

Maternal-Fetal Medicine Units (MFMU) studies of inhaled corticosteroids during pregnancy

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Few prospective clinical trials exist to address the use of asthma medications during pregnancy in relation to neonatal outcomes. There is a need to identify favorable pregnancy outcomes in relation to the successful treatment of pregnant women with asthma. To this end, 3 studies have been initiated: (1) a retrospective analysis of inhaled steroid use in a maternal-fetal medicine research center, (2) a large observational cohort study assessing the effects of different types of asthma treatments on perinatal outcomes, and (3) a randomized clinical trial comparing theophylline and inhaled beclomethasone in the treatment of pregnant women with moderately severe asthma. Preliminary information on all 3 studies is described. (*J Allergy Clin Immunol* 1999;103:S356-9.)

There is clearly a need for more information regarding the successful treatment of pregnant women with asthma and favorable pregnancy outcomes. Toward this effort, we have initiated 3 studies: (1) a retrospective analysis of inhaled steroid use in one maternal-fetal medicine research center, (2) a large observational cohort study to evaluate the effects of asthma treatment regimens on perinatal outcome, and (3) a randomized clinical trial comparing theophylline and inhaled beclomethasone in the treatment of pregnant women with moderate asthma. These latter 2 studies are being conducted by the Maternal Fetal Medicine Units Network (a group, listed in Appendix 1, of clinical centers conducting trials and observational studies in maternal-fetal medicine), jointly supported by the National Heart, Lung, and Blood Institute and the National Institute of Child Health and Human Development. This article describes the retrospective study and the methodological issues related to the prospective studies; final results of these latter studies are not yet available.

PRELIMINARY DATA ON INHALED STEROID USE DURING PREGNANCY

Approximately 1.5 years of data, entered prospectively into a database, was retrospectively analyzed for asthma

medication use, asthma control, and pregnancy outcome.¹ Subpopulations of women who had received long-term treatment with either the inhaled steroid triamcinolone acetonide ($n = 16$) or beclomethasone ($n = 14$) or with oral theophylline ($n = 25$) were identified. These 3 groups were well matched for age (mean ages between 25 ± 6 and 26 ± 7 years) and ethnicity (African descent constituted 68% for theophylline to 80% for triamcinolone acetonide). The maternal and neonatal outcome data are provided in Table I.

Because patient numbers in these 3 treatment groups were small, the information to be drawn from these clinical end points is limited. As with other retrospective studies, there are confounding factors (eg, patients were not matched for asthma severity and varied exposure to systemic steroids) that limit interpretation of the results.

Although the average birth weight in the beclomethasone group was approximately 500 g less than that in the triamcinolone group, the difference was not statistically significant ($P > .05$). There were no clinically important differences between the groups for gestational age or 5-minute Apgar scores, and the cord arterial pH was normal in all groups. Number of days in the neonatal intensive care unit differed between the groups, but because of the limited number of subjects, statistical analysis of these results was not conducted.

A statistically significant difference ($P < .05$) was observed for the rate of hospital admission for treatment of an asthma exacerbation between triamcinolone acetonide (33%) and beclomethasone (79%) groups. The overall admission rate for all 3 groups was 42.6%, which compares favorably with Mabie's 42.5%.² A trend, but not statistically significant between-group difference in the use of oral steroids was observed, although from the available data, it is not known whether the patients received oral steroids specifically for the treatment of asthma exacerbations or for general asthma control.

From these preliminary results, there are several important observations regarding the use of asthma treatments in pregnancy. Triamcinolone use during pregnancy was not associated with increased asthma-related hospitalizations or with decreased birth weight compared with beclomethasone. In fact, there was a trend for larger birth weights in the triamcinolone group compared with the beclomethasone group. Patients in the triamcinolone group required fewer hospitalizations for treatment of asthma exacerbations than patients treated with beclomethasone. Additional information is needed to more fully understand these observations. A randomized

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TABLE I. Maternal and neonatal outcomes

	Triamcinolone acetonide (n = 15)	Beclomethasone (n = 14)	Theophylline (n = 25)
Mother			
Term*	1.1 ± 1.1	1.4 ± 1.6	1.1 ± 1.0
Preterm†	0.2 ± 0.5	0.1 ± 0.3	0.2 ± 0.7
Systemic steroids‡	5 (33%)	9 (64%)	4 (16%)
Admitted to hospital§	5 (33%)	11 (79%)	7 (28%)
Total admissions	8	18	10
Neonate			
Birth weight (g)	3300 ± 678	2798 ± 759	2984 ± 826
Gestational age at delivery (wk)	39.2 ± 2.0	38.0 ± 3.1	37.8 ± 3.9
Apgar score at 5 min	8.8 ± 0.9	8.6 ± 0.9	8.7 ± 0.6
Cord arterial pH	7.27 ± 0.07	7.24 ± 0.11	7.24 ± 0.09
NICU days	2.7 ± 7.0	4.8 ± 9.4	6.2 ± 17.0

Data are presented as incidence (%) or mean ± SD.

NICU, Neonatal intensive care unit.

*Previous deliveries ≥37 weeks' gestation.

†Previous deliveries <37 weeks' gestation.

‡Systemic steroid use during pregnancy.

§P < .05 when compared with triamcinolone acetonide group.

||At least once because of asthma exacerbation.

clinical trial would provide a more accurate and controlled assessment of these effects.

PROSPECTIVE COHORT STUDY

The results of previous studies in pregnant women with asthma have suggested that asthma is associated with an increased risk of perinatal death, premature birth, low birth weight, neonatal hypoxia, and cesarean delivery (see "Interrelationships between asthma and pregnancy: A literature review," in this supplement). The Maternal-Fetal Medicine Units Network has undertaken an observational cohort study to determine whether the frequency of preterm delivery (ie, delivery at less than 32 weeks' gestation) is higher among patients with moderate to severe asthma than among nonasthmatic control subjects. The secondary objectives are to determine: (1) whether the incidence of preeclampsia and maternal morbidity is higher for patients with asthma; (2) whether there is an increased risk of "small-for-gestational-age" infants (or low birth weights) born to mothers with asthma (the incidence of premature rupture of the membranes, cesarean section rate, gestational diabetes, perinatal death, and other neonatal morbidities is also being assessed); and (3) whether adverse outcomes can be related to asthma control, severity, or treatment.

There are 3 cohorts in this prospective study: control patients, patients with mild asthma, and patients with moderate-to-severe asthma. Within each center, the control cohort is group-matched to the moderate-to-severe cohort for smoking status and race, and the mild asthma cohort is matched for smoking status. For all groups, ges-

TABLE II. Asthma self-management algorithm provided to study patients

The patients will be instructed to follow the following steps in case of increased symptoms:

1. Inhale albuterol 2 to 4 puffs, wait 20 minutes, and obtain peak flow rate.
2. If peak flow rate remains less than 50% of personal best, contact physician or go for emergency care.
3. If peak flow rate is greater than 80% of personal best, continue inhaled albuterol 2 to 4 puffs every 3 to 4 hours for 6 to 12 hours as needed.
4. If peak flow rate is still 50% to 80% of personal best 20 minutes after first treatment, repeat albuterol treatment and wait another 20 minutes.
5. If peak flow rate remains 50% to 80% of personal best, contact clinic or caregiver or go for emergency care.

tational age must be less than 26 weeks on entry into the study, with no lower limit. Exclusion criteria for entry include: multifetal gestation, major fetal anomaly or fetal demise, imminent danger of delivery, pulmonary disease other than asthma, oral steroid use for indications other than asthma, or inability to perform adequate follow-up throughout the entire pregnancy. For purposes of the study, severe asthma is defined as the regular use of oral steroids (at least 1 dose every other day) for 4 weeks before screening and/or an FEV₁ less than 60% predicted. Patients are classified as having moderate asthma if they have had one or more of the following: symptoms for at least 8 days (excluding upper respiratory tract infections) of the 4 weeks before screening, use of regular asthma medication(s) (not including oral steroids), or an FEV₁ value between 60% and 80% predicted. Patients are classified as having mild asthma if they have experienced some asthma symptoms in the past 6 months but have had less than 8 days with symptoms during the 4 weeks before entry and an FEV₁ of at least 80% predicted. The control group includes patients with no history of asthma.

Sample size calculation was based on the comparison of the moderate cohort with the control cohort. For the end point of preterm delivery rate (delivery at less than 32 weeks' gestation), sample size was calculated based on a projected incidence of preterm delivery of between 2% and 3% in the control cohort. The sample size was then calculated to be large enough to show relative risk of 2.3 for preterm delivery. When a power of 80% with type I error of 5%, 2-sided, was used, a sample of 900 patients in each of the 3 groups was determined.

At the initial screening visit, patients are interviewed for eligibility, a dating sonogram is performed (if not previously done), and spirometry is conducted (at least 4 hours after bronchodilator use) to classify the patient's asthma severity. A stress assessment questionnaire is administered, and asthma management is assessed. Patients enrolled in the moderate-severe cohort group are expected to visit the investigational centers every 4 weeks for spirometry and review of medication use and

asthma exacerbations. In all cohorts, information is collected at labor and delivery, and neonatal data are collected up to the point of discharge. For the asthma cohorts, a postpartum assessment is conducted to obtain data from the period of the last study visit through delivery. As of March 1998, 807 women with moderate-severe asthma, 813 women with mild asthma, and 815 control women have entered the Observational Cohort Study.

RANDOMIZED CLINICAL TRIAL

Well-designed randomized trials provide the most rigorous evaluation of specific issues related to use of a pharmacologic agent because of their identification of the appropriate patient population, controlled use of treatments, minimization of the introduction of confounding factors, and prospective collection of data. We are using an ongoing randomized trial design to compare the use of inhaled beclomethasone with theophylline for controlling moderate asthma during pregnancy. The primary end points are maternal asthma exacerbations requiring hospitalization, emergency visits, or administration of oral corticosteroids. Secondary outcomes include asthma symptom frequency, rescue β -agonist use, peak flow rates, quality of life, maternal pregnancy complications, and fetal outcome.

This study is a multicenter, double-blind, randomized clinical trial. Qualified patients are randomly assigned to treatment with either (1) theophylline, 400 to 800 mg every day (to achieve serum levels between 8 and 12 μ g/mL), and placebo inhaler or (2) beclomethasone, 4 puffs 3 times daily, and placebo capsules. Inhaled albuterol is allowed as needed to control acute asthma symptoms, and oral corticosteroids are used for severe exacerbations. Subjects with moderate asthma (as defined in the Observational Cohort Study) who are less than 26 weeks' gestation at randomization are candidates for the study. Exclusion criteria for this study include preeclampsia or gestational hypertension at screening, pregestational diabetes, current use of cimetidine, coexisting maternal conditions (eg, epilepsy, liver disease, heart disease, endocrine or hematologic disorder), known allergy or sensitivity to study medications, use of more than 4 courses of oral steroids in the past year, use of 16 or more puffs of inhaled steroid or 600 mg or more of theophylline and 12 or more puffs of inhaled steroids daily in the 4 weeks before the study, and more than one hospital admission for treatment of asthma since the start of pregnancy. Study medication is discontinued if a hospital admission for treatment of asthma occurs or if 3 other primary outcome events (emergency visits because of asthma or oral corticosteroid courses) occur.

Spirometry is performed to obtain baseline pulmonary function data at the initial screening visit. Patients are given peak flow meters and trained in their use and are given symptom and medication diary cards. If patients qualify for randomization, they return to the clinic with-

in 14 days of the screening visit to be provided: (1) study medication and inhaler technique training; (2) a self-management algorithm (Table II), based on the personal best peak flow rate determined between the screening and randomization visits; (3) environmental control instructions and plastic pillow and mattress encasings; and (4) new diaries. A urine sample is collected for testing of cotinine levels. Patients are scheduled to return to the clinic every 2 weeks for spirometry; collection of information on asthma symptoms, exacerbations, and medication use; return of study medications; and issue of new study medications.

Adjustments for the theophylline dose are conducted as follows. Each patient begins receiving 400 mg of theophylline or matching placebo every day. The patient's status is assessed after 3 days. If she does not report symptoms of theophylline side effects, the theophylline dose is increased to 600 mg. Seven days after increasing the dose to 600 mg, the patient's plasma theophylline levels are assessed and the results reported directly to the Biostatistical Coordinating Center. Depending on the serum theophylline level, the investigational center is notified to maintain the current dose or increase or decrease the theophylline dose by 200 mg. If the dose is changed, the serum theophylline levels are again assessed after 7 days. Additional theophylline levels are obtained around 30 and 37 weeks' gestation. An approximately equal number of theophylline dosage change messages are given to the centers by the Biostatistical Coordinating Center for patients receiving placebo. As of March 1998, 262 women with moderate asthma had entered the Randomized Clinical Trial.

CONCLUSION

Given the small number of large prospective clinical trials that have been conducted, there are many issues concerning the use of asthma treatment in pregnancy and neonatal outcome that have not been investigated. It is hoped that the current ongoing studies will help to answer some of the most important current questions regarding the treatment of asthma during pregnancy. It is probable that additional well-designed studies will be necessary to answer all of the relevant questions.

REFERENCES

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APPENDIX 1

Clinical Centers Currently Participating in Maternal-Fetal Medicine Units Network

Magee-Womens Hospital, Pittsburgh, Pennsylvania
Ohio State University, Columbus, Ohio
Thomas Jefferson University, Philadelphia, Pennsylvania

University of Alabama-Birmingham, Birmingham,
Alabama
University of Chicago, Chicago, Illinois
University of Cincinnati, Cincinnati, Ohio
University of Miami, Miami, Florida
University of Tennessee, Memphis, Tennessee

University of Texas-San Antonio, San Antonio, Texas
University of Texas-Southwestern, Dallas, Texas
University of Utah, Salt Lake City, Utah
Wake Forest University School of Medicine,
Winston-Salem, North Carolina
Wayne State University, Detroit, Michigan