



# Motherisk Update

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## Using corticosteroids during pregnancy

*Are topical, inhaled, or systemic agents associated with risk?*

### ABSTRACT

**QUESTION** I am concerned about use of corticosteroids during pregnancy. Some of my women patients of reproductive age are using topical, inhaled, or oral preparations, and I am not sure what to advise.

**ANSWER** Both topical and systemic corticosteroids are used for a variety of autoimmune and inflammatory conditions. Results of first-trimester studies were inconclusive and underpowered. Recent meta-analyses suggest a small but significant association between use of systemic corticosteroids during the first trimester and oral clefts. This is consistent with results of animal studies. No similar evidence exists for topical or inhaled corticosteroids, probably because of much lower systemic exposure.

### RÉSUMÉ

**QUESTION** Je m'inquiète à propos du recours aux corticostéroïdes pendant la grossesse. Certaines de mes patientes en âge de procréer utilisent des préparations topiques, inhalées ou par voie orale et je ne suis pas sûr des conseils à leur donner.

**RÉPONSE** Les corticostéroïdes, sous forme tant topique que systémique, sont utilisés pour une variété de problèmes inflammatoires et immunitaires. Les résultats d'études pendant le premier trimestre de la grossesse ne se prêtaient pas à des conclusions convaincantes ou concluantes. De récentes méta-analyses font valoir une association faible mais significative entre l'utilisation des corticostéroïdes systémiques durant le premier trimestre et les fissures orales. Ceci corrobore les études chez l'animal. Aucune donnée probante n'existe pour les corticostéroïdes sous forme topique ou inhalée, probablement en raison de la plus faible exposition systémique.

Corticosteroids are used to treat a variety of conditions; discontinuing them during pregnancy sometime exacerbates these conditions. Corticosteroids are available alone or in combination with other drugs for systemic, inhaled, and topical use. Systemic corticosteroids are used for autoimmune and inflammatory conditions. Inhaled steroids are now first-line treatment for asthma. Topical corticosteroids are frequently used to treat allergic and inflammatory dermatologic diseases, such as atopic dermatitis and psoriasis. Existing data on the safety of corticosteroids during pregnancy, particularly during the first trimester, are often conflicting and difficult to interpret.

### Systemic corticosteroids

Commonly used systemic corticosteroids include prednisone, cortisone, and the active metabolites of prednisone and dexamethasone. Corticosteroids cross human placenta<sup>1</sup>; fluorinated corticosteroids penetrate the placenta more rapidly.<sup>2</sup> The increased incidence of low birth weight and stillbirths reported in fetuses exposed to corticosteroids can often be linked to the conditions for which the mothers were given the drugs.<sup>3</sup>

Several studies have suggested an association between oral clefts and use of systemic corticosteroids,<sup>4-6</sup> but one case-control and several prospective cohort studies failed to show such an

## Motherisk Update

association.<sup>7-12</sup> A meta-analysis conducted by the Motherisk program of 123 175 women who received oral corticosteroids during the first trimester showed a slightly increased risk of oral clefts. Pooled results of odds ratios (ORs) in case-control studies showed a threefold increase in oral clefts among offspring of women who received oral corticosteroids during pregnancy. When results of six cohort studies were pooled, no significant increase in oral clefts was seen. When the largest study (50 282 patients) was excluded because it did not distinguish between major and minor malformations, however, the OR increased to 3.03 (95% confidence interval 1.08 to 8.54) for major malformations in children whose mothers received corticosteroids during the first trimester of pregnancy.<sup>3</sup>

A recent prospective, controlled study followed 311 women who used various corticosteroids during the first trimester. Both corticosteroid-exposed women and controls had malformation rates within the expected baseline risk for the general population. The authors also recalculated a cumulative OR from seven controlled studies, including their own study, and found no significant increase in risk of major anomalies.<sup>13</sup>

Because most human studies of systemic corticosteroid use during pregnancy have looked at the drugs in combination with other medications, it is difficult to assess the risk of individual corticosteroids. While systemic corticosteroids do not seem to pose a major teratogenic risk for humans, there is a small but significantly increased risk of oral clefts with first-trimester exposure. These results are consistent with results of extensive studies in animals.<sup>14,15</sup>

### Inhaled corticosteroids

Inhaled corticosteroids used to treat asthma or other respiratory symptoms include beclomethasone, budesonide, flunisolide, fluticasone, mometasone, and triamcinolone.<sup>16</sup>

It is estimated that up to 4% of all pregnancies are complicated

by maternal asthma,<sup>17</sup> making asthma one of the most common respiratory complications seen in pregnancy. Poor control of chronic asthma and exacerbation of acute asthma during pregnancy can result in adverse maternal and fetal outcomes, such as hypoxia, low birth weight, and intrauterine growth restriction.<sup>18-20</sup> A randomized controlled study has shown that long-term use of low-dose budesonide decreases the risk of severe exacerbations and improves asthma control in patients with mild, persistent asthma of recent onset.<sup>19</sup> Inhaled steroids have also been shown to reduce risk of hospitalization due to asthma.<sup>21,22</sup>

Epidemiologic data on inhaled corticosteroids have shown no increase in rates of congenital malformations. A retrospective study of women treated with triamcinolone, beclomethasone, and oral theophylline for asthma during pregnancy found no congenital abnormalities in any treatment groups.<sup>23</sup> In addition, START (Inhaled Steroid Treatment As Regular Therapy), the first long-term, multicentre, prospective, double-blind study, reported that treating asthmatic pregnant women with 400 µg of budesonide is safe.<sup>24</sup> These results corroborate data from the Swedish Registry Study<sup>25</sup> of about 3000 pregnancies, which showed a normal rate of malformations in newborns exposed to budesonide during the first trimester.

Inhaled corticosteroids are currently recommended as part of routine management of moderate-to-severe chronic asthma during pregnancy.<sup>26</sup>

### Topical corticosteroids

Commonly used topical corticosteroids include hydrocortisone and betamethasone. The systemic effects of topical corticosteroids are generally limited because only about 3% of the medication in topical preparations is absorbed systemically following 8 hours of contact with normal skin.<sup>27</sup> Absorption varies with different types and doses of preparations and the nature and

extent of underlying skin conditions. When corticosteroids are used long term or on large areas of skin, they might have systemic effects.<sup>28-34</sup>

Epidemiologic fetal safety data on topical corticosteroids are sparse. Two population-based studies found that treatment with topical corticosteroids during pregnancy did not increase risk of congenital abnormalities in humans.<sup>35,36</sup>

## Discussion

The apparent increased risk of oral clefts associated with systemic corticosteroid use has to be balanced against potentially serious implications for mothers (and indirectly fetuses) if needed steroid therapy is discontinued or not initiated for underlying maternal conditions. Since oral clefts occur at about one per thousand births, this increased risk will have a minimal absolute effect on the overall malformation rate of 3%. Since palate formation is completed by 12 weeks' gestation, no risk of oral clefts exists thereafter.

When exposure has already occurred, a level II ultrasound scan might be able to detect clefting. More studies are needed to determine which cleft phenotype is associated with corticosteroids and whether it is cleft lip (with or without palate) or cleft palate alone, or both.

## MOTHERISK

Motherisk questions are prepared by the Motherisk Team at the Hospital for Sick Children in Toronto, Ont. Ms Oren, Dr Nulman, Ms Makhija, and Dr Ito are members and Dr Koren is Director of the Motherisk Program. Dr Koren is a Senior Scientist at the Canadian Institutes of Health Research and holder of the Ivey Chair in Molecular Toxicology at the University of Western Ontario in London.

Do you have questions about the safety 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 College of Family Physicians of Canada website ([www.cfpc.ca](http://www.cfpc.ca)). Some articles are published in *The Motherisk Newsletter* and on the Motherisk website ([www.motherisk.org](http://www.motherisk.org)) also.

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