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Agent Number #3104 Budesonid

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Agent Summary

Quick take: Human experience with use of budesonide in pregnancy has been reassuring, and this medication has been recommended for the treatment of asthma during pregnancy. Systemic glucocorticoids have been associated with facial clefts in some studies.

Budesonide (Pulmicort, Rhinocort, Horacort) is a glucocorticoid **#1054** given by inhalation to control the symptoms of asthma. Oral tablets or capsules of budesonide have been marketed as Ortikos, Entocort, Tarpeyo, and Uceris. Budesonide and formoterol **#4360** combined in an aerosol have been marketed as Breyna. A combination of budesonide, glycopyrrolate **#1323**, and formoterol in an aerosol has been marketed as Breztri. Budesonide has been used topically, nasally, orally, or rectally to treat allergic or inflammatory diseases. The product labeling for Uceris indicated that bioavailability is approximately 4-fold higher in patients with hepatic impairment and 8-fold higher with ingestion of grapefruit juice (27). It was suggested that bioavailability to patients with Crohn disease might be higher due to increased intestinal absorption (28).
Experimental animal development

In rabbits, budesonide 0.29 nmol/kg/day caused abortion and lower dose levels, down to 0.01 nmol/kg, caused fetal growth restriction and skeletal delay (1). Budesonide increased lung maturity in premature sheep and rabbits (25,30). Pregnant mice dosed intravenously with radiolabeled budesonide or fluticasone **#3419** transferred less of the budesonide to the fetuses (32). When injected into the amnion of chick embryos on day 4 or 5 of incubation, budesonide increased orofacial clefts and gastroschisis (34).

Human pregnancy reports

Among offspring of eight women treated with budesonide for up to six months during pregnancy, there were no congenital anomalies or other adverse effects (29). Four women with inflammatory bowel disease received budesonide treatment during pregnancy (31). The infants were born healthy, achieved developmental milestones at between 6 and 20 months of age, and received vaccines without complications. Six women on budesonide throughout pregnancy gave birth to healthy infants, two of whom were born preterm with intrauterine growth restriction (33). A woman on budesonide for the first six months of gestation gave birth to a normal infant who remained healthy at one year of age (35).

In a registry study with more than 10,000 exposed pregnancies, budesonide was not associated with malformations including orofacial clefts (2,6,21). There was no medication-associated change in gestational age, birth weight, length, stillbirth, or multiple birth associated with early pregnancy exposure to budesonide in almost 3000 pregnancies (3). Birth weight, length, and head circumference were not different in offspring of 41 women with asthma, 14 of whom used budesonide, and 20 women without asthma (18). The offspring of 96 pregnant women who used budesonide 400 mcg twice/day for allergic symptoms had no adverse effects on development (24). An increase in facial clefts was associated with some glucocorticoids, with risk estimates generally in the 3-5 range (9-17).

There was an association between the receipt of a prescription for high-dose inhaled corticosteroids during pregnancy and congenital malformations in the offspring, adjusted odds ratio 1.66, 95% confidence interval 1.02-2.68 (22). High dose corticosteroids included beclomethasone, budesonide, fluticasone, flunisolide **#1493**, or triamcinolone **#1487** prescribed at a level equivalent to more than 1000 mg/dose of beclomethasone. This study lacked information for individual agents, evaluation of individual malformations, ability to adjust for severity of asthma, and ability to adjust for use of cigarettes, ethanol, or illicit drugs. Children with a median age 6.1 years at time of follow-up who were prenatally exposed to budesonide were more likely to develop endocrine, metabolic, and nutritional disorders, hazard ratio 1.72, 95% CI 1.07-2.77 (23). Increased infection risk was reported among

infants who were exposed to immunosuppressive agents in utero, RR 1.35, 95% CI 1.24-1.46 (26). Although some infants in this study were exposed to budesonide, the study did not evaluate results by individual agent.

A 2000 position statement on the use of asthma medications during pregnancy suggested that beclomethasone **#1024** or budesonide were the preferred choices when asthma therapy was initiated during pregnancy (4). A 2005 review (5) and a 2006 meta-analysis on inhaled corticosteroids (19) concluded that budesonide studies did not suggest this agent was associated with increased congenital malformations or other adverse fetal outcomes including preterm delivery, low birth weight, or pregnancy-induced hypertension.

Lactation

Eight women using inhaled budesonide 200 or 400 mcg twice daily had peak milk budesonide concentrations of 168 ng/L and 335 ng/L at the 200 mcg and 400 mcg doses, respectively. The mean milk/plasma ratio was 0.46. Infant budesonide plasma concentration was less than the limit of quantification. Infant exposure was estimated based on average milk budesonide concentrations at 6.8 and 14.2 ng/kg daily for the 200 mcg and 400 mcg dosages or up to 0.3% of the weight-adjusted maternal dosage, assuming 100% oral bioavailability (20). Reviewers and an expert panel classified inhaled corticosteroids acceptable for use during breastfeeding (7,8).

When taken by mouth, budesonide was only about 9% bioavailable in healthy patients, and bioavailability in the infant was likely to be similarly low for any budesonide that entered human milk. The Uceris product labeling notes that, when mothers use rectal budesonide, the infant exposure via nursing may be up to 4-fold higher than the infant exposure when the mother uses inhaled budesonide (27). In three infants of mothers using budesonide throughout pregnancy, no adverse effects were observed on breastfeeding (33). It is not clear if budesonide use continued during lactation.

Reproduction

According to the product labeling, no effect on fertility was observed in rats at subcutaneous dose levels up to 80 mcg/kg (27). Offspring

viability was decreased prenatally and postnatally during lactation at dose levels of 20 mcg/kg and above. Maternal body weight gain was decreased at these dose levels. No effects on fertility or maternal body weight gain were observed at 5 mcg/kg.

Selected References

1. Kihlstrom I, Lundberg C: Teratogenicity study of the new glucocorticosteroid budesonide in Arzneimittelforschung 37:43-6, 1987.
2. Kallen B, Rydhstroem H, Aberg A: Congenital malformation after the use of inhaled budesonide in early pregnancy. Obstet Gynecol 93:392-5, 1999.
3. 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;111:736-42.
4. Position statement. The American College of Obstetrics and Gynecologists (ACOG) and the American College of Allergy, Asthma and Immunology (ACAAI). The use of newer asthma and allergy medications during pregnancy. Ann Allergy Asthma Immunol 2000;84:475-80.
5. Gluck PA, Gluck JC: A review of pregnancy outcomes after exposure to orally inhaled or intranasal budesonide. Curr Med Res Opin 2005;21:1075-84.
6. START Investigators Group: Silverman M, Sheffer A, Diaz PV et al: Outcome of pregnancy in a randomized controlled study of patients with asthma exposed to budesonide. Ann Allergy Asthma Immunol 2005;95:566-70.
7. Ellsworth A. Pharmacotherapy of asthma while breastfeeding. J Hum Lact 1994;10:39-41.
8. National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program Asthma and Pregnancy Working Group. NAEPP expert panel report. Managing asthma during pregnancy: recommendations for pharmacologic treatment-2004 update. 2004;1-57. https://www.nhlbi.nih.gov/files/docs/astpreg_qr.pdf

9. Rodriguez-Panilla E, Martinez-Frias ML. Corticosteroids during pregnancy and oral clefts: A case-control study. Teratology 1998;58:2-5.
10. Robert E, Vollset SE, Botto L, Lancaster PAL, Merlob P, Cocchi G, Ashizawa M, Sakamoto S, Orioli I. Malformation surveillance and maternal drug exposure: the MADRE project. Risk Safety Med 1994;6:78-118.
11. Czeizel AE, Rockenbauer M. Population-based case-control study of teratogenic potential of corticosteroids. Teratology 1997;56:335-40.
12. Carmichael SL; Shaw GM: Maternal corticosteroid use and risk of selected congenital anomalies. Am J Med Genet 1999;86:242-4.
13. Park-Wyllie L, Mazzotta P, Pastuszak A et al: Birth defects after maternal exposure to corticosteroids: Prospective cohort study and meta-analysis of epidemiological studies. Teratology 2000;62:385-392.
14. Carmichael SL, Shaw GM, Ma C, Werler MM, Rasmussen SA, Lammer EJ. Maternal corticosteroid use and orofacial clefts. Am J Obstet Gynecol 2007;197:585.e1-585.e7.
15. Pradat P, Robert-Gnansia E, Di Tanna GL, Rosano A, Lisi A, Mastroiacovo P, Contributors to the MADRE database. First trimester exposure to corticosteroids and oral clefts. Birth Defects Res A Clin Mol Teratol. 2003;67:968-70.
16. Kallen B. Maternal drug use and infant cleft lip/palate with special reference to corticoids. Cleft Palate Craniofac J. 2003 Nov;40(6):624-8.
17. Edwards MJ, Agho K, Attia J, Diaz P, Hayes T, Illingworth A, Roddick LG. Case-control study of cleft lip or palate after maternal use of topical corticosteroids during pregnancy. Am J Med Genet A. 2003;120:459-63.
18. Clifton VL, Rennie N, Murphy VE. Effect of inhaled glucocorticoid treatment on placental 11beta-hydroxysteroid dehydrogenase type 2 activity and neonatal birthweight in pregnancies complicated by asthma. Aust N Z J Obstet Gynaecol 2006; 46(2):136-40.
19. 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.

20. Falt A, Bengtsson T, Kennedy BM, et al: Exposure of infants to budesonide through breast milk of asthmatic mothers. J Allergy Clin Immunol. 2007;120(4):798-802.
21. Kallen B, Otterblad Olausson P. Use of anti-asthmatic drugs during pregnancy. 3. Congenital malformations in the infants. Eur J Clin Pharmacol. 2007Apr;63(4):383-388.
22. Blais L, Beauchesne M-F, Lemire C, Elftouh N. High doses of inhaled corticosteroids during the first trimester of pregnancy and congenital malformations. J Allergy Clin Immunol 2009;124:1229-1234.
23. 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. PMID: 22198975.
24. Shaikh WA, Shaikh SW: A prospective study on the safety of sublingual immunotherapy in pregnancy. Allergy 67(6):741-743, 2012.
25. Li L, Yang C, Feng X, Du Y, Zhang Z, Zhang Y. Effects of intratracheal budesonide during early postnatal life on lung maturity of premature fetal rabbits. Pediatr Pulmonol. 2018 Jan;53(1):28-35. doi: 10.1002/ppul.23889. PMID: 29028158.
26. Palosse-Cantaloube L, Hurault-Delarue C, Beau AB, Montastruc JL, Lacroix I, Damase-Michel C. 2016. Risk of infections during the first year of life after in utero exposure to drugs acting on immunity: A population-based cohort study. Pharmacol Res 113(Pt A): 557-562.
27. Salix Pharmaceuticals, Inc. 2020. Uceris product labeling. https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=230e4596-2a9b-4d55-b0a0-0cabbcff5289&type=display
28. El Fakih R, Obi GA, Scholoff A, Carrum G, Kamble RT. 2012. Letter to the editor. Systemic effects of oral budesonide in hematopoietic transplant: implication of drug interaction with azoles. Bone Marrow Transplant. 47: 1370-1371.
29. Beaulieu DB, Ananthakrishnan AN, Issa M, Rosenbaum L, Skaros S, Newcomer JR, Kuhlmann RS, et al. 2009. Budesonide induction and maintenance therapy for Crohn's disease during pregnancy. Inflamm Bowel Dis 15(1): 25-28.
30. Kothe TB, Royse E, Kemp MW, Schmidt AF, Salomone F, Saito M, Usuda H, Watanabe S, Musk GC, Jobe AH, Hillman NH.

Effects of budesonide and surfactant in preterm, fetal sheep. Am J Physiol Lung Cell Mol Physiol. 2018 Apr 19. doi:10.1152/ajplung.00528.2017. PMID: 29671605.

31. Vestergaard T, Jorgensen SMD, Christensen LA, Julsgaard M. 2018. Pregnancy outcome in four women with inflammatory bowel disease treated with budesonide MMX. Scand J Gastroenterol 53(12): 1459-1462.
32. Zaidi S, Chen MJ, Lee DT, Neubart E, Ewing P, Miller-Larsson A, Hochhaus G. Fetal concentrations of budesonide and fluticasone propionate: A study in mice. AAPS J. 2019 Apr 16;21(4):53. doi: 10.1208/s12248-019-0313-2. PubMed PMID: 30993489.
33. Rahim MN, Ran S, Shah S, Hughes S, Heneghan MA. 2020. Safety and efficacy of budesonide during pregnancy in women with autoimmune hepatitis. Hepatology PMID: 33188708. DOI: 10.1002/hep.31634.
34. Peterka M, Heringova LH, Sukop A, Peterkova R. Anti-asthma drugs formoterol and budesonide (Symbicort) induce orofacial clefts, gastroschisis and heart septum defects in an in vivo model. In Vivo. 2021 May-Jun;35(3):1451-1460. doi: 10.21873/invivo.12397. PMID: 33910822.
35. Wiest I, Roig A, Antoni C, Ebert M, Teufel A. 2022. Safety and efficacy of budesonide during pregnancy in women with autoimmune hepatitis. J Gastrointest Liver Dis 31(2): 256-257. https://www.jgld.ro/jgld/index.php/jgld/article/view/4315/1841/rtc