Is it safe to use inhaled corticosteroids in pregnancy?

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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.

Asthma is a chronic inflammatory disease that frequently results in bronchial obstruction with symptoms of dyspnea and coughing. It affects up to 8.4% of pregnant women in the United States and, if uncontrolled, can lead to decreased fetal oxygen supply. Popular inhaled corticosteroids (ICSs) currently available globally include budesonide, fluticasone propionate, beclomethasone dipropionate, triamcinolone acetonide, flunisolide, mometasone furoate, and ciclesonide. 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, pregnancy-induced hypertension, and delivery by cesarean section. 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 and having small for gestational age or low-birth-weight neonates (relative risk = 3.02, 95% CI 1.87 to 4.89). 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). Generally, asthma does not pose an increased risk of major malformations.

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). Use of ICSs is the preferred long-term treatment of asthma in pregnancy.

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. As well, no adverse outcomes were found in terms of gestational age, birth weight, birth length, or stillbirths. No significant associations have been found between the use of other ICSs during pregnancy and adverse perinatal outcomes. 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) or any congenital malformations (OR = 0.96, 95% CI 0.89 to 1.04, n = 17,220 exposed to ICSs), 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.

A large Canadian cohort study (n = 4392), included in the meta-analysis discussed above, confirmed the safety of using low to moderate doses (0 to 1000 µg/d chlorofluorocarbon beclomethasone equivalent) of ICSs in the first trimester. 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 ICSs 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

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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).