

THE MANAGEMENT OF SEVERE ASTHMA DURING PREGNANCY

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Management of gravidas with severe asthma involves identification of patients with persistent asthma who have potentially fatal asthma,¹³ have had "near miss" attacks of asthma, have difficulty controlling asthma, require multiple medications for optimal management, or have experienced marked, acute deteriorations in respiratory status in the past. The physician managing the asthma should attempt to maximize respiratory status preconception, or if asthma is being ineffectively controlled during gestation, rapidly gain control of the gravida's asthma. Asthma is considered an inflammatory disorder,²² but the extent of inflammation during gestation has not been evaluated and perhaps never will be. A number of studies have suggested that even with daily use of inhaled beclomethasone dipropionate and use of alternate day or daily prednisone, the maternal-fetal outcome can be normal or close to it.^{10, 17}

SEVERITY OF ASTHMA

Chronic severe asthma as defined by the Working Group on Asthma and Pregnancy of the National Institutes of Health National Asthma Education Program is asthma characterized by "continuous symptoms,

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limited activity level, frequent exacerbations, frequent nocturnal symptoms, and occasional hospitalization and emergency treatment."²² Maternal pulmonary function would be variable with a baseline forced expiratory volume in one second (FEV₁) or peak expiratory flow rate (PEFR) of less than 60%²² (i.e., a percentage of standardized norms or the gravida's personal best). Moderate severity asthma was characterized by "symptoms greater than 1 to 2 times weekly, exacerbations affecting sleep or activity level, exacerbations that might last several days, and occasional emergency care required."²² Baseline FEV₁ or PEFR is from 60% to 80%. Physicians should not be satisfied with such respiratory status for most cases of asthma during pregnancy and should attempt to avoid nocturnal asthma symptoms, limitations of activities, impaired respiratory status, and emergency department care or hospitalizations.

Because the risk of a fatality from asthma is greatly increased in certain populations of patients with asthma, it is helpful to identify gravidas who meet criteria for the diagnosis of potentially fatal asthma¹³ or malignant potentially fatal asthma.⁸ Such criteria are listed in Box 1.

Box 1. Criteria for the Diagnosis of Potentially Fatal Asthma and Malignant Potentially Fatal Asthma

Potentially Fatal Asthma

Any one of the following criteria makes the diagnosis:

1. Respiratory arrest from asthma
2. Intubation for status asthmaticus or acute respiratory acidosis without intubation
3. Two or more hospitalizations for status asthmaticus despite courses of oral corticosteroids administered to try to prevent the hospitalization
4. Episodes of acute pneumomediastinum or pneumothorax during status asthmaticus

Malignant Potentially Fatal Asthma

1. Any of the above criteria in a patient who is so nonadherent with advice that an asthma fatality is considered likely if control of asthma is not obtained. Patients are a threat to themselves because of "near miss" asthma attacks or their being impossible to manage.

Gravidas with mild asthma may develop severe asthma although that scenario is uncommon in prospectively managed women.^{25, 26} Some examples of coexisting conditions that may complicate asthma during pregnancy include the following:

- Potentially fatal asthma
- Malignant potentially fatal asthma
- Allergic bronchopulmonary aspergillosis (stages IV or V)
- Cystic fibrosis
- Severe persistent asthma and a history of pulmonary embolism

- Severe persistent asthma and congenital heart disease
- Severe persistent asthma and diabetes
- Severe persistent asthma and psychiatric or psychologic disorders

EMERGENCY THERAPY FOR GRAVIDAS WITH ASTHMA

When a gravida presents with acute asthma in the emergency room or labor and delivery area, assessments of arterial hypoxemia, acid-base abnormalities, the possibility of maternal dehydration, and chest pain need to be considered. The latter could represent rib fracture from coughing, community-acquired pneumonia, pulmonary infarction, or pneumomediastinum. In a study of 51 gravidas compared with 500 nonpregnant women with acute asthma who presented to 1 of 36 emergency rooms in 18 states, 24% and 21% of the women, respectively, required hospitalization for asthma.⁶ PEFR was similar at 211 and 216 L/min, or 51% and 53% of predicted in both groups; however, pregnant women with asthma were less likely to have received corticosteroids acutely (44% versus 66%) or on discharge (38% versus 64%) from the emergency room.⁶ The women were contacted over the next 2 weeks. A relapse was defined when a visit was referred to the emergency room or physician office for increased symptoms. Such relapses were recorded for the minority of women (11% gravid versus 15% nongravid). Nevertheless, many women still had "severe symptoms" after 2 weeks consisting of asthma symptoms "most of the time," "severe distress" from asthma, or severe activity limitation from asthma. Thirty-five percent of gravidas had these "ongoing asthma exacerbations," compared with 23% of nongravid women.⁶ The results from this study are consistent with the observation that gravidas receive less appropriate care during emergency room treatment regarding corticosteroids, either acutely or on discharge.

OUTCOMES OF PREGNANCIES IN GRAVIDAS WITH ASTHMA

Severe Asthma

A series was reported of 80 pregnancies in 73 gravidas with asthma of such severity that daily medications were required, including bronchodilators and at least inhaled beclomethasone dipropionate and courses of prednisone.¹⁷ Prednisone was administered in 69 pregnancies, including throughout the pregnancy in 21 gravidas and in 23 other patients during the first trimester. Beclomethasone dipropionate was used by 44 gravidas. No maternal deaths occurred, and there was one intrauterine death and one stillbirth. Premature births (<37 weeks) occurred in 4 of 55 (7.3%) pregnancies where no emergency therapy

(office or hospital) was needed, compared with 4 of 26 (15.4%) pregnancies where emergency therapy was required.¹⁷ Although a trend existed, statistical differences were not present, likely because of the small sample size; however, a significant difference was detected for birth weight when the presence of status asthmaticus during pregnancy was considered. Specifically, birth weight was 3354 g in the absence of a hospitalization for status asthmaticus, as compared with 3048 g when status asthmaticus occurred.¹⁷ The stillbirth occurred during a twin delivery in the absence of respiratory symptoms. The intrauterine death occurred at 23 weeks' gestation in a woman with severe hypertension. She was receiving prednisone 35 mg on alternate days, but asthma was considered controlled at the time of the fetal demise. Severe hypertension during two other pregnancies had resulted in fetal loss as well. Analysis of these pregnancies suggests that, despite severe persistent asthma requiring prednisone and inhaled beclomethasone dipropionate, avoidance of status asthmaticus is associated with a favorable outcome for mother and infant.

Severe asthma during pregnancy was reported in 21 adolescents who had 28 pregnancies.³ There were 56 exacerbations of asthma that were caused by upper respiratory infections in 33 (59%) pregnancies and nonadherence with medications or office visits in 15 (27%) pregnancies.³ No obvious factor was identified in 12 (21%) exacerbations, whereas smoking in 4 (7%) exacerbations and possibly pets in 1 (2%) exacerbation were noted. Prednisone was administered along with beclomethasone dipropionate, if the gravida would use it, for exacerbations that could be managed as an outpatient. At the time of this study (1978–1988), theophylline was used by 23 of 28 gravidas. It is considered safe during pregnancy but is out of favor now because it is not clearly an anti-inflammatory medication. Fortunately there were no fetal or maternal deaths or evidence for growth retardation in the pregnancies in this series. These findings suggest that aggressive care of adolescents with severe asthma can result in favorable outcomes for mother and infant. The interventions included skin testing for allergies, use of theophylline unless it was not tolerated, beclomethasone dipropionate by inhalation, and prednisone for acute exacerbations of asthma. Usually, prednisone 30 to 60 mg as a single daily dose was administered for acute exacerbations of asthma. Gravidas were examined in the office every 1 to 4 weeks for asthma, in addition to visits to the obstetrician. A 24-hour answering system was staffed by an allergy-immunology fellow with backup by the attending physician.

In a study of 30,940 live births at Long Beach Medical Center from 1985 to 1990, of which maternal asthma was present in 183 deliveries (0.59%), medications were studied in 81 women.²⁴ Thirty-one gravidas were steroid dependent in contrast to 50 non-steroid-dependent women with asthma. A cohort of 130 pregnancies was used as controls where the mother did not have asthma. There were rather striking differences in outcomes between the two groups and compared with nonasthmatic control pregnancies. Gestational diabetes mellitus was present in 12.9%

of steroid-dependent gravidas, compared with 4.0% of gravidas with non-steroid-dependent asthma, and in 1.5% of nonasthmatic controls. Pre-eclampsia was present more often as well in 9.7%, 2.0%, and 2.3% of the groups, respectively. Admissions for exacerbations of asthma occurred in 71% of the steroid-dependent gravidas and 30% of the non-steroid-dependent gravidas. Adverse pregnancy outcomes were more common in the steroid-dependent gravidas than in non-steroid-dependent gravidas and nonasthmatic controls for preterm labor (48.4% versus 10.0% versus 1.6%), preterm rupture of membranes (25.8% versus 10.0% versus 1.6%), and preterm delivery (<37 weeks' gestation) (54.8% versus 14.0% versus 3.9%). Deliveries less than 32 weeks were not increased, however. Fetal outcomes were striking in that low birth weight (birth weight <2500 g) occurred in 45.2% of pregnancies where the gravida had steroid-dependent asthma, 14.0% in non-steroid-dependent asthma, and in 4.6% of control pregnancies. Intrauterine growth retardation occurred similarly in 39.0%, 22.0%, and 7.7% of the groups, respectively. It was not stated whether the gravidas in this study received specialist care for asthma, which might be a difference between this study²⁴ and the previous ones cited^{3, 10, 17} in gravidas with severe asthma.

Mild to Moderate Asthma

One might suspect that less than severe maternal asthma would be associated with more favorable maternal-fetal outcomes. That is true in some studies^{26, 28} but not necessarily others. In a prospective study from 1978 to 1989 of 486 gravidas with known asthma and 486 gravidas without asthma and with normal expiratory flow rates, the maternal and fetal outcomes were almost identical.²⁸ The gravidas with asthma were managed by allergist-immunologists, whereas the control gravidas received care presumably from the obstetrician but not from the allergist-immunologist. For the gravidas with asthma, no antiasthma medications were used by 60 (12.3%) gravidas, inhaled bronchodilators only by 119 (24.5%) gravidas, theophylline or cromolyn, but not inhaled corticosteroids, by 186 (38.3%) gravidas, inhaled corticosteroids by 39 (8%) gravidas, and oral corticosteroids by 83 (16.9%) gravidas. The number of gravidas who required maintenance oral corticosteroids is not clearly specified, but this range of medications can serve as a proxy for severity. Maternal complications were similar in both groups for preterm labor, pre-eclampsia, and gestational diabetes. Infant outcomes were comparable as well for fetal demise after 20 weeks of gestation (5 from the gravidas with asthma and 4 from control gravidas), neonatal (first 28 days of life) deaths (3 from the gravidas with asthma and 0 from control gravidas), preterm deliveries of less than 37 weeks (4.8% versus 2.9%), small for gestational age (6.0% versus 4.5%), and for birth weight less than 2500 g (4.1% versus 2.5%).²⁸ The data are consistent with the observation that prospectively managed gravidas with primarily mild to

moderate asthma can undergo pregnancies without statistically significant abnormal maternal or fetal outcomes.

The same investigative team used these pregnancies to determine changes in asthma course during the pregnancy and then afterward. The authors had reported on changes in the overall course of asthma during pregnancy and then when assessed 3 months post partum in the first 386 pregnancies in 330 gravidas.²⁶ Asthma was believed to have worsened in 35% of women, was unchanged in 33%, and improved in 28%. It was noted that asthma seemed to revert to its prepregnancy status in 73% of women.²⁶

Two studies^{1, 7} that did not report that the maternal and infant outcomes were essentially normal have been published that emphasize the challenges remaining. In a study from Halifax, Nova Scotia of 817 gravidas with asthma during 1991 to 1993, the prevalence of asthma increased from 4.8% of asthma during pregnancy in 1991 to 6.9% during 1993.¹ This prevalence is higher than the 4% reported previously.²² Medication use was classified as follows: none in 375 (45.9%), β -adrenergic agonists in 303 (37.1%), and "steroids" and β -adrenergic agonists in 139 (17.0%).¹ The pregnancies in gravidas with asthma were associated with an increased incidence of antepartum and postpartum hemorrhage compared with control pregnancies.¹ Medication intensity was not a contributing factor. Congenital anomalies were identified in 7.7% of infants born to mothers without asthma and to 6.0% of gravidas with asthma who did not use medications, 8.5% of gravidas using just β -adrenergic agonists, and in 6.2% of gravidas requiring corticosteroids and β -adrenergic agonists.¹ This study suggests that asthma during pregnancy could be associated with an increased incidence of antepartum or postpartum hemorrhages. The mechanism of this observation, if correct, remains speculative.

In what was described as representative of the "real world," pregnancy outcomes from 2289 women with asthma were compared with 9156 controls.⁷ Singleton births from 1989 to 1992 in New Jersey were identified from an administrative database of birth certificates, infant death certificates, and hospital discharges for mothers and neonates.⁷ The prevalence of asthma on the hospital discharges was just 0.5% from 447,963 singleton live births.⁷ One could speculate that this number is an underestimate. Asthma was associated with low birth weight, slower intrauterine growth, maternal complications of preterm labor, placenta previa, pre-eclampsia, and hypertension during pregnancy, and increased incidence of cesarean deliveries.⁷ Neonatal hospital stay of more than 3 days occurred in 44.7% of neonates if the mother had asthma, versus 31.7% if the mother did not have asthma listed.⁷ There was a modest increased risk of congenital anomalies in neonates born to women with asthma (6.4% versus 4.9% of controls).⁷ The methodology of this study did not provide information about control of asthma, severity of asthma, episodes of status asthmaticus, and whether asthma specialists were involved with management. Nevertheless, the findings are consistent with some previous studies where, as a group, maternal

and fetal complications were increased in pregnancies complicated by asthma.^{1, 4, 12, 28}

SPECIFIC MANAGEMENT OF SEVERE ASTHMA

Under ideal circumstances, a woman with asthma contemplating a pregnancy should discuss this issue with her physician, who should inquire as to the status of her medical conditions and make referrals to specialists if indicated. For example, hypertension, diabetes mellitus, smoking status, or asthma should be addressed so that, before conception, the woman's health status is maximized. Because many pregnancies are unplanned or the goals of having maternal medical status as optimal as possible is still relevant but often must be addressed after conception has occurred. Some goals of management of asthma include the following:

- No hospitalizations for asthma or a maternal death from asthma
- Avoid emergency room visits
- Appropriate medications
- Communication with gravida and other physicians
- Plan for intensification of therapy for worsening of asthma
- Healthy infant without congenital anomalies

If the gravida has acute wheezing dyspnea from an exacerbation of asthma or persistent severe asthma and presents in the office, a short course of prednisone likely will be necessary to improve respiratory status and reduce coughing episodes that can be associated with oxygen desaturation (Box 2).

Box 2. Example of Status Asthmaticus with Oxygen Desaturation

- 39-year-old gravida of 19 weeks' gestation is admitted in status asthmaticus
 - Blood pressure is 160/90; pulse 140 bpm; respirations 30 with use of accessory muscles of respiration
 - One albuterol metered dose inhaler canister was being used weekly (200 actuations)
- Room air: $pO_2 = 62$ mm Hg
 $pCO_2 = 25$ mm Hg
 $pH = 7.47$
 O_2 saturation = 90%
- Peak expiratory flow rate = 220 L/min; after albuterol = 220 L/min
 - Vital capacity = 750 mL
 - After 48 hours of albuterol and methylprednisolone,
vital capacity = 2200 mL
 O_2 saturation = 95%; after coughing five times while sitting in bed,
 O_2 saturation = 86%

Such a regimen is indicated and is not deleterious to the mother or fetus.^{3, 10, 16, 17, 22, 27} There is the possibility that prednisone of 40 to 60 mg as a single daily dose may induce gestational diabetes. Overall, the maternal-fetal gradients are as follows: betamethasone 3:1, cortisol (hydrocortisone) 5.8:1, and prednisone/prednisolone 10:1. Because acute severe asthma can be expected to cause maternal arterial hypoxemia, which may be a threat to the developing fetus, reversal of exacerbations and control of asthma must be achieved. Prednisone may be administered to suppress asthma-related wheezing that may or may not be symptomatic; in the latter case, it is identified by spirometry, where the FEV₁ is excessively decreased. Usually, a short course of 5 to 7 days is sufficient, and then moderate- to high-dose inhaled corticosteroid treatment can be used along with albuterol.^{10, 14, 17} Some gravidas will clear with the short course of prednisone but will develop cough, dyspnea, or wheezing such that inhaled corticosteroids are not sufficient to control the patient adequately. In some cases, alternate-day prednisone will be indicated in this setting. There are no convincing data that prednisone in human pregnancies is teratogenic.^{3, 5, 10, 14, 17, 22, 27} A physician may want to refer the gravida with severe or moderately severe asthma to an asthma specialist if he or she is uncomfortable managing such women. There are a growing number of publications demonstrating improved outcomes or cost savings when an allergist-immunologist participates in care of nongravid women with asthma.^{2, 9, 31} Alternatively, assigning a physician to a patient with difficult-to-manage asthma and creating an environment to minimize hospitalizations was successful in a study of indigent patients using general internists.²⁰ In management of gravidas with severe asthma or acute exacerbations of asthma requiring emergency room care, some of the coexisting conditions that may complicate asthma management may make ideal maternal-fetal outcomes impossible. Indeed, fetal demise, stillbirths, and maternal deaths may occur because of uncontrolled asthma during pregnancy.^{12, 18}

If the gravida is examined in the emergency room because of severe asthma, consideration should be given to reversing the asthma as quickly as possible, assessing the status of the fetus, providing discharge planning with follow-up care, and in nearly all cases, administering a course of prednisone (40–60 mg daily, usually as a single morning dose) for the next 5 to 7 days. The latter helps prevent a return to the hospital or emergence of status asthmaticus. The gravida may have arterial hypoxemia, acid-base abnormalities, dehydration, or chest pain in association with wheezing dyspnea from an asthma exacerbation. Chest pain does not accompany asthma exacerbations, so its presence should raise the possibility of community-acquired pneumonia, pulmonary infarction, rib fracture from coughing, pleurisy, or rarely, pneumomediastinum or pneumothorax.

If the gravida does not improve sufficiently with systemic corticosteroids (intravenous methylprednisolone 40–60 mg stat or prednisone 60 mg orally) and β -adrenergic agonists or two injections of epinephrine 0.3 mL of a 1:1000 concentration, the patient is in status asthmaticus and

hospitalization is indicated. Oxygen should be administered. Some issues that need to be considered in management of such gravidas include the following:

- Gain control of maternal asthma rapidly
- This episode may be new onset of asthma or potentially fatal asthma or malignant potentially fatal asthma
- Lack of effectiveness of β -adrenergic agonists, theophylline, ipratropium bromide, inhaled corticosteroids, and leukotriene inhibitors
- Fetal assessment
- Prevention of future episodes of status asthmaticus
- Arrange outpatient care

OUTPATIENT MANAGEMENT OF SEVERE ASTHMA

Outpatient management of gravidas with severe asthma during pregnancy should include control of asthma to avoid nocturnal coughing and wheezing, permit satisfactory exercise activities, achieve satisfactory respiratory status and function, avoid prolonged periods of asthma exacerbations, have an emergency plan in place for asthma exacerbations, and provide advice on appropriateness of medications. Allergy-immunology consultation can be helpful in providing confirmation or exclusion of IgE-mediated triggers of asthma, helping to diagnose and treat sinusitis, gastroesophageal reflux, or allergic bronchopulmonary aspergillosis that may be a trigger of asthma, and improving use of metered dose inhalers or other medications for asthma. Chest physicians can be of help to the grvida with severe asthma as well, and series are being reported of cystic fibrosis during pregnancy.¹¹

Medications recommended for management of gravidas with severe asthma during pregnancy include albuterol,^{14, 22, 25} beclomethasone dipropionate,^{10, 15, 17, 22} prednisone or methylprednisolone,^{16, 22, 27} cromolyn,^{16, 22} theophylline^{16, 22} (although it is used less now), and, in malignant potentially fatal asthma,⁸ depot methylprednisolone. All of these medications have proved safe in human pregnancies and are not considered to be teratogenic. In terms of alternative inhaled corticosteroids, the very nature of the topical route of drug delivery, the microgram quantities of drug administered, and the safety of beclomethasone dipropionate should imply potential safety of the other inhaled corticosteroids. Budesonide was administered to 102 gravidas seemingly at conception, and neither it nor beclomethasone dipropionate in 157 gravidas was associated with congenital malformations.²⁹ There is a paucity of published human data, but some data with other inhaled corticosteroids are being collected by way of a registry.¹⁹ It would seem that the most experience with inhaled corticosteroids during pregnancy is with beclomethasone dipropionate and budesonide, and data would support their appropriate use. Avoidance of asthma exacerbations must be the

goal to avoid deleterious effects of maternal hypoxemia and either acute respiratory alkalosis or acute respiratory acidosis on the developing fetus and the gravida herself. In a randomized, controlled study, inhaled beclomethasone dipropionate has been shown to reduce acute asthma exacerbations during pregnancy.³⁰

The leukotriene antagonists, zafirlukast and montelukast, are listed as pregnancy category B and may result in reduced inhaled corticosteroid dose or even reduced prednisone requirements. Zileuton, which blocks 5-lipoxygenase activity, is labeled as pregnancy category C. None of these leukotriene modifiers are absolutely essential in the management of severe asthma during pregnancy, and the author could not obtain pregnancy experiences with them to verify appropriateness during pregnancy. Their use would have to be in special situations until safety data are accumulated. A new medication might have adverse effects in pregnancy that are not present when administered in the nongravid state. Thus, caution is advised.

Nedocromil is listed as pregnancy category B and inhibits early and late bronchoconstriction following allergen inhalation. It also has no published data and was not recommended for administration by the Working Group on Asthma and Pregnancy.

Ipratropium bromide, a topically active anticholinergic agent, would seem to be suitable for use in pregnancy, as it is truly topical in its activity. Nevertheless, there appear to be few gravidas with severe asthma who would benefit from its use on a chronic basis when it is added to a regimen of beclomethasone dipropionate or budesonide with albuterol with or without alternate-day prednisone. It is not contraindicated either for acute use in the emergency room or hospital or for maintenance therapy.

OTHER MODALITIES

Annual influenza immunization is recommended and is administered in the second or third trimester. Allergen immunotherapy can be continued during gestation without untoward effects on the mother or fetus (assuming no severe anaphylaxis occurs from injections).²¹ Gravidas must stop cigarette smoking and not use illicit drugs that could prove fatal.¹⁸ Antibiotics for acute or chronic sinusitis include penicillins, preferably older before newer cephalosporins, and erythromycin or azithromycin. The latter is listed as pregnancy category B whereas clarithromycin is category C. Clarithromycin and erythromycin can slow theophylline elimination. Quinolones and tetracyclines should be avoided, and many physicians avoid use of sulfonamides throughout pregnancy. Sulfonamides especially should be avoided in the last trimester, as they may result in hemolytic anemia in the newborn. Intranasal beclomethasone dipropionate or budesonide can assist with decreasing allergic nasal inflammatory obstruction of the sinus ostia.

Another modality is communication. The physician managing a

gravida with severe asthma needs to have communicated with the patient and, in some situations, the physician managing the pregnancy.²³ Lack of communication between patient and physician should be avoided as much as possible. Regrettably, gravidas who disregard physician advice and do not increase their medications when an exacerbation occurs may die or have a stillborn fetus because of the ill effects from inadequately controlled asthma during pregnancy. Fortunately, effective control of severe asthma can result in normal pregnancy outcomes, and that remains the goal, even if it is not achievable in all cases.

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