

Are inhaled corticosteroids taken during pregnancy harmless?

Catherine Lemiere, MD, MSc, and Lucie Blais, PhD Montreal, Quebec, Canada

Key words: Asthma, pregnancy, corticosteroids

Asthma is a frequent condition encountered during pregnancy.^{1,2} Uncontrolled asthma has been associated with several maternal and infant adverse outcomes, such as pregnancy-induced hypertension,^{1,3} retarded growth of the fetus,^{4,5} and stillbirth.^{3,4} It is recommended that pregnant women with persistent asthma take antiasthmatic medication to maintain adequate control of their asthma. In fact, 4% to 7% of women take asthma medication while pregnant.⁶ Establishing the respective risk of an adverse outcome caused by asthma medication or asthma severity is difficult because subjects with severe asthma, uncontrolled asthma, or both are usually treated with inhaled corticosteroids (ICSs), with or without add-on therapy. The effect of asthma medication during pregnancy has been scarcely studied. The nature of the population to study greatly limits the type of studies that can be performed. Large randomized controlled trials are difficult to perform in this population because of ethical concerns and the difficulty in identifying a large number of potential participants.

In this issue of the *Journal*, Bakhrieva et al⁷ assessed the effect of asthma medication use on fetal growth during pregnancy. They compared the mean birth weight, length, and head circumference in full-term infants and the incidence of small for gestational age (SGA) in all infants born to asthmatic women who used inhaled or systemic corticosteroids compared with the incidence in asthmatic women using exclusively β_2 -agonists and nonasthmatic control subjects. The authors performed telephone interviews with 957 women who participated in a prospective multicenter controlled cohort study of asthma medication

Abbreviations used

ICS: Inhaled corticosteroid

SGA: Small for gestational age

use during pregnancy, which was conducted between 1998 and 2003 by the Organization of Teratology Information Services. The participants were classified into 4 groups: 438 pregnant women taking ICSs but not systemic steroids with or without other asthma medications (ICS group); 113 pregnant women taking systemic steroids with or without other asthma medications any-time during pregnancy (systemic corticosteroid group); 103 pregnant women who exclusively used β_2 -agonists throughout pregnancy (asthmatic control group); and 303 pregnant women who were nonasthmatic control subjects. Telephone interviews were performed at enrolment; at 20, 26, 32, and 38 weeks' gestation; and within 4 to 6 weeks after delivery. During these interviews, the authors collected data on demographic characteristics, medical and pregnancy history, and asthma control and medication use. These interviews were complemented by the review of the maternal and infant medical records. Although the infants of the women taking ICSs during pregnancy did not have a lower birth weight compared with those of the control subjects, there was a significant decrease of about 200 g in birth weight in the pregnant women taking systemic steroids compared with that seen in the control subjects and exclusive β_2 -agonist users.

Bakhrieva et al⁷ should be commended for performing a study with a relatively large sample size of pregnant asthmatic women, who are a challenging population to study. Although this study has its merits, it also has important limitations. Therefore the findings need to be interpreted cautiously.

The population was characterized through telephone interviews, and thus asthma severity could not be accurately assessed. The population taking oral steroids had poorly controlled asthma and was likely to have much more severe disease than the other groups. Therefore even if the authors adjusted for the control of asthma in their analysis, it is impossible to conclude with certainty that the reduction in birth weight observed in this group was only caused by oral steroids because asthma severity, which is a major confounding factor, was not taken into account.

From Hôpital du Sacré-Coeur de Montréal, University of Montreal.

C. L. and L. B. are scholars of the Canadian Institutes of Health Research.

L. B. holds the Endowment pharmaceutical chair AstraZeneca in respiratory health.

Disclosure of potential conflict of interest: C. Lemiere—none disclosed.

L. Blais—none disclosed.

Received for publication June 9, 2005; accepted for publication June 13, 2005. Available online August 1, 2005.

Reprint requests: Catherine Lemiere, MD, MSc, Department of Chest Medicine, Sacré-Coeur Hospital, 5400 West Gouin, Montreal, Quebec, Canada, H4J 1C5. E-mail: catherine.lemiere@umontreal.ca.

J Allergy Clin Immunol 2005;116:501-2.

0091-6749/\$30.00

© 2005 American Academy of Allergy, Asthma and Immunology

doi:10.1016/j.jaci.2005.06.009

Asthma treatment was self-reported by the pregnant women obtained through the telephone interview process and verified by their medical records. It is well known that compliance to ICS use is a major problem in patients with asthma.⁸⁻¹¹ Preliminary data suggest that poor compliance is also a major issue during pregnancy (Lucie Blais, personal data). The medical records indicated what was prescribed to the women, but there was no objective measure, such as pharmacy printouts, to ensure that the patient had actually purchased the prescribed medication. Therefore the treatment reported by the patients might have been overestimated, and the lack of effect on birth weight in the ICS group might be due to the fact that the women were receiving a much lower dose than the one actually reported, which corresponded to the prescribed dose.

Finally, this study is underpowered to show the potential effect of inhaled steroids on SGA birth weight. This study has only a 22% power to show a 2-fold increase in the risk of SGA birth weight in the ICS group compared with in the exclusive β_2 -agonist group, assuming a rate of SGA of 3.9% in the exclusive β_2 -agonist group, and a 27% power to show a 1.55-fold increase in the risk of SGA birth weight in the ICS group compared with that in the nonasthmatic control group, assuming a rate of SGA of 5% in the nonasthmatic control group. Moreover, with only 4 cases of birth weight of the 10th percentile or less in the exclusive β_2 -agonist group, the statistical adjustment for potential confounding variables in the logistic regression analysis might easily be inadequate. Because of the lack of statistical power to detect clinically significant differences, the results of this study should be interpreted cautiously.

In conclusion, ICSs are still the best treatment to control asthma and do not seem to significantly impair fetal growth. However, before ruling out with confidence any potential adverse effect of ICSs on fetal growth, there is a need for larger studies adequately powered to answer this question.

REFERENCES

1. Nelson-Piercy C. Asthma in pregnancy. *Thorax* 2001;56:325-8.
2. Campbell LA, Klocke RA. Implications for the pregnant patient. *Am J Respir Crit Care Med* 2001;163:1051-4.
3. Passalacqua G, Albano M, Canonica GW, Bachert C, van Cauwenberge P, Davies RJ, et al. Inhaled and nasal corticosteroids: safety aspects. *Allergy* 2000;55:16-33.
4. Lipkowitz MA, Schatz M, Cook TJ, Ford L, Frankel SJ, Gluck J, et al. When allergies and asthma complicate pregnancy. *Ann Allergy Asthma Immunol* 1998;81:30-4.
5. Tan KS, Thomson NC. Asthma in pregnancy. *Am J Med* 2000;109:727-33.
6. Schatz M. Asthma treatment during pregnancy. What can be safely taken? *Drug Saf* 1997;16:342-50.
7. Bakhireva LN, Jones KL, Schatz M, Johnson D, Chambers CD. Asthma medication use in pregnancy and fetal growth. *J Allergy Clin Immunol* 2005;116:503-9.
8. Dorais M, Blais L, Chabot I, LeLorier J. Treatment persistence with leukotriene-receptor antagonists and inhaled corticosteroids. *J Asthma* 2005;42:385-93.
9. Cochrane MG, Bala MV, Downs KE, Mauskopf J, Ben Joseph RH. Inhaled corticosteroids for asthma therapy: patient compliance, devices, and inhalation technique. *Chest* 2000;117:542-50.
10. Jones C, Santanello NC, Boccuzzi SJ, Wogen J, Strub P, Nelsen LM. Adherence to prescribed treatment for asthma: evidence from pharmacy benefits data. *J Asthma* 2003;40:93-101.
11. Williams LK, Pladevall M, Xi H, Peterson EL, Joseph C, Lafata JE, et al. Relationship between adherence to inhaled corticosteroids and poor outcomes among adults with asthma. *J Allergy Clin Immunol* 2004;114:1288-93.