Is it safe to use inhaled corticosteroids in pregnancy?

Laura Smy Alvin C.H. Chan Pina Bozzo Gideon Koren MD FRCPC FACMT

Abstract

Question A healthy woman with mild to moderate asthma came to my clinic today after learning that she was pregnant. She inquired about continuing her inhaled corticosteroid (ICS) medication and whether there would be any risks to her unborn child if she were to do so. What would you advise?

Answer Given the published evidence, ICSs should be continued throughout pregnancy at low to moderate doses sufficient to control asthma symptoms and prevent exacerbations. However, caution must be taken with doses greater than 1000 µg/d (chlorofluorocarbon beclomethasone equivalent), although whether such doses cause adverse effects is currently still questionable. Patient education on proper ICS administration and adherence, including during the first trimester, must be ongoing. Well controlled asthma will reduce the need for higher ICS doses and possible exposure to systemic corticosteroids, and might decrease the risk of adverse pregnancy or perinatal outcomes.

This article is eligible for Mainpro-M1 credits. To earn credits, go to **www.cfp.ca** and click on the Mainpro link.

La traduction en français de cet article se trouve à **www.cfp.ca** dans la table des matières du numéro **de septembre 2014** à la **page e433**.

Asthma is a chronic inflammatory disease that frequently results in bronchial obstruction with symptoms of dyspnea and coughing.[1] It affects up to 8.4% of pregnant women in the United States[2] and, if uncontrolled, can lead to decreased fetal oxygen supply.[1] Popular inhaled corticosteroids (ICSs) currently available globally include budesonide, fluticasone propionate, beclomethasone dipropionate, triamcinolone acetonide, flunisolide, mometasone furoate, and ciclesonide.[1] To date, the number of adequately controlled studies on ICS use during pregnancy is still small. The newer ICSs, mometasone and ciclesonide, have not yet been studied in pregnancy.

Effect of asthma on pregnancy outcomes

Typically, pregnant women with asthma can experience pregnancy or perinatal complications such as intrauterine growth restriction,[3] pregnancy-induced hypertension, and delivery by cesarean section.[3,4] The literature also reports that uncontrolled asthma or asthma complicated by exacerbations in pregnancy puts women at increased risk of various complications including preterm delivery[5,6] and having small for gestational age or low-birth-weight neonates (relative risk = 3.02, 95% CI 1.87 to 4.89).[7] A small risk of congenital malformations (major and minor) has been reported for offspring of women who experience an exacerbation during the first trimester (odds ratio [OR] = 1.48, 95% CI 1.04 to 2.09).[8] Generally, asthma does not pose an increased risk of major malformations.[8-10]

Women treated with ICS therapy during pregnancy have a significantly lower risk of exacerbations when compared with women not treated with ICSs (relative risk = 0.22, 95% CI 0.11 to 0.44).[11] Use of ICSs is the preferred long-term treatment of asthma in pregnancy.[12,13]

Safety of ICSs and pregnancy outcomes

Currently, budesonide is the ICS most studied during pregnancy. Data from the Swedish birth and health registries reported no significant increase in congenital malformations in more than 10 000 exposed infants.[14] As well, no adverse outcomes were found in terms of gestational age, birth weight, birth length, or stillbirths.[15] No significant associations have been found between the use of other ICSs during pregnancy and adverse perinatal outcomes.[1,16] Meta-analyses did not find associations between use of ICSs, as a group, and increased risk of major malformations (OR = 0.96, 95% CI 0.51 to 1.83, n = 847)[16] or any congenital malformations (OR = 0.96, 95% CI 0.89 to 1.04, n = 17 220 exposed to ICSs),[10] when compared with outcomes for women with asthma not using ICSs. Further, active management of asthma was found to decrease the odds of preterm delivery.[6]

A large Canadian cohort study (n = 4392), included in the meta-analysis discussed above,[10] confirmed the safety of using low to moderate doses (0 to 1000 µg/d chlorofluorocarbon beclomethasone equivalent) of ICSs in the first trimester.[17] Of interest, they also included a cohort of women taking high-dose ICSs

(>1000 µg/d, n=154), and although they reported no increased risk of major malformations, they did report a small but statistically significant higher risk of having a baby with congenital malformations (major and minor) compared with those who used 1000 µg/d or less (adjusted risk ratio=1.63, 95% CI 1.02 to 2.60).[17] Women with moderate to severe asthma would likely be prescribed high-dose ICSs and experience increased exacerbations, which can confound the effects found with the high-dose ICSs. As a result, it is difficult to distinguish the effects of asthma from those of ICS use.

Oral corticosteroids have been associated with an increased risk of oral clefts, particularly cleft palate.[18] However, a case-control study examining the association between corticosteroids and oral clefts in the offspring of women using ICSs during pregnancy, including nasal sprays, did not report an increased risk of these birth defects.[19] Further, a large Danish study compared outcomes for women who used ICSs in early pregnancy (n=1223) with those not exposed (n=80950), and the results did not identify an increased risk of oral clefts (0.08% vs 0.2%).[20]

One study followed children born to women with asthma treated with ICSs up to a median age of 6.1 years (range 3.6 to 8.9 years, n=1231).[21] Budesonide, and all ICSs used, were associated with an increased risk of endocrine and metabolic disorders; however, there was no association with 14 other disease categories.[21] The study did not report the details of the disorders or account for asthma severity, oral corticosteroid use, or low birth weight, which might confound the results.[22,23] The use of ICSs was still supported by the authors, and they emphasized the need for continued research.[21]

Education, adherence, and technique

Despite research supporting the use of ICSs during pregnancy, scepticism still exists among patients and their caregivers.[24] It has been estimated that only 15% of those with asthma have good adherence, and 56% have poor adherence.[25] In fact, it appears that 23% to 36% of women discontinue ICS use in their first or second trimester.[26,27] This drop is thought to exist because oral corticosteroids are known to increase the risk of oral clefts.[18] Besides the concerns discussed above with asthma and asthma exacerbations during pregnancy, discontinuation of treatment has been associated with perinatal consequences, as reported by a Danish study that followed 108 women prescribed ICSs during their pregnancies. The women who discontinued or decreased their ICSs when they became pregnant (n=22, 20.4%) gave birth to offspring with decreased adjusted mean birth weight and birth length compared with women who adhered to ICS therapy.[28] Thus, it is important to educate women with asthma, who are or who might become pregnant, to reassure them about the safety of ICS use during all trimesters of pregnancy.

In addition to understanding the need for adherence, it is equally important to educate patients on proper inhalation technique. Luskin et al estimated that only 24% of those who used metered-dose inhalers used proper technique, compared with 63% of those using turbo-inhalers or 96% of those using disk-inhalers; regardless, most users receive less than 50% of the dose.[25] Technique errors include improper timing of inhalation with inhaler actuation or not holding the breath long enough after inhalation (10 seconds).[25] Poor technique might increase swallowing of the ICS, thus reducing the amount reaching the lungs.[29] This might render the treatment ineffective, leading to exacerbations requiring administration of systemic corticosteroids.

Conclusion

Given the current research, it is still difficult to distinguish if effects on pregnancy and outcomes noted among women treated with ICSs are due to the underlying disease or the treatment, but there is substantial evidence that ICSs do not

increase the risk of congenital malformations and that they are safe to use throughout pregnancy at low to moderate doses. The ICS should be used at the lowest effective dose to control asthma symptoms and prevent exacerbations. More research is needed to understand the safety of high doses of ICSs and whether there are any long-term adverse effects for the children.

Competing interests
None declared

References

1. Rocklin RE. Asthma, asthma medications and their effects on maternal/fetal outcomes during pregnancy. *Reprod Toxicol* 2011;32(2):189-97.
2. Kwon HL, Belanger K, Bracken MB. Asthma prevalence among pregnant and childbearing-aged women in the United States: estimates from National Health Surveys. *Ann Epidemiol* 2003;13(5):317-24.
3. Sheiner E, Mazor M, Levy A, Wiznitzer A, Bashiri A. Pregnancy outcome of asthmatic patients: a population-based study. *J Matern Fetal Neonatal Med* 2005;18(4):237-40.
4. Liu S, Wen SW, Demissie K, Marcoux S, Kramer MS. Maternal asthma and pregnancy outcomes: a retrospective cohort study. *Am J Obstet Gynecol* 2001;184(2):90-6.
5. Bakhireva LN, Schatz M, Jones KL, Chambers CD; Organization of Teratology Information Specialists Collaborative Research Group. Asthma control during pregnancy and the risk of preterm delivery or impaired fetal growth. *Ann Allergy Asthma Immunol* 2008;101(2):137-43.
6. Murphy VE, Namazy JA, Powell H, Schatz M, Chambers C, Attia J, et al. A meta-analysis of adverse perinatal outcomes in women with asthma. *BJOG* 2011;118(11):1314-23.
7. Namazy JA, Murphy VE, Powell H, Gibson PG, Chambers C, Schatz M. Effects of asthma severity, exacerbations and oral corticosteroids on perinatal outcomes. *Eur Respir J* 2013;41(5):1082-90.
8. Blais L, Forget A. Asthma exacerbations during the first trimester of pregnancy and the risk of congenital malformations among asthmatic women. *J Allergy Clin Immunol* 2008;121(6):1379-84, 1384.e1. Epub 2008 Apr 14.
9. Tata LJ, Lewis SA, McKeever TM, Smith CJ, Doyle P, Smeeth L, et al. Effect of maternal asthma, exacerbations and asthma medication use on congenital malformations in offspring: a UK population-based study. *Thorax* 2008;63(11):981-7.
10. Murphy VE, Wang G, Namazy JA, Powell H, Gibson PG, Chambers C, et al. The risk of congenital malformations, perinatal mortality and neonatal hospitalisation among pregnant women with asthma: a systematic review and meta-analysis. *BJOG* 2013;120(7):812-22.
11. Stenius-Aarniala BS, Hedman J, Teramo K. Acute asthma during pregnancy. *Thorax* 1996;51(4):411-4.
12. Busse WW, Cloutier M, Dombrowski MP, Nelson HS, Reed M, Schatz M, et al. *NAEPP working group report on managing asthma during pregnancy: recommendations for pharmacologic treatment. Update 2004*. Bethesda, MD: National Institutes of Health; 2005. Available from: **www.nhlbi.nih.gov/health/prof/lung/asthma/astpreg/astpreg_full.pdf**. Accessed 2013 Dec 2.
13. Global Initiative for Asthma [website]. *Pocket guide for asthma management and prevention. Updated 2012*. Bethesda, MD: Global Initiative for Asthma; 2012. Available from: **www.ginasthma.org/local/uploads/files/GINA_Pocket2013_May15.pdf**. Accessed on 2013 Dec 2.
14. Källén B, Otterblad Olausson P. Use of anti-asthmatic drugs during pregnancy. Congenital malformations in the infants. *Eur J Clin Pharmacol* 2007;63(4):383-8.
15. Norjavaara E, de Verdier MG. Normal pregnancy outcomes in a population-based study including 2968 pregnant women exposed to budesonide. *J Allergy Clin Immunol* 2003;111(4):736-42.
16. Rahimi R, Nikfar S, Abdollahi M. Meta-analysis finds use of inhaled corticosteroids during pregnancy safe: a systematic meta-analysis review. *Hum Exp Toxicol* 2006;25(8):447-52.
17. Blais L, Beauchesne MF, Lemiere C, Elftouh N. High doses of inhaled corticosteroids during the first trimester of pregnancy and congenital malformations. *J Allergy Clin Immunol* 2009;124(6):1229-34.e4.
18. Park-Wyllie L, Mazzotta P, Pastuszak A, Moretti ME, Beique L, Hunnisett L, et al. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. *Teratology* 2000;62(6):385-92.
19. Carmichael SL, Shaw GM, Ma C, Werler MM, Rasmussen SA, Lammer EJ. Maternal corticosteroid use and orofacial clefts. *Am J Obstet Gynecol* 2007;197(6):585.e1-7.
20. Bay Bjørn AM, Ehrenstein V, Hundborg HH, Nohr EA, Sørensen HT, Nørgaard M. Use of corticosteroids in early pregnancy is not associated with risk of oral clefts and other congenital malformations in offspring. *Am J Ther* 2014;21(2):73-80.
21. Tegethoff M, Greene N, Olsen J, Schaffner E, Meinlschmidt G. Inhaled glucocorticoids during pregnancy and offspring pediatric diseases: a national cohort study. *Am J Respir Crit Care Med* 2012;185(5):557-63.
22. Barne M, Brashier B, Kodgule R, Apte K, Salvi S. Is it really time to reconsider use of inhaled corticosteroids for control of asthma in pregnancy? *Am J Respir Crit Care Med* 2012;185(12):1327-8.
23. George J, Abramson MJ, Walker SP. Asthma in pregnancy: are inhaled corticosteroids safe? *Am J Respir Crit Care Med* 2012;185(5):476-8.
24. Lim AS, Stewart K, Abramson MJ, George J. Management of asthma in pregnant women by general practitioners: a cross sectional survey. *BMC Fam Pract* 2011;12:121.
25. Luskin AT, Bukstein D, Ben-Joseph R. The relationship between prescribed and delivered doses of inhaled corticosteroids in adult asthmatics. *J Asthma* 2001;38(8):645-55.
26. Enriquez R, Wu P, Griffin MR, Gebretsadik T, Shintani A, Mitchel E, et al. Cessation of asthma medication in early pregnancy. *Am J Obstet Gynecol* 2006;195(1):149-53.
27. Schatz M, Liebman C. Inhaled corticosteroid use and outcomes in pregnancy. *Ann Allergy Asthma Immunol* 2005;95(3):234-8.
28. Olesen C, Thrane N, Nielsen GL, Sørensen HT, Olsen J; EuroMAP Group. A population-based prescription study of asthma drugs during pregnancy; changing the intensity of asthma therapy and perinatal outcomes. *Respiration* 2001;68(3):256-61.
29. Allen DB, Bielory L, Derendorf H, Dluhy R, Colice GL, Szefler SJ. Inhaled corticosteroids: past lessons and future issues. *J Allergy Clin Immunol* 2003;112(3):S1-40.

MOTHERISK Motherisk questions are prepared by the Motherisk Team at the Hospital for Sick Children in Toronto, Ont. **Ms Smy** is a pharmaceutical sciences doctoral candidate in the Leslie Dan Faculty of Pharmacy at the University of Toronto in Ontario. **Mr Chan** is a medical student at St George's University in Grenada. **Ms Bozzo** is Assistant Director and **Dr Koren** is Director of the Motherisk Program. **Dr Koren** is supported by the Research Leadership for Better Pharmacotherapy during Pregnancy and Lactation.

Do you have questions about the effects of drugs, chemicals, radiation, or infections in women who are pregnant or breastfeeding? We invite you to submit them to the Motherisk Program by fax at 416 813-7562; they will be addressed in future **Motherisk Updates**. Published Motherisk Updates are available on the *Canadian Family Physician* website (**www.cfp.ca**) and also on the Motherisk website (**www.motherisk.org**).