

Acid Suppressant Use in Pregnancy and Asthma in Offspring: Should We Be Worried?

Bronwyn K. Brew, PhD,^a Catarina Almqvist, PhD, MD^{a,b}

Gastroesophageal reflux disease (GERD) is the most common medical complaint in pregnancy, manifesting as heartburn and regurgitation. GERD occurs in 25% to 80% of women, with the prevalence varying according to definition and nationality.^{1–3} Initial management involves lifestyle changes and/or antacids, followed by a standard treatment of acid-suppressive medications such as histamine-2 receptor antagonists and proton pump inhibitors (PPIs).¹

Maternal use of PPIs in pregnancy has been shown to be safe in relation to birth defects, spontaneous abortions, and preterm delivery.^{4,5} However, there is a growing number of epidemiologic studies to suggest that maternal use of acid-suppressive medications in pregnancy is associated with an increased risk of asthma in the offspring. In the current edition of *Pediatrics*, Lai et al⁶ have published a meta-analysis of 8 such studies, concluding that there is a risk of children developing asthma with prenatal exposure to PPIs (odds ratio: 1.34; 95% confidence interval [CI]: 1.18–1.52) and histamine-2 receptor antagonists (odds ratio: 1.57; 95% CI: 1.46–1.69).

To explore this further, it is interesting to first ask the following question: why study prenatal acid-suppressive medication exposure and asthma in offspring?

There are several reasons. First, animal studies have revealed that progeny of mice that are given acid suppressants may develop an allergic

profile.^{7,8} Secondly, asthma and GERD are often concomitant in humans. It has been reported in some studies that up to 80% of patients with asthma have GERD.⁹ The mechanisms are unclear, but it is suggested that GERD may induce asthma symptoms by directly affecting airway hyperresponsiveness or via aspiration-induced inflammation.⁹ Alternatively, bronchoconstriction in asthma may induce GERD, and asthma medications such as β 2-agonists may decrease tone in the lower esophageal sphincter, thereby increasing the risk of acid reflux.⁹ However, the close relationship between GERD and asthma brings to light 2 possible explanations for the findings in the Lai et al⁶ meta-analysis. The first explanation is potential confounding by maternal asthma,¹⁰ and the second is that GERD itself, rather than the medication for GERD, is influencing fetal programming for asthma, also known as confounding by indication.¹¹

Because asthma is highly heritable¹² and women with asthma are likely to also have GERD and, therefore, be taking medication, it is perhaps not surprising that we may find maternal prenatal acid suppressant use to be associated with asthma in offspring. On the whole, possible confounding by maternal asthma has been considered thoughtfully in the articles included in the Lai et al⁶ meta-analysis, including adjusting the analyses for maternal asthma,^{13–16} excluding women with asthma from the analyses,¹⁰ and family designs^{17,18} such as sibling

^aDepartment of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; and ^bPediatric Allergy and Pulmonology Unit, Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm, Sweden

Opinions expressed in these commentaries are those of the authors and not necessarily those of the American Academy of Pediatrics or its Committees.

DOI: <https://doi.org/10.1542/peds.2017-3741>

Accepted for publication Nov 14, 2017

Address correspondence to Bronwyn K. Brew, PhD, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Nobels vag 12a, Stockholm 17177, Sweden. E-mail: bronwyn.haasdyk.brew@ki.se

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2018 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Supported by the Swedish Research Council for Health, Working Life and Welfare, Forte (grant 2015-01208).

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

To cite: Brew BK and Almqvist C. Acid Suppressant Use in Pregnancy and Asthma in Offspring: Should We Be Worried?. *Pediatrics*. 2018;141(2):e20173741

comparison^{19,20} and paternal prenatal use of acid suppressants as a negative control.¹⁴

However, few of the studies included by Lai et al⁶ were written by researchers who considered the possibility of confounding by indication, which admittedly can be hard to adjust for in an observational study.²¹ The ideal method would be a randomized controlled trial in which pregnant women diagnosed with GERD were assigned to acid-suppressive drugs or to a placebo and their children followed. However, we know of no such clinical trials. The next best thing would be to emulate the target trial using observational data.²² This would mean following a pregnant group with GERD who did not take medication and comparing them with a group who did. In only 1 of the studies included in the Lai et al⁶ meta-analysis was a GERD diagnosis investigated in addition to acid suppressants.¹⁵ This study, based on The Health Improvement Network cohort, revealed a nonsignificant but increased risk for pregnancy-diagnosed GERD and asthma in offspring (hazard

ratio: 1.17; 95% CI: 0.92–1.48). Furthermore, after adjusting for GERD and other comorbidities, there was no association found between prenatal maternal PPI use and asthma in offspring.¹⁵

Another interesting finding from The Health Improvement Network study was that the risk of asthma in offspring when taking acid suppressants during prepregnancy was actually higher than when taking acid suppressants during pregnancy.¹⁵ Similarly, in other studies, a positive association with asthma in offspring has been found for medication taken only after pregnancy.^{13,16} Taken together, these findings could indicate that women taking acid suppressants outside of pregnancy, but not during pregnancy, actually do have GERD during pregnancy, which may be affecting fetal development. However, we can only surmise. Another possibility is confounding by behavior; that is, women more inclined to seek medical help for GERD (in any period) may also be more inclined to seek medical help for their children regarding asthma.

Whatever the reason, there is doubt raised about the fetal programming hypothesis by acid-suppressive drugs on asthma development presented in the well-conducted meta-analysis by Lai et al.⁶ To better address the issues of confounding, more studies are needed, including GERD diagnoses and attempts to employ more sophisticated methods such as family designs,¹⁷ propensity scoring, instrumental variables, and restriction.²¹ As authors of another recent meta-analysis concluded,²³ we advise clinicians not to jump too quickly to decide that pregnant women should not be taking acid suppressants to prevent asthma in their children⁶ but rather call for more careful research into the mechanisms that may be causing the observed associations.

ABBREVIATIONS

CI: confidence interval

GERD: gastroesophageal reflux disease

PPI: proton pump inhibitor

COMPANION PAPER: A companion to this article can be found online at www.pediatrics.org/cgi/doi/10.1542/peds.2017-0889.

REFERENCES

1. Ali RA, Egan LJ. Gastroesophageal reflux disease in pregnancy. *Best Pract Res Clin Gastroenterol*. 2007;21(5):793–806
2. Rey E, Rodríguez-Artalejo F, Herraiz MA, et al. Gastroesophageal reflux symptoms during and after pregnancy: a longitudinal study. *Am J Gastroenterol*. 2007;102(11):2395–2400
3. Malfertheiner SF, Malfertheiner MV, Kropf S, Costa SD, Malfertheiner P. A prospective longitudinal cohort study: evolution of GERD symptoms during the course of pregnancy. *BMC Gastroenterol*. 2012;12:131
4. Gill SK, O'Brien L, Einarson TR, Koren G. The safety of proton pump inhibitors (PPIs) in pregnancy: a meta-analysis. *Am J Gastroenterol*. 2009;104(6):1541–1545; quiz 1540, 1546
5. Pasternak B, Hviid A. Use of proton-pump inhibitors in early pregnancy and the risk of birth defects. *N Engl J Med*. 2010;363(22):2114–2123
6. Lai T, Wu M, Liu J, et al. Acid-suppressive drug use during pregnancy and the risk of childhood asthma: a meta-analysis. *Pediatrics*. 2018;141(2):e20170889
7. Untersmayr E, Schöll I, Swoboda I, et al. Antacid medication inhibits digestion of dietary proteins and causes food allergy: a fish allergy model in BALB/c mice. *J Allergy Clin Immunol*. 2003;112(3):616–623
8. Schöll I, Ackermann U, Özdemir C, et al. Anti-ulcer treatment during pregnancy induces food allergy in mouse mothers and a Th2-bias in their offspring. *FASEB J*. 2007;21(4):1264–1270
9. Parsons JP, Mastrorade JG. Gastroesophageal reflux disease and asthma. *Curr Opin Pulm Med*. 2010;16(1):60–63
10. Källén B, Finnström O, Nygren KG, Otterblad Olausson P. Maternal drug use during pregnancy and asthma risk among children. *Pediatr Allergy Immunol*. 2013;24(1):28–32

11. Psaty BM, Koepsell TD, Lin D, et al. Assessment and control for confounding by indication in observational studies. *J Am Geriatr Soc*. 1999;47(6):749–754
12. Ullemar V, Magnusson PK, Lundholm C, et al. Heritability and confirmation of genetic association studies for childhood asthma in twins. *Allergy*. 2016;71(2):230–238
13. Andersen AB, Erichsen R, Farkas DK, Mehnert F, Ehrenstein V, Sørensen HT. Prenatal exposure to acid-suppressive drugs and the risk of childhood asthma: a population-based Danish cohort study. *Aliment Pharmacol Ther*. 2012;35(10):1190–1198
14. Mulder B, Schuiling-Veninga CC, Bos HJ, De Vries TW, Jick SS, Hak E. Prenatal exposure to acid-suppressive drugs and the risk of allergic diseases in the offspring: a cohort study. *Clin Exp Allergy*. 2014;44(2):261–269
15. Cea Soriano L, Hernández-Díaz S, Johansson S, Nagy P, García-Rodríguez LA. Exposure to acid-suppressing drugs during pregnancy and the risk of asthma in childhood: an observational cohort study. *Aliment Pharmacol Ther*. 2016;43(3):427–437
16. Yitshak-Sade M, Gorodischer R, Aviram M, Novack L. Prenatal exposure to H2 blockers and to proton pump inhibitors and asthma development in offspring. *J Clin Pharmacol*. 2016;56(1):116–123
17. Gong T, Brew B, Sjölander A, Almqvist C. Towards non-conventional methods of designing register-based epidemiological studies: an application to pediatric research. *Scand J Public Health*. 2017;45(suppl 17):30–35
18. Brew BK, Gong T, Williams DM, Larsson H, Almqvist C. Using fathers as a negative control exposure to test the developmental origins of health and disease hypothesis: a case study on maternal distress and offspring asthma using Swedish register data. *Scand J Public Health*. 2017;45(suppl 17):36–40
19. Hak E, Mulder B, Schuiling-Veninga CC, de Vries TW, Jick SS. Use of acid-suppressive drugs in pregnancy and the risk of childhood asthma: bidirectional crossover study using the general practice research database. *Drug Saf*. 2013;36(11):1097–1104
20. Mulder B, Schuiling-Veninga CC, Bos JH, de Vries TW, Hak E. Acid-suppressive drug use in pregnancy and the toddler's asthma risk: a crossover, case-control study. *J Allergy Clin Immunol*. 2013;132(6):1438–1440
21. Bosco JL, Silliman RA, Thwin SS, et al. A most stubborn bias: no adjustment method fully resolves confounding by indication in observational studies. *J Clin Epidemiol*. 2010;63(1):64–74
22. Hernán MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. *Am J Epidemiol*. 2016;183(8):758–764
23. Devine RE, McCleary N, Sheikh A, Nwaru BI. Acid-suppressive medications during pregnancy and risk of asthma and allergy in children: a systematic review and meta-analysis. *J Allergy Clin Immunol*. 2017;139(6):1985–1988.e12

Acid Suppressant Use in Pregnancy and Asthma in Offspring: Should We Be Worried?

Bronwyn K. Brew and Catarina Almqvist
Pediatrics originally published online January 11, 2018;

Updated Information & Services	including high resolution figures, can be found at: http://pediatrics.aappublications.org/content/early/2018/01/09/peds.2017-3741
References	This article cites 23 articles, 1 of which you can access for free at: http://pediatrics.aappublications.org/content/early/2018/01/09/peds.2017-3741.full#ref-list-1
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): Evidence-Based Medicine http://classic.pediatrics.aappublications.org/cgi/collection/evidence-based_medicine_sub Pulmonology http://classic.pediatrics.aappublications.org/cgi/collection/pulmonology_sub Asthma http://classic.pediatrics.aappublications.org/cgi/collection/asthma_subtopic
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: https://shop.aap.org/licensing-permissions/
Reprints	Information about ordering reprints can be found online: http://classic.pediatrics.aappublications.org/content/reprints

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since . Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2018 by the American Academy of Pediatrics. All rights reserved. Print ISSN:

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Acid Suppressant Use in Pregnancy and Asthma in Offspring: Should We Be Worried?

Bronwyn K. Brew and Catarina Almqvist

Pediatrics originally published online January 11, 2018;

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/early/2018/01/09/peds.2017-3741>

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since . Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2018 by the American Academy of Pediatrics. All rights reserved. Print ISSN:

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

