Prenatal exposure to acid suppressant medications and the risk of recurrent wheeze at 3 years of age in children with a history of severe bronchiolitis

Lacey B. Robinson, MD[a], **Anna J. Chen Arroyo, MD MPH**[b], **Marina A. S. Dantas, MD**[c], **Janice A. Espinola, MPH**[c], **Ashley F. Sullivan, MPH MS**[c], **Carlos A. Camargo Jr., MD DrPH FAAAAI**[a,c]

[a:]Division of Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Harvard Medical School, 55 Fruit Street, Cox 201 Boston MA 02114, USA, lbrobinson@mgh.harvard.edu

[b:]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, 60 Fenwood Road, Building of Transformative Medicine 5002B, Boston MA 02115, USA, acarroyo@bwh.harvard.edu

[c:]Emergency Medicine Network, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, 125 Nashua Street, Suite 920, Boston MA 02114, USA. mdantas@mgh.harvard.edu, espinola@helix.mgh.harvard.edu, afsullivan@partners.org, ccamargo@partners.org

To the Editor:

Asthma, one of the most common chronic diseases of childhood, develops through complex interactions between genetic susceptibilities and environmental exposures.[1, 2] In the U.S., acid suppressant medications (ASM) are available widely, either by prescription or over-the-counter purchase, and are commonly used throughout the lifespan, including during pregnancy.[3,4] Recent evidence from outside the U.S. suggests that prenatal exposure to ASM may be associated with an increased risk of asthma in children.[5,6] These previous studies were performed in mostly European populations and were conducted retrospectively in large databases and thus relied primarily on prescription records and diagnosis codes to identify exposures and outcomes.[7] Despite efforts to control for bias and confounding, these retrospective observational studies were potentially affected by misclassification of both the exposure and outcome and inability to adjust for a variety of factors, including maternal atopy.[7]

Corresponding author: Lacey B. Robinson MD, Massachusetts General Hospital, 55 Fruit Street, Cox 201 Boston MA 02114, USA. Phone: 303-668-5477 lbrobinson@mgh.harvard.edu.

Conflicts of Interest: The authors report no conflicts of interest.

Our objective was to evaluate whether prenatal exposure to ASM increases the risk of recurrent wheeze in a population of racially/ethnically diverse U.S. children who already are at high-risk of developing asthma due to severe bronchiolitis in infancy. We investigated the 35th Multicenter Airway Research Collaboration (MARC-35) cohort composed of children with a history of severe bronchiolitis in infancy. This population is novel due to their racial/ethnic diversity as well as their increased risk of developing asthma due to their bronchiolitis event.[8]

Among the 921 participants in the MARC-35 longitudinal cohort, 900 (98%) had complete exposure and outcome data. Exposure was defined by parental report of maternal use of ASM during pregnancy with either histamine-2 receptor antagonists (H2RA) or proton pump inhibitors (PPI). The outcome of recurrent wheeze by 3 years of age was defined per the 2007 National Institutes of Health (NIH) asthma guidelines: 1) having at least 2 corticosteroid-requiring exacerbations within 6 months, or 2) having at least 4 wheezing episodes within one year, each lasting at least one day and affecting sleep.[9] Unadjusted and adjusted analyses were performed using Cox proportional hazards modeling stratified by age, with multivariable models adjusted for 9 potential confounders (see Table 2) using STATA SE 15.1 (College Station, TX). (See supplement for detailed methods and results)

In this cohort of geographically and racial/ethnically diverse children in the U.S., 16% (144/900) of mothers reported using ASM during pregnancy (Table 1). Of these mothers, 17% (24/144) reported use for 1 month or less, 31% (44/144) for 2–3 months, 20% (29/144) for 4–5 months, 32% (46/144) for 6 months or more and <1% (1/144) had an unknown duration of use. At enrollment, the median total serum IgE level did not differ significantly between the exposed children at 4.64 kU/L (IQR 1.9–15.5) as compared to the unexposed children at 4.20 kU/L (IQR 1.9–12.15) (P=0.70). Recurrent wheeze developed in 32% (289/900) of children by 3 years of age. In unexposed children, 31% (233/756) developed recurrent wheeze as compared to 39% (56/144) of exposed children (unadjusted HR 1.38; 95%CI, 1.03–1.85). The increased risk persisted despite adjustment for potential confounders (adjusted HR 1.40; 95%CI, 1.02–1.91) (Table 2 and Figure E1). Although statistical power was low we preformed exploratory analyses to investigate the relationship between duration of exposure to ASM during pregnancy and the risk of recurrent wheeze. Those exposed for < 2 months during pregnancy had a lower risk of developing recurrent wheeze (aHR 1.27; 95%CI, 0.64–2.54) than those exposed for > 2 months during pregnancy (aHR 1.42; 95%CI, 1.02–1.98).

To our knowledge, this is the first study to investigate prenatal exposure to ASM and recurrent wheeze in a prospective U.S. based-cohort, and the first to investigate this issue among infants at high-risk of developing asthma. The study design and analysis enabled us to limit several potential sources of bias. Direct ascertainment of maternal ASM use from the parent decreases misclassification of the exposure. In the U.S. maternal report of ASM use is likely superior to medical record documentation due to availability of these medications by over-the-counter purchase. We report that 16% of mothers used ASM during pregnancy, however, the baseline population rates of ASM use in pregnancy in the U.S. have not been accurately identified due to easy over-the-counter purchase. Recurrent wheeze was determined by detailed parental interviews every 6 months and is consistent with current

NIH guidelines.[9] Thus, we expect less outcome misclassification. Our cohort is racially/ethnically diverse (>50% non-white) which may be more generalizable to the U.S. population than prior studies performed primarily in European populations. Lastly, we gathered detailed information directly from the children's parents regarding many potential confounders including parental history of allergic disease, sociodemographic and perinatal factors. Despite these adjustments, prenatal ASM exposure had a consistent association with the development of recurrent wheeze in all main analyses.

The underlying mechanism by which ASM may increase the risk of recurrent wheeze and subsequent asthma is not known. There is evidence to suggest that ASM, including PPI and H2RA, may predispose to allergic sensitization, the propensity to express Th2 cytokines, and dysbiosis of the microbiome.[7, 10, 11] These effects are thought to be related to their common function of suppressing gastric acid. In our study, we found no significant difference in the total IgE between exposed and unexposed infants. However, these samples were collected at enrollment (median age 3.2 months) which may either be too distant from the exposure or too early in infancy to detect meaningful differences. Likewise, the role of the microbiome is increasingly recognized in the development of asthma;[7] however, more research is needed to determine if ASM use is associated with alterations in the microbiome that predispose individuals to developing asthma.

Limitations of our study include the observational design, which precludes strong statements about causality. Despite efforts to adjust for confounding it is possible that unmeasured confounding remains, including confounding by indication. Prenatal exposure to ASM was obtained at the time of study enrollment which raises the possibility of recall bias. However, all children were young infants (median age 3.2 months) at the time of enrollment and all were currently hospitalized for an acute illness, thus we would not expect maternal recall bias. Based on the nature of the data we are limited in our ability to determine the trimester of exposure in which the effect of ASM may be the greatest. Most mothers (52%) reported use of ASM for at least 4 months, inherently accounting for exposure in more than one trimester. All the children in the cohort are at high-risk for developing recurrent wheeze due to their shared history of severe bronchiolitis in infancy, which limits the generalizability of the study. However, bronchiolitis is not a rare infection in childhood and is the most common cause of hospitalization in U.S. infants (130,000 hospitalizations/year), thus while our study is not generalizable to all children it is generalizable to a large patient population.[8]

In conclusion, prenatal ASM exposure appears to further increase the risk of recurrent wheeze in children with a history of severe bronchiolitis in infancy. This finding is important as prenatal exposure to ASM is modifiable. Although further research is needed in low-risk populations, clinicians may wish to discuss the potential risks and benefits of elective ASM therapy prior to initiation in pregnancy. We will continue to follow these children for the development of asthma and plan to investigate the association of ASM exposure with this important outcome. We encourage future research on the risk of ASM exposure in a low-risk general population, the risk of bronchiolitis after prenatal exposure to ASM, the potential for a dose-dependent or trimester dependent effect of ASM exposure, potential confounding (including confounding by indication) and elucidating the potential underlying mechanism.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Centers for Disease Control and Prevention: national current asthma prevalence Atlanta, GA: National Center for Environmental Health; 2015 Available at: https://www.cdc.gov/asthma/most_recent_data.htm. Accesssed 4 18, 2018.

2. Bonnelykke K, Ober C. Leveraging gene-environment interactions and endotypes for asthma gene discovery. J Allergy Clin Immunol 2016;137(3):667–79. [PubMed: 26947980]

3. Richter JE. Review article: the management of heartburn in pregnancy. Aliment Pharmacol Ther 2005;22(9):749–57. [PubMed: 16225482]

4. Gawron AJ, Feinglass J, Pandolfino JE, Tan BK, Bove MJ, Shintani-Smith S. Brand name and generic proton pump inhibitor prescriptions in the United States: insights from the national ambulatory medical care survey (2006–2010). Gastroenterol Res Pract 2015;2015:689531. [PubMed: 25733976]

5. 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):1985–88. [PubMed: 28081850]

6. Lai T, Wu M, Liu J, Luo M, He L, Wang X, et al. Acid-suppressive drug use during pregnancy and the risk of childhood asthma: a meta-analysis. Pediatrics 2018;141(2):e20170889 Epub 2018 Jan 11. [PubMed: 29326337]

7. Robinson LB, Camargo CA Jr. Acid suppressant medications and the risk of allergic diseases. Expert Rev Clin Immunol 2018; 14(9):771–780. Epub 2018 Aug 24. [PubMed: 30113236]

8. Hasegawa K, Mansbach JM, Camargo CA Jr. Infectious pathogens and bronchiolitis outcomes. Expert Rev Anti Infect Ther 2014; 12: 817–828. [PubMed: 24702592]

9. Expert Panel Report 3 (EPR-3): guidelines for the diagnosis and management of asthma-summary report 2007. J Allergy Clin Immunol 2007;120(5 Suppl):S94–138. [PubMed: 17983880]

10. Untersmayr E, Bakos N, Scholl I, Kundi M, Roth-Walter F, Szalai K, et al. Anti-ulcer drugs promote IgE formation toward dietary antigens in adult patients. FASEB J 2005;19(6):656-

11. Scholl I, Ackermann U, Ozdemir C, Blumer N, Dicke T, Sel S, 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):1264–70. [PubMed: 17227952]

Clinical Implications:

Acid suppressant medications are commonly used during pregnancy. In a cohort of U.S. children at high-risk for asthma due to severe bronchiolitis in infancy, we found prenatal exposure to acid suppressant medications increased the risk of developing recurrent wheeze. Future research is needed on this topic. During the interim, clinicians may wish to discuss with patients the potential risks and benefits of acid suppressant medication use in pregnancy.

Table 1.

Baseline characteristics of infants hospitalized for bronchiolitis by prenatal acid suppressant medication exposure

Demographics	Analytical Cohort (n=900)	ASM Exposed (n =144)	ASM Unexposed (n= 756)	P value
Age at Enrollment-*months* [median(IQR)]	3.22 (1.67– 6.00)	3.42 (1.81 – 6.05)	3.20 (1.64–5.93)	0.48
Sex				0.61
Female	361 (40)	55 (38)	306 (40)	
Male	539 (60)	89 (62)	450 (60)	
Race/Ethnicity				<0.001
Non-Hispanic white	396 (44)	93 (65)	303 (40)	
Non-Hispanic black	201 (22)	22 (15)	179 (24)	
Hispanic	268 (30)	27 (19)	241 (32)	
Other	35 (4)	2 (1)	33 (4)	
Insurance Status				<0.001
Private	367 (41)	88 (61)	279 (37)	
Public	519 (58)	54 (38)	465 (62)	
Uninsured	12 (1)	2 (1)	10 (1)	
Median Household Income				0.03
< $40,000 per year	304 (34)	37 (26)	267 (35)	
$ 40,000 per year	596 (66)	107 (74)	489 (65)	
Gestational Age at Birth				<0.001
> 40 weeks	352 (39)	38 (26)	314 (42)	
> 37 to 40 weeks	382 (42)	59 (41)	323 (43)	
> 34 to 37 weeks	134 (15)	39 (27)	95 (13)	
> 32 to 34 weeks	32 (4)	8 (6)	24 (3)	
Birth Weight				0.15
< 5 lbs	57 (6)	13 (9)	44 (6)	
5 lbs	838 (94)	131 (91)	707 (94)	
Mode of Delivery				0.07
Vaginal	589 (66)	85 (59)	504 (67)	
C- Section	310 (34)	59 (41)	251 (33)	
Multiple Birth (i.e. twin)				<0.001
Yes	41 (5)	16 (11)	25 (3)	
No	859 (95)	128 (89)	731 (97)	
Maternal Antibiotics Prior to Labor				0.004
Yes	242 (27)	52 (37)	190 (25)	
No	647 (73)	88 (63)	559 (75)	
Maternal Smoking During Pregnancy				0.16
Yes	123 (14)	25 (17)	98 (13)	
No	776 (86)	119 (83)	657 (87)	
Maternal History of Asthma				0.002

Demographics	Analytical Cohort (n=900)	ASM Exposed (n =144)	ASM Unexposed (n= 756)	P value
Yes	192 (21)	45 (31)	147 (20)	
No	702 (79)	98 (69)	604 (80)	
Maternal History of Atopic Condition [*]				<0.001
Yes	208 (23)	50 (35)	158 (21)	
No	689 (77)	93 (65)	596 (79)	

Data are expressed as n (%) unless otherwise indicated.

[*] Atopic conditions include asthma, allergic rhinitis, food allergy and eczema. Abbreviations-ASM: acid suppressant medications, C-section: cesarean section.

Table 2.

Prenatal exposure to acid suppressant medications and risk of recurrent wheeze by age 3 years

	Exposed (n=144, cases=56)	Unexposed (n=756, cases=233)
Cox-proportional hazards [*]		
Unadjusted	1.38 (1.03–1.85) [†]	1.00 (reference)
Adjusted Model A	1.40 (1.03–1.89) [†]	1.00 (reference)
Adjusted Model B	1.40 (1.02–1.91) [†]	1.00 (reference)

[*] All models were stratified by age at enrollment.

Model A: Adjusted for sex, insurance, race/ethnicity and median household income.

Model B: Adjusted for sex, insurance, race/ethnicity, median household income, maternal history of atopic disease (asthma, allergic rhinitis, food allergy and eczema), maternal smoking during pregnancy, gestational age at birth, multiple gestation (e.g. twin), mode of delivery and maternal use of antibiotics during pregnancy prior to labor.

[†] Statistically significant with P <0.05.