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Balancing competing risks: perinatal exposure to macrolides increases the risk of infantile hypertrophic pyloric stenosis

Margaret A. Honein, PhD, MPH and
Centers for Disease Control and Prevention

Janet D. Cragan, MD, MPH
Centers for Disease Control and Prevention

Context

Infantile hypertrophic pyloric stenosis (IHPS) is a potentially life-threatening condition for which surgical treatment is effective with excellent patient outcomes.¹ However, the etiology of IHPS remains elusive. Prior studies have implicated early neonatal exposure to erythromycin as a strong risk factor for IHPS,² but it is less clear whether maternal use in late pregnancy or while breastfeeding also poses a risk. Perinatal exposure to macrolide antibiotics is not uncommon. About 1% of pregnant women report use in the third trimester,³ and while no macrolides are licensed by the U.S. Food and Drug Administration for use in infants less than 6 months of age, they are recommended both for prophylaxis and treatment of pertussis in this age group.⁴ Particularly for neonatal pertussis, the severity and potential mortality of disease clearly outweigh the risk of IHPS with macrolide use. However, a full understanding of the risks of perinatal macrolide exposure is critical to an informed risk-benefit evaluation of treatment options for less severe conditions with effective therapeutic alternatives.

Methods

This cohort study assesses the association between macrolide use and the occurrence of IHPS among all liveborn, singleton infants in Denmark from 1996 through 2011. It uses data from the Danish Civil Registration System to identify cases of IHPS and maternal and infant exposure to macrolides. Exposure was based on pharmacy records of prescriptions filled. Maternal macrolide use during pregnancy was assessed for two periods: gestational weeks 0-27 and gestational week 28 or later. Postnatal exposure during days 0-13 and days 14-120 following delivery was assessed for mother and infant separately. Extensive sensitivity analyses were undertaken to assess the risk of different macrolides, potential confounders and effect modifiers, and impact of breastfeeding patterns.

Correspondence address: Centers for Disease Control and Prevention, Mailstop E-86, 1600 Clifton Road, Atlanta, GA 30333, MHonein@cdc.gov.

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Competing interests: None

Findings

IHPS was associated with macrolide exposure in infants during days 0-13 (rate ratio [RR] 29.8, 95% confidence interval [CI] 16.4-54.1), and during days 14-120 (RR 3.24, 95% CI 1.20-8.74). IHPS was not associated with maternal macrolide use from gestational weeks 0-27, but was nonsignificantly associated with use after week 28 (RR 1.77, 95% CI 0.95-3.31). IHPS was associated with maternal macrolide use during days 0-13 after delivery (RR 3.49, 95% CI 1.92-6.34) but not during days 14-120.

Commentary

This nationwide cohort study of nearly 1 million births expands our understanding of the risks associated with perinatal macrolide exposure, providing helpful data to inform risk versus benefit assessments for health care providers and their patients. The findings support prior evidence of the high risk of IHPS with early neonatal exposure to macrolides, and further explore the risk of maternal exposure during pregnancy and postnatally.

While the risk is clearly highest for neonates exposed in the first 13 days of life, the report suggests a need to carefully consider options for macrolide use in breastfeeding mothers during the early neonatal period.

This report also highlights some of the challenges in examining the risk of birth defects associated with maternal medication exposures. While macrolide use among pregnant women in this population was not infrequent (about 3%), the relative rarity of IHPS (0.9 per 1000 births) resulted in somewhat sparse data. The mothers of 20 infants with IHPS took a macrolide during the first two trimesters of pregnancy; the mothers of only 10 took a macrolide during the third trimester. The study also had no information on actual consumption of medication. Macrolides might not have been taken as prescribed due to concerns about potential effects on the pregnancy or to side effects, resulting in exposure misclassification.

Despite the limitations, this report provides important data to better characterize the risk of both maternal and neonatal exposure to macrolides. Improved estimation of both the relative and absolute risk of macrolide exposure will inform clinical care decisions and minimize associated neonatal morbidity.

Acknowledgments

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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