinitis and sinusitis. Oral steroids may be needed in severe cases. Exercise may also be useful because it causes nasal vasoconstriction.

PHARMACOLOGIC AGENTS USED IN PREGNANCY FOR ATOPIC DISEASES

Local Anesthetics

Local anesthetics are mostly protein bound but have high lipid solubility and therefore cross the placenta. In the CPP, no increase in malformations was observed when they were used in the first 4 months. No adverse fetal effects were observed when they were used any time during pregnancy.

Antihistamines

Overall, antihistamines appear to be safe medications for pregnant women.^{25, 41} There has been one report of increased retrolental fibroplasia in premature infants born to women using antihistamines.⁹

Of the propylamines (brompheniramine, chlorpheniramine, dexchlorpheniramine, and triprolidine), only brompheniramine was associated with congenital defects (but not causative according to CPP).²² Other studies have shown no increased risk in humans or animals.⁹

Of the ethanolamines (bromodiphenhydramine, carbinoxamine, and clemastine), there have been no animal studies of bromodiphenhydramine or clemastine. Carbinoxamine and dimenhydrinate have shown no increased risk.⁹ The CPP reviewed only 10 cases of bromodiphenhydramine, and there was no association with increased risk. Doxylamine (Bendectin) has been reported to be associated with diaphragmatic her-

nias, congenital heart disease, and pyloric stenosis, but other studies have shown no correlation. More than 1100 infants were studied in whom the drug was used in the first trimester. There was no correlation with congenital heart disease in a case-controlled study, and no teratogenic risk in one animal study⁹; therefore, it is believed to be safe to use in pregnancy. It has been implicated in many law suits, however, and, rightfully, has been called a potent "litogen" and has been removed from the market.

Of the piperadines (azatadine, cyproheptadine, diphenylpraline) there have been no studies of adverse fetal effects, but there is conflicting data regarding the teratogenicity of cyproheptadine.⁹

Of the ethylenediamines (tripelennamine and pyrilamine) there has been no increased risk of congenital malformations in more than 100 cases.²² There have been reports of increased pregnancy losses with pyrilamine but no animal teratology studies with tripelennamine.

Of the butyrophenones (terfenadine and fexofenadine) there have been no human studies; they are not teratogenic in animals but have been associated with decreased pup weight in nursing rats.

Of the piperazines (cyclizine, buclizine, and meclizine), there have been no adverse effects noted in more than 1000 cases of first trimester use in the CPP.²² There have been mixed reports in animal studies.

Astemizole has not been studied in pregnant women. Cetirizine and loratadine have shown no adverse effects in animals, but human studies are few.

Hydroxyzine has been found to be teratogenic in rats but not in humans. In the CPP there was no increase in congenital defects in 50 women with first trimester use. A double-blind controlled study of 74 newborns exposed to hydroxyzine during the first trimester (50 mg per diem) found no increase in congenital defects.

In summary, a recent review⁴¹ of the use of antihistamines in pregnancy concludes that chlorpheniramine should be considered the antihistamine of choice, with tripelennamine as a second choice. Newer second-generation antihistamines should be reserved for patients who experience significant side effects and ideally used after the first trimester.

Decongestants

Data from many studies (more than 1000 pregnancies) in which pseudoephedrine was used in the first trimester showed no association of use with congenital anomalies, and for years it has been considered the oral decongestant of choice for use during pregnancy.⁹ Recent case-controlled studies, however, have associated the first trimester use of pseudoephedrine and other decongestants with an increased risk of infant gastroschisis (abdominal wall defect with visceral protrusion).

Phenylephrine and phenylpropranolamine may interfere with uterine blood flow. There was a possible association with fetal malformations

noted in the CPP, but this was not thought to be causal. No long-term animal studies have been done.

Topical decongestants such as oxymetazoline, xylometazoline, naphazoline, and phenylephrine may be absorbed systemically. There are no reports of adverse fetal effects or congenital anomalies.⁹

External Nasal Dilator

This device is designed to slightly open the nares at the anterior aspect of the nasal valve, providing a greater initial diameter and a decreased air flow resistance. Use of this drug-free external dilator improved the ease of breathing among patients with pregnancy-related nocturnal congestion.⁵¹

Expectorants and Antitussives

Guiafenesin has not been studied in animals but was not found to be teratogenic in more than 1000 human pregnancies.²² Dextromethorphan has shown no adverse effects in 300 cases of first trimester use.²² Benzonatate, a local anesthetic, has had no large studies.⁹

Iodides, however, do cross the placenta and can cause fetal goiter and should be *avoided*.⁹ Narcotic agents may result in neonatal addiction, withdrawal, and respiratory depression.

Antibiotics and Antimicrobials

Upper and lower respiratory infections occur commonly in all patients but may occur more frequently in patients with allergic rhinitis and asthma. The need for antibiotics must be viewed with consideration for the effect that those drugs may have on the pregnant mother or fetus. Almost all antibiotics and antimicrobials cross the placenta. Maternal serum levels are probably reduced 10% to 15% primarily because of an increased blood volume.¹⁰ All may have the usual side effects on the mother.

Penicillins are not teratogenic. Erythromycin crosses the placenta poorly and shows no adverse fetal effects.¹⁰ The usual maternal effects may be seen (gastrointestinal, hepatic hypersensitivity).

Cephalosporins are the most commonly used antibiotic in obstetrics and are not teratogenic in humans. There are potential adverse effects in rats with the specific MTT side chain (*N*-methylthiotetrazole) present in all second and third generation cephalosporins (except cefoxitin).¹⁰

Tetracyclines should be avoided, especially in the last half of the pregnancy, because they can cause yellow-brown discoloration of infant teeth. They may also cause fatty necrosis of the liver, pancreatitis, and possible renal damage in pregnant females.¹⁰

Aminoglycosides may cause possible eighth nerve damage in the fetus with long-term use, but the risk is low if use is short-term.¹⁰

Clindamycin has had no adequate human studies but is not teratogenic in animals.¹⁰

Metronidazole can show high levels in the fetus and is carcinogenic in rats. It is not teratogenic in humans or animals but is *not recommended* for use in the first trimester.¹⁰

Chloramphenicol has shown no increase in congenital malformations in the CPP (more than 100 infants) and no effects on the fetus in utero. In premature neonates given large doses, however, it is associated with the "gray baby syndrome" consisting of cyanosis, vascular collapse, and death.¹⁰

Sulfonamides are not teratogenic but can compete with bilirubin binding sites and cause hyperbilirubinemia, especially in premies or if given near term.¹⁰

Trimethoprim has shown no adverse fetal effects, but as a folate antagonist it is not recommended in pregnancy.¹⁰

Nitrofurantoin has shown no adverse fetal effects but can cause hemolytic anemia if there is glucose 6-phosphate deficiency disease present in the pregnant woman or fetus; this is theoretical and was not seen in a study of more than 1000 women.¹⁰

Vancomycin has had no studies but theoretically may cause nephrotoxicity and ototoxicity in both mother and fetus.¹⁰

Aztreonam and imipenem have had no human studies but are not teratogenic in animal studies.¹⁰

Ciprofloxacin and norfloxacin have had no studies in pregnant women. Norfloxacin is not teratogenic in monkeys, but quinolones may cause irreversible arthropathy in immature dog pups and, therefore, they are *not recommended for use in pregnancy*.¹⁰

Griseofulvin has shown two cases of conjoined twins and central nervous system and skeletal anomalies in animals at large doses.¹⁰ It is *not recommended* for use in pregnancy.

Warfarin may cause malformations and dysfunction in one out of three exposed fetuses.²

Anticonvulsants increase the risk for maldevelopment.²

Isotretinoin has long been known to be teratogenic in animals and has resulted in infants with multiple anomalies, one of which is phenotypically similar to DiGeorge syndrome.²⁸

Maternal alcohol ingestion of more than 2 to 3 oz per day is considered to be toxic. Fetal alcohol syndrome is seen in about one third of offspring of active alcoholics, and about two thirds of pregnancies in active alcoholics will have significant complications including prematurity, growth retardation, and perinatal asphyxia.

Cocaine crosses the placenta easily and can cause ischemic injury in the fetal central nervous system, limbs, intestines, and kidneys. As many as one third of infants born to women abusing "crack" cocaine together with alcohol and other substances will have intracranial hemorrhages and porencephalic cysts.

Immunotherapy

Metzger³¹ analyzed 121 pregnancies in 90 atopic patients and found no increase in abortion, prematurity, preeclampsia, or congenital anomalies. Graft studied one woman on venom immunotherapy and noted no problems with the pregnancy or any fetal adverse effects. Venom-specific IgG antibodies were elevated in both mother and child at birth falling to undetectable in the child by 6 months; venom-specific IgE antibodies were elevated in the mother but not in the child at birth or at 6 months.

The Insect Allergy Committee of the American Academy of Allergy, Asthma and Immunology studied 22 pregnancies in 15 women and noted 19 normal pregnancies, 1 first trimester miscarriage, 1 placenta previa with fetal loss, and 1 multiple congenital abnormalities, but no overall increased risk.

In a follow-up study of offspring of atopic mothers receiving immunotherapy during pregnancy, Settupane et al⁴⁷ noted 15 of 40 (31%) children of mothers on allergy shots developed asthma or allergic rhinitis, whereas 17 of 38 (45%) of controls did so.

In general, it is not recommended to begin immunotherapy during pregnancy. For patients already on allergen desensitization shots, it is recommended that they remain at their current dose and that they not advance on the shot schedule until after delivery.⁴⁸

Vaccines

Toxoids (tetanus-diphtheria) have shown no known adverse fetal effects. They are recommended for pregnant women with no primary immunization because disease mortality is high, and immunization will provide protection to 80% to 95% of neonates if the mother has had at least two doses at least 2 weeks before delivery.

Inactivated bacterial vaccines (cholera, meningococcus, plague, pneumococcus, typhoid) have shown no reports of adverse fetal outcomes but are *not recommended* except for travel or high risk of close exposure.

Immune globulins (hepatitis B, rabies, varicella) have no known fetal effects.

Live attenuated viral vaccines (mumps, measles, polio, rubella, and yellow fever) *are not recommended* for pregnant women. MMR is *contraindicated* and polio and yellow fever may be used if there is significant risk of exposure; however, none has had fetal risk confirmed. Inactivated viruses such as influenza and rabies may be used in pregnant women, and neither has shown increased fetal risk.

MANAGEMENT OF ASTHMA IN PREGNANCY

The goals of asthma management for pregnant patients are the same as for nonpregnant patients: maintenance of normal (best) pulmonary

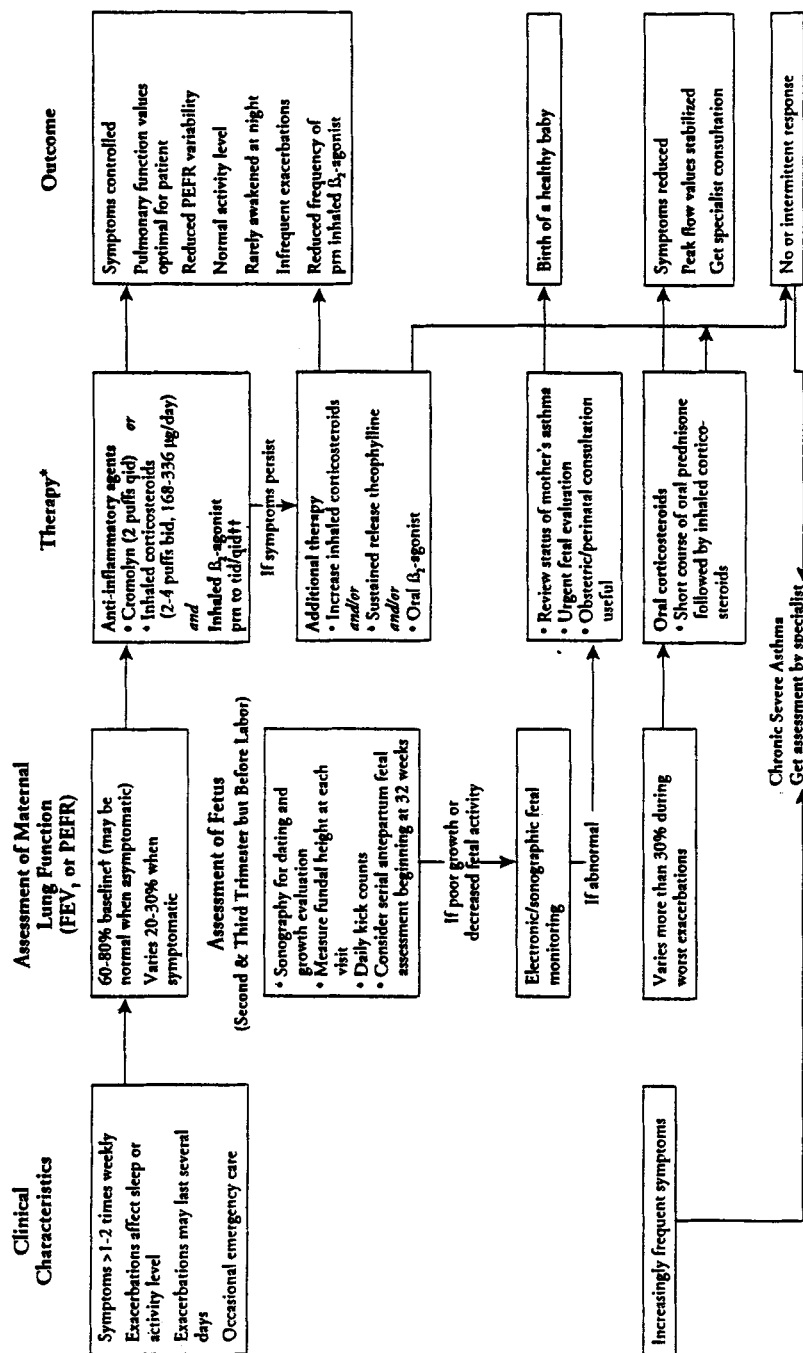


Figure 1. See legend on opposite page

function, control of symptoms, prevention of asthma attacks, maintenance of normal activity, and avoidance of adverse effects from medications.⁷ In addition, with pregnant patients, one wishes to maintain optimal maternal health for optimal fetal development, resulting in the birth of a normal, healthy baby.

Objective measures of lung function are essential to monitor pulmonary function. Office spirometry coupled with personal peak flow meter use helps to assess the status of pulmonary function and the need to change treatment.⁷ Fetal monitoring for growth, activity, development, and well-being can be accomplished using standard techniques.

Avoidance and control of asthma triggers is very important.⁷ These may include allergens in the environment, exercise, stress, infection, and associated other diseases such as allergic rhinitis, sinusitis, and gastroesophageal reflux.

Pharmacologic therapy should follow the guidelines for step-care management, treatment of acute exacerbations, and use of specific drugs.⁷ Table 4 shows the drugs and dosages for asthma and associated conditions preferred for use during pregnancy, as recommended by the Working Group on Asthma and Pregnancy of the National Asthma Education Program. Figure 1 displays the step-care algorithm for the management of chronic moderate asthma. (Other algorithms can be found in the NAEP guidelines cited.)⁷

The most important component in good asthma management for *all* asthma patients is patient education. Patients really are their own doctors. Health care providers must help patients to understand the asthma disease process, its chronicity and variations, and to know the tools to monitor their asthma and the drugs to use. Most of all, health care providers must empower patients to take charge of their illness and control their disease. Support for the patient from family members, friends and providers is especially important during the time of physical and psychological stress of pregnancy.

CONCLUSION

Pregnant women will have the same atopic diseases as nonpregnant women. The state of pregnancy may make the underlying disease better

Figure 1. Management of chronic, moderate asthma during pregnancy. *All therapy must include patient education about prevention (including environmental control where appropriate), as well as control of symptoms. †PEFR percent baseline refers to the norm for the individual, which is established by the clinician. This norm may be percent-predicted based on standardized norms of percent of patient's personal best. ††If exceeds 3–4 dosages/d, consider additional therapy other than inhaled β_2 -agonist. (From Management of Asthma during Pregnancy: Report of the Working Group on Asthma and Pregnancy. National Asthma Education Program, National Institutes of Health, National Heart, Lung, and Blood Institute, US Department of Health and Human Services, Public Health Services. NIH Publication No. 93-3279, September 1993.)

Table 4. DRUGS AND DOSAGES FOR ASTHMA AND ASSOCIATED CONDITIONS PREFERRED FOR USE DURING PREGNANCY*

Drug Class	Specific Drug	Dosage
Anti-inflammatory	Cromolyn sodium	2 puffs qid (inhalation) 2 sprays in each nostril bid-qid (intranasal for nasal symptoms)
	Beclomethasone	2-5 puffs bid-qid (inhalation) 2 sprays in each nostril bid (intranasal for allergic rhinitis)
	Prednisone	Burst for active symptoms: 40 mg a day, single or divided dose for 1 week, then taper for 1 week. If prolonged course is required, single a.m. dose on alternate days may minimize adverse effects.
Bronchodilator	Inhaled β_2 agonist	2 puffs every 4 hours as needed
	Theophylline	Oral: Dose to reach serum concentration level of 8-12 $\mu\text{g/mL}$
Antihistamine	Chlorpheniramine	4 mg by mouth up to qid 8-12 mg sustained-release bid
	Tripelennamine	25-50 mg by mouth up to qid 100 mg sustained-release bid
Decongestant	Pseudoephedrine	60 mg by mouth up to qid 120 mg sustained-release bid
	Oxymetazoline	Intranasal spray or drops up to 5 days for rhinosinusitis
Cough	Guaifenesin	2 tsp by mouth qid
Antibiotics	Dextromethorphan	
	Amoxicillin	3 weeks therapy for sinusitis

*This table presents drugs and suggested dosages for the home management of asthma and associated conditions. Drugs and dosages for the treatment of exacerbations in the emergency department or hospital are presented in the full report of the working group.

From Management of Asthma During Pregnancy, Report of the Working Group on Asthma and Pregnancy, National Asthma Education Program, National Institutes of Health, National Heart, Lung, and Blood Institute, U.S. Department of Health and Human Services, Public Health Service, NIH Publication No. 93-3279, September 1993; with permission.

or worse, and pregnancy itself seems to cause new symptoms that mimic atopic disease. The approach to diagnosis and management is generally the same except that the choice of drugs used for treatment must be tempered by considerations of the effect of those drugs not only on the mother but also on the developing fetus. Fortunately, most atopic diseases are not life threatening and can be managed easily. Uncontrolled asthma is deleterious to both mother and fetus, whereas well-controlled asthma, albeit with aggressive treatment, clearly benefits both. Good guidelines are available to health care practitioners; patient education and good self management are crucial to maternal and fetal well-being and the successful delivery of a healthy infant.

References

1. Barker AF: Strategies in managing asthma. *West J Med* 150:303-308, 1989
2. Berkowitz RL, Coustan DR, Mochizuki TK: *Handbook for Prescribing Medication During Pregnancy*, ed 2. Boston, Little, Brown & Company, 1986

3. Bjorksten B, Kjellman NIM: Perinatal factors influencing the development of allergy. *Clin Rev Allergy* 5:339-347, 1987
- 3a. Brent RL: Teratogen update: Bendectin [editorial comments]. *Teratology* 31:429, 1985
4. Chung KF, Barnes PJ: Treatment of asthma. *BMJ* 294:103-105, 1987
5. DiMarco AF: Asthma in the pregnant patient: A review. *Ann Allergy* 62:527-533, 1989
6. Entman SS, Moise KJ: Anaphylaxis in pregnancy. *South Med J* 77:402, 1984
7. Executive Summary: Management of Asthma During Pregnancy. National Heart, Lung, and Blood Institute. NIH Publication No. 93-3279A, March 1993
8. Falkoff R: Maternal immunologic changes during pregnancy: A critical appraisal. *Clin Rev Allergy* 5:287-300, 1987
9. Gilstrap LC, Little BB: Antihistamines, decongestants, and expectorants during pregnancy. In Gilstrap LC, Little BB (eds): *Drugs and Pregnancy*. New York, Elsevier, 1992, pp 269-276
10. Gilstrap LC, Little BB: Antimicrobial agents during pregnancy. In Gilstrap LC, Little BB (eds): *Drugs and Pregnancy*. New York, Elsevier, 1992, pp 39-68
11. Gilstrap LC, Little BB: Legal considerations of drugs in pregnancy. In Gilstrap LC, Little BB (eds): *Drugs and Pregnancy*. New York, Elsevier, 1992, pp 31-38
12. Gilstrap LC, Little BB: Use of dermatologics during pregnancy. In Gilstrap LC, Little BB (eds): *Drugs and Pregnancy*. New York, Elsevier, 1992, pp 255-268
13. Gluck JC, Gluck PA: The effects of pregnancy on asthma: A prospective study. *Ann Allergy* 37:164, 1976
14. Graft DF: Venom immunotherapy during pregnancy. *Allergy Proc* 9:563-565, 1988
15. Greenberg F: The potential teratogenicity of allergy and asthma treatment in pregnancy. *Immunology Allergy Practice* 7:4-9, 1985
16. Greenberger P: Pregnancy and asthma. *Chest* 87:85S-87S, 1985
17. Greenberger PA: Asthma during pregnancy. *J Asthma* 27:341-347, 1990
18. Greenberger PA, Patterson R: Beclomethasone dipropionate for severe asthma during pregnancy. *Ann Intern Med* 98:478-481, 1983
19. Greenberger PA, Patterson R: The management of asthma during pregnancy and lactation. *Clin Rev Allergy Immunol* 5:317-324, 1987
20. Greenberger PA, Patterson R: The outcome of pregnancy complicated by severe asthma. *Allergy Proc* 9:539-543, 1988
21. Guerin JM: L'asthme au cours de la grossesse. *Rev Pneumol Clin* 43:156-159, 1987
22. Heinonen OP, Slone D, Shapiro S: *Birth Defects and Drugs in Pregnancy*. Littleton, MA, Publishing Sciences Group, Inc, 1977
23. Hill RM, Tennyson LM: The effect of maternal allergy medications on the fetus. *Immunol Allergy Prac* 7:80-91, 1985
24. Hornby PJ, Abrahams TP: Pulmonary pharmacology. *Clin Obstet Gynecol* 39:17-35, 1996
25. Incaudo GA: Diagnosis and treatment of rhinitis during pregnancy and lactation. *Clin Rev Allergy* 5:325-337, 1987
26. Incaudo G, Schatz M: Introduction. *Clin Rev Allergy* 5:285-186, 1987
27. Little BB, Gilstrap LC: Counseling and evaluation of the drug-exposed pregnant patient. In Gilstrap LC, Little BB (eds): *Drugs and Pregnancy*. New York, Elsevier, 1992, pp 23-30
28. Little BB, Gilstrap LC: Human teratology principles. In Gilstrap LC, Little BB (eds): *Drugs and Pregnancy*. New York, Elsevier, 1992, pp 5-22
29. Little BB, Gilstrap LC: Introduction to drugs in pregnancy. In Gilstrap LC, Little BB (eds): *Drugs and Pregnancy*. New York, Elsevier, 1992, pp 1-4
30. Mawhinney H, Spector SL: Optimum management of asthma in pregnancy. *Drugs* 32:178-187, 1986
31. Metzger WJ, Turner E, Patterson R: The safety of immunotherapy during pregnancy. *J Allergy Clin Immunol* 61:268, 1978
32. Noble PW, Lavee AE, Jacobs MM: Respiratory diseases in pregnancy. *Obstet Gynecol Clin North Am* 15:391-428, 1988
33. Skidmore RL: *Nursing Drug Reference*. St. Louis, Mosby, 1997
34. Physicians' Desk Reference. Montvale, NJ, Medical Economics Data Production Company, 1998

35. Ramin SM, Little BB, Gilstrap LC: Antiasthma agents during pregnancy. *In* Gilstrap LC, Little BB (eds): *Drugs and Pregnancy*. New York, Elsevier, 1992, pp 93-110
36. Schatz M: Asthma during pregnancy: Interrelationships and management. *Ann Allergy* 68:123-137, 1992
37. Schatz M: Asthma treatment during pregnancy: What can be safely taken? *Drug Safety* 16:342-350, 1997
38. Schatz M, Harden K, Forsythe A, et al: The course of asthma during pregnancy, post partum and with successive pregnancies: A prospective analysis. *J Allergy Clin Immunol* 81:509-517, 1988
39. Schatz M, Hoffman C: Interrelationships between asthma and pregnancy: Clinical and mechanistic considerations. *Clin Rev Allergy* 5:301-315, 1987
40. Schatz M, Hoffman CP, Zeiger RS, et al: The course and management of asthma and allergic diseases during pregnancy. *In* Middleton E, Reed CE, et al (eds): *Allergy: Principles and Practice*. St. Louis, The C.V. Mosby Company, 1988, pp 1093-1155, 1301-1342
41. Schatz M, Petitti D: Antihistamines and pregnancy. *Ann Allergy* 78:157, 1997
42. Schatz M, Zeiger RS: Diagnosis and management of rhinitis during pregnancy. *Allergy Proc* 5:545-554, 1988
43. Schatz M, Zeiger RS: Treatment of asthma and allergic rhinitis during pregnancy. *Ann Allergy* 65:427-429, 1990
44. Schatz M, Zeiger RS, Harden KM, et al: The safety of inhaled beta-agonist bronchodilators during pregnancy. *J Allergy Clin Immunol* 82:686-695, 1988
45. Schatz M, Zeiger RS, Hoffman CP, et al: Increased transient tachypnea of the newborn in infants of asthmatic mothers. *Am J Dis Child* 145:156-158, 1991
46. Schatz M, Zeiger RS, Hoffman CP, et al: Intrauterine growth is related to gestational pulmonary function in pregnant asthmatic women. *Chest* 98:389-392, 1990
47. Settiple RA, Chafee FH, Settiple GA: Pollen immunotherapy during pregnancy: Long-term follow-up of offsprings. *Allergy Proc* 5:555-561, 1988
48. Shaikh WA: A retrospective study on the safety of immunotherapy in pregnancy. *Clin Exp Allergy* 23:857-860, 1993
49. Stenius-Aarniala B, Piirila P, Teramo K: Asthma and pregnancy: A prospective study of 198 pregnancies. *Thorax* 43:12-18, 1988
50. Stewart JM, et al: Genetics and Dysmorphology. *In* Hay Jr WW (ed): *Pediatric Diagnosis and Treatment*, ed 12. Norwalk, CT, Appleton and Lange, 1995, pp 947-988
51. Turnbull GL, Rundell OH, Rayburn WF, et al: Managing pregnancy-related nocturnal nasal congestion: The external nasal dilator. *J Reprod Med* 41:897-902, 1996
52. Weber RW, Nelson HS: Immunologic and atopic aspects of pregnancy and lactation. *Ann Allergy* 57:159-168, 1986
53. Wendel GD, Stark BJ, Jamison RB, et al: Penicillin allergy and desensitization in serious infections during pregnancy. *N Engl J Med* 312:1229, 1985
54. Williams DA: Asthma and pregnancy. *Acta Allergol (Kbh)* 221:311, 1967

Address reprint requests to

Dominick A. Minotti, MD, MPH
 Northwest Asthma and Allergy Center
 4540 Sand Point Way NE
 Seattle, WA 98105

Appendix

PREGNANCY RISK CATEGORIES OF SELECTED DRUGS*

Anti-inflammatories

acetaminophen	NR	flurbiprofen	B	nalbuphine	C
acetylsalicylic acid	C†	ibuprofen	NR	naproxen	NR
D in 3rd trimester		indomethacin	NR	oxaprozin	C
choline magnesium salic.	C	ketoprofen	NR	piroxicam	NR
diclofenac	B	ketorolac	C	salsalate	C
diflunisal	C	magnesium salicylate	NR	sodium salicylate	NR
etodolac	C	meclofenamate	NR	sulindac	NR
fenoprofen	NR	mefenamic acid	C	tolmetin	C

Antivirals

famciclovir	B	ganciclovir	C	stavudine (d4T)	C
amantadine	C	lamivudine	C	valacyclovir	B
acyclovir	C	ribavirin	X	zalcitabine (ddC)	C
didanosine (ddl)	B	rimantadine	C	zidovudine (AZT)	C
foscarnet sodium	C	saquinavir	B		

CNS stimulants

amphetamines	C	diethylpropion	B	pemoline	B
benzphetamine	X	fenfluramine	C	phendimetrazine	NR
caffeine	C	methamphetamine	C	pheniramine	NR
dextroamphetamine	C	methylphenidate	NR		

Anti-infectives

aminoglycosides (most)	D	dirithromycin	C	polymyxin B	NR
azithromycin	B	erythromycin	B	rifabutin	B
aztreonam	B	fluoroquinolones (most)	C*	spectinomycin	NR
bacitracin	NR	imipenem	C	sulfonamides	C*
cephalosporins	B	lincomycin	NR	tetracyclines (most)	D
chloramphenicol	NR	methanamine	C	trimethoprim	C
clarithromycin	C	nitrofurantoin	B	trimetrexate	D
clindamycin	NR	penicillins (most)	B	vancomycin	C

Bronchodilators

albuterol (salbutamol)	C	ethynorepinephrine	C	pirbuterol	C
aminophylline	C	ibratropium	B	salmeterol	C
bitolterol	C	isoetharine	NR	terbutaline	B
dyphylline	C	isoproterenol	C	theophylline	C
ephedrine	C	metaproterenol	C		
epinephrine	C	oxtriphylline	C		

Anticholinergics

atropine	C	hyoscyamine	C		
dicyclomine	B	scopolamine	C		

Adrenergics, sympathomimetics

phenylephrine	C	pseudoephedrine	C		
---------------	---	-----------------	---	--	--

Antihistamines

astemizole	C	cyproheptadine	B	fexofenadine	C
azatadine	B	dexchlorpheniramine	B	trimeprazine	NR
brompheniramine	C	diphenhydramine	B	tripelennamine	NR
cetirizine	B	methdilazine	B	triprolifine	C
chlorpheniramine	B	promethazine	NR		
clemastine	B	terfenadine	C		

Nasal Drugs

beclomethasone	C	flunisolide	C	tetrahydrozoline	C
budesonide	C	fluticasone	C	triamcinolone	C
dexamethasone	C	naphazoline	NR	xylometazoline	NR
ephedrine	NR	oxymetazoline	NR		
epinephrine	NR	phenylephrine	NR		

Appendix continued on following page

PREGNANCY RISK CATEGORIES OF SELECTED DRUGS* (Continued)

Expectorants, antitussives					
benzonatate	C	dextromethorphan	C	hydromorphone	C
codeine	C	guaifenesin	C		
Respiratory drugs					
beclomethasone	NR	flunisolide	C	montelukast	B
budesonide	C	fluticasone	C	zafirlukast	B
cromolyn sodium	B	nedocromil	B	zileuton	C
dexamethasone	NR	triamcinolone	C		
Antianxiety drugs					
alprazolam	D	diazepam	NR	midazolam	D
buspirone	B	hydroxyzine	NR	oxazepam	NR
chlordiazepoxide	NR	lorazepam	NR	prazepam	NR
chlorazepate	NR	meprobamate	NR		
Narcotic and opioid analgesics (most)					
	C				
Sedative hypnotics					
amobarbital	D	ethchlorvynol	C	temazepam	X
aprobital	D	flurazepam	NR	triazolam	X
butabarbital	D	pentobarbital	D	zolpidem	B
chloral hydrate	C	quazepam	X		
estazolam	X	secobarbital	D		
Antidepressants					
amitriptyline	NR	imipramine	NR	phenelzine	C
bupropion	B	maprotiline		sertraline	B
desipramine	NR	nefazodone	C	tranycpromine	NR
doxepin	NR	nortriptyline	NR	trazodone	C
fluoxetine	B	paroxetine	B	venlafaxine	C
Corticosteroids (most)					
fludrocortisone	NR				
	C	triamcinolone	C		
Topical steroids					
	C				
Miscellaneous					
danazol	D	stanazolol	D		
Miscellaneous CNS drugs					
nicotine polacrilex resin	C	nicotine transdermal	D	sumatriptan	C
Local anti-infectives					
acyclovir	C	econazole	C	mupiricin	B
bacitracin	NR	erythromycin	B	neomycin	NR
chloramphenicol	NR	gentamicin	NR	nystatin	NR
clindamycin	B	ketoconazole	C	silver sulfadiazine	B
clotrimazole	B	metronidazole	B	terbinafine	B
Immune serums					
	C				
Ophthalmic drugs					
dexamethasone	C	levocabastine	C	oxymetazoline	C
diclofenac	B	lodoxamide	B	prednisolone	C
ketorolac	C	naphazoline	C	tetrahydrozoline	C
Vaccines and toxoids					
BCG	C	Japanese encephalitis	C	rabies	C
cholera	C	measles, mumps, rubella	C	tetanus toxoid	C
diphtheria and tetanus	C	meningococcal	C	typhoid oral	C
hepatitis A	C	plague	C	typhoid vaccine	C
hepatitis B	C	pneumococcal	C	varicella	C
influenza	C	poliovirus	C	yellow fever	C

*Current risk categories are defined in Display Box 2 in this article.

†Contraindicated at term.

NR = Not Reported

Data from Physicians' Desk Reference, ed 52. Montvale, NJ, Medical Economics Company, 1998.