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Prenatal Exposure to H_2 Blockers and to Proton Pump Inhibitors and Asthma Development in Offspring

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Abstract

Fetal exposure to H_2 blockers (H_2Bs) or proton pump inhibitors (PPIs) has been reported to be associated with asthma in children. We evaluated the risk of asthma in offspring following prenatal H_2Bs. We enrolled 91 428 children and their mothers who resided in southern Israel during 1998–2011. The computerized medications database was linked with records from the district hospital. Of the eligible children, 11 227 developed asthma, and overall 5.5% had been exposed to H_2Bs or PPIs prenatally. The risk of developing asthma was slightly higher in the group exposed to H_2Bs or PPIs (RR, 1.09; $P = .023$). At greater risk were children whose mothers purchased these medications more than 3 times (RR, 1.22; $P = .038$) or exposed to >20 defined daily doses or prenatally exposed to lansoprazole. The statistical association was significant and depended on magnitude of exposure and specific medication, but the absolute risk was low. The association between maternal consumption of H_2Bs or PPIs and asthma and childhood remained statistically significant 2 years after delivery, raising the possibility of confounding by the indication phenomenon. In view of the findings, a causal relationship could not be ascertained, and an unidentified etiological factor could be operative.

Keywords

H_2 blockers, famotidine, cimetidine, ranitidine, omeprazole, pantoprazole, lansoprazole, asthma, prenatal exposure, number needed to harm (NNTH)

A growing interest exists in the study of early factors involved in the development of asthma in children and, in particular, prenatal exposure to xenobiotics. Maternal intake of proton pump inhibitors (PPIs) and of H_2 blockers (H_2Bs)[1] during pregnancy has been implicated. The rational basis for this association is unclear. In adults consumption of antacids carries a risk of developing food and drug allergies, as a result of suppression of acid- mediated breakdown of antigens in the stomach and sensitization of the immune system.[2] It has been suggested that antacidtreatment during pregnancy is responsible for sensitizations against food allergens in children.[3,4] However, Dehlink et al's study[3] found that in utero exposure to antacids was associated with asthma but not with the development of other allergies in offspring. As opposed to fetal sensitization, in certain circumstances, transplacental allergen transfer might rather induce tolerance to allergens in the fetus.[5]

If at all causal, the pathophysiology of the putative development of asthma in the offspring following prenatal exposure to H_2Bs and to PPIs is speculative. Exposure to H_2Bs and PPIs during pregnancy has been shown to be safe for the newborn.[6,7] H_2Bs and PPIs cross the human placenta;[8,9] however, little is known about potential biochemical and immunological effects of H_2Bs and PPIs on the fetus. It has been shown that cimetidine influences the histamine-induced fetal pulmonary vasodilatation,[10] but this does not explain the bronchial immune response to allergens after birth.

Interestingly, the association of prenatal exposure to H_2Bs and PPIs and asthma in children is similar to that reported for other xenobiotics. An increased risk of asthma has been found for children born after infertility treatment[11] and after in utero exposure to acetaminophen,[12] antibiotics,[13] and other pollutants and toxins (tobacco smoke, polychlorinated biphenols, bisphenol A).[14]

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By inhibiting gastric secretion, H_2Bs such as cimetidine, famotidine and ranitidine and PPIs such as omeprazole, pantoprazole, and lansoprazole are frequently used in the treatment of acid reflux, a condition that affects up to 50% of pregnant women.

The purpose of this investigation was to evaluate the purported association and to identify factors that could be related to the risk of asthma development in childhood following prenatal exposure to H_2Bs or PPIs by the use of a population-based design.

Methods

Study Population

This retrospective cohort investigation included individuals registered in "Clalit" Health Services (HMO) in the Southern District of Israel. "Clalit" is the largest HMO in the country; it insures approximately 70% of the district population of 630 000 inhabitants. Essentially all deliveries and hospitalizations take place at the district hospital, the 1000-bed Soroka Medical Center, the only medical center in the area, which serves nearly 1 million people as a tertiary hospital. Approximately half the children in the district are born to Jewish, and half to Bedouin-Muslim parents (ethnicity is determined by the Interior Ministry).

All children registered in the "Clalit" HMO living in the Southern District, born at Soroka Medical Center between the years 1999 and 2008 and aged 3–13 years by the end of 2011, and their mothers were included in this study. Health services status was defined on mothers' "Clalit" membership during their pregnancy.

The study was approved by the local institutional Ethics Committee in accordance with the principles of the Declaration of Helsinki.

Databases. The demographic, clinical, and medication data of "Clalit" members are gathered in a computerized repository and can be retrieved at a level of an individual member. The medication database contains the Anatomical Therapeutic Chemical classification code (including brand and generic names), dose schedule, and dose dispensed in terms of defined daily dose. Information on maternal consumption of medications prior to delivery and medications consumed by their children was obtained from the "Clalit" database.

Data of births and hospitalizations were obtained from the Soroka Medical Center Admission-Transfer-Discharge computerized database; it includes demographic and medical diagnoses drawn directly from the hospital medical records. All diagnoses are classified according to the International Classification of Diseases, 9th revision.[15]

"Clalit" and Soroka Medical Center databases were encoded and linked to create a single registry of demographic and clinical data and medications dispensed to children, and to their mothers before and during pregnancy.

Exposure Definition

The "Clalit" medication dispensing registry was used to identify children whose mothers purchased H_2Bs or PPIs 2 months prior to conception and during pregnancy. To standardize the comparison of the different H_2Bs (ie, famotidine, ranitidine, and cimetidine) and PPIs (ie, omeprazole, pantoprazole, and lansoprazole), the defined daily dose (DDD) was used (defined daily dose is the assumed average maintenance dose per day for a drug used for its main indication in adults).[16] One DDD of famotidine is 40 mg per day, of ranitidine is 300 mg per day, of cimetidine is 800 mg per day, of omeprazole is 20 mg per day, of pantoprazole is 40 mg per day, and of lansoprazole is 30 mg per day. DDDs were divided into 0–10, 10–20, and >20.

Asthma Definition. The health status of children was assessed to the end of 2011, to include the 3-year follow-up period for children born in 2008. We used 2 definitions of asthma in children: 1 based on hospitalization data, and the other on antiasthma medications dispensed. Children were defined as asthmatic if they were hospitalized with asthma or recurrent wheezing diagnoses between the ages of 2 and 13 years in the absence of the following diagnoses: ICD-9 — 277, 428, 469, 516, 519, 530, and 745 (cystic fibrosis, acute bronchiolitis, bronchitis, heart failure, chronic airway obstruction, pulmonary diseases, gastroesophageal reflux, and heart defects, respectively).

Wheezing is common in infants, usually triggered by viral infections,[17] for which antiasthma medications are often prescribed. It is difficult to identify an infant with wheezing episodes who will develop asthma in the future,[18] as this symptom often subsides in preschool years. To reduce the chance of positive case selection, only children older than 2 years were assigned the diagnosis.

For the definition of asthma, medications were classified into 6 categories: A, inhaled β adrenergics; B, oral corticosteroids; C, inhaled corticosteroids; D, combined inhalers; E, montelukast; and F, ipratropium bromide or cromoglycate. Children were defined as asthmatic by documentation of at least 1 of the following dispensed medications over 1 year: (1) 2 or more of 1 of group A medications in addition to 2 or more of group B medications; (2) 2 or more of 1 of group D medications; (3) 2 or more of 1 of group A medications in addition to 1 of group C medications; (4) 2 or more of 1 of group A medications in addition to medication E; (5) 2 or more of 1 of group B medications in addition to medication E; (6) 1 or more of 1 of group F medications in addition to 1 or more of group A, C, or D medications.

To adjust the main analysis for maternal asthma, mothers were defined as asthmatic using the same

composite asthma definition accounting for either medications purchased or hospitalization events.

Statistical Analysis

Results are presented as mean ± SD, median and range for continuous variables, and as percentages for categorical data. A 2-sided $P < .05$ was considered statistically significant. Analyses were performed using SAS 9.2 software.

We estimated relative risks (RR) of developing asthma in offspring using a generalized estimating equation method with Poisson-distributed outcome as a dependent variable and scaled deviance to correct for overdispersion. Each woman in the study population could have given birth to more than 1 child during the study period, so the method accounted for clustering within deliveries of the same woman and for different follow-up used for each child by including years of follow-up as an offset variable. Models were adjusted for well-established risk factors for developing asthma or factors found significantly related to exposure and the outcome of the study. The list of covariates included maternal allergies and asthma, maternal age, infertility treatment, lack of prenatal care, gestational age at delivery, cesarean section delivery, birth weight and sex, birth year, dispensing PPIs or H_2Bs for children aged 0 to 2 years of age, and maternal use of the following medications during the exposure period: antibiotics, nonsteroidal-anti-inflammatory drugs (naproxen, diclofenac, indomethacin, etodolac, or rofecoxib), metoclopramide, and insulin, but not for socioeconomic status (SES), which was available for fewer than 80% of women.[19] Sensitivity analysis with the adjustment for SES showed no difference in statistical inference. An adjustment to the year of birth was not necessary to control for the constantly increasing incidence of asthma in Israel and worldwide.[20]

To investigate a possible dose–response association, we compared DDD categories of H_2Bs and PPIs and the number of times H_2Bs and PPIs were dispensed. We explored an effect of the timing of exposure on the outcome by analyzing when H_2Bs or PPIs were first dispensed, specifically, (1) if the medication was first dispensed within 2 months prior to conception or during the (2) first, (3) second, and (4) third trimester of pregnancy.

The obtained propensity scores did not efficiently discriminate between women who purchased the H_2Bs or PPIs and those who did not and therefore, adjustment to propensity score could not be useful in the analysis.

As a part of a sensitivity analysis, we tested the association between maternal consumption of PPIs and H_2 blockers 2 years after birth and asthma in childhood in a subset of mothers who did not take the medication in pregnancy, before pregnancy and up to 2 years after delivery and their children did not receive PPIs or H_2 blockers. This analysis was supposed to refute the possibility of confounding by indication, possible in this type of study.

Results

A total of 131 263 children were born at the Soroka Medical Center between the years 1999 and 2008. Of these, 91 459 were born to mothers registered in "Clalit." Personal identification number was not available for 31 children, and they were excluded from the analysis, reducing the effective sample size to 91 428 children who were born to 34 260 mothers.

Overall 10 534 children (11.5%) were defined as asthmatic based on medications purchased and 693 children (0.8%) based on hospitalization events. We used a composite asthma definition accounting for either medications purchased or hospitalization events in the analysis.

The proportion of women purchasing H_2Bs or PPIs during pregnancy increased over the years (Figure 1).

The prevalence of maternal allergies did not differ substantially by exposure to H_2Bs or PPIs. Mothers in the group exposed to H_2Bs or PPIs were characterized by a higher proportion of asthma, lack of prenatal care, higher gravidity and parity, and lower socioeconomic status, as compared with nonexposed mothers (Table 1).

Birth rate, APGAR score, sex, and preterm deliveries did not differ in offspring by in utero exposure to H_2Bs or PPIs. The prevalence of H_2B or PPI dispensing to children was higher in offspring exposed in utero to H_2Bs or PPIs (Table 2).

After adjustment for known potential confounders, the risk of developing asthma was significantly higher in the group prenatally exposed to H_2Bs or PPIs: RR, 1.09; $P = .023$ (Table 3). When assessing the association with H_2Bs and PPIs separately, we found that the risk among offspring prenatally exposed to PPIs (RR, 1.10; 95%CI, 0.98–1.22) was similar to the risk observed among offspring prenatally exposed to H_2Bs (RR, 1.06; 95%CI, 0.97–1.15). A dose–response relationship was demonstrated with a significantly higher risk of asthma within mothers prenatally purchasing H_2Bs or PPIs 3 times or more during the study period (RR,1.22; 95%CI, 1.00–1.47). Similarly, analysis by DDD categories showed a higher risk for exposure to >20 defined daily doses (RR, 1.12; 95%CI, 1.06–1.18; Figure 2).

About a third of the exposed mothers (32%) purchased H_2Bs or PPIs for the first time within 2 months prior to conception, 39% in the first trimester, 14.5% in the second, and 14.5% in the third.

The risk for asthma in the offspring of mothers who first purchased H_2Bs or PPIs within 2 months prior to

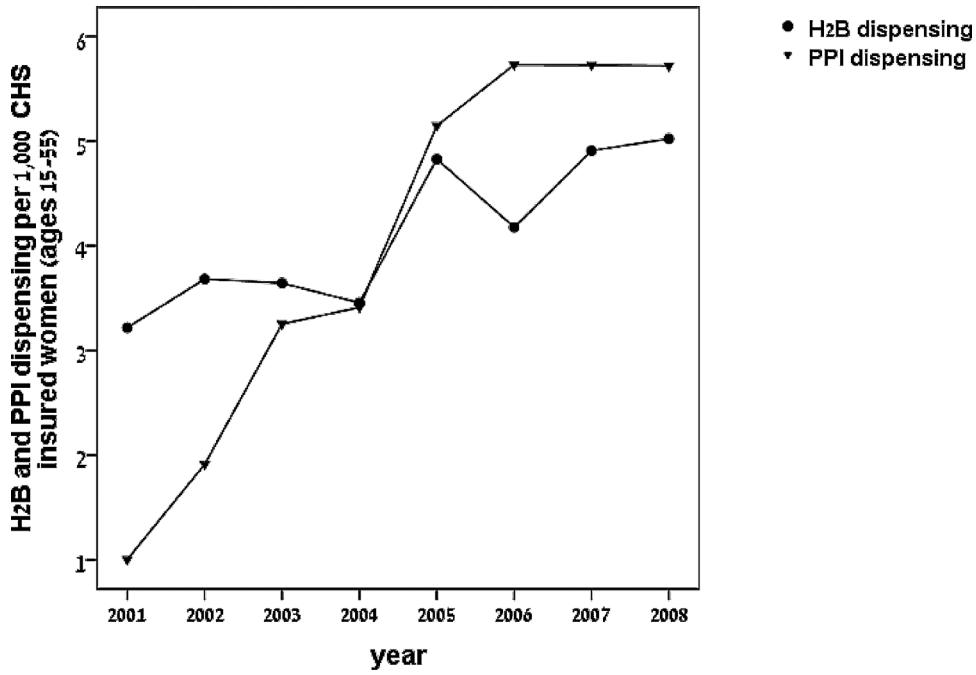

Figure 1. Annual dispensing rates of H_2B and PPI medications, per 1000 CHS insured women aged 15–55 between 2001 and 2008.

conception was not significant and 1.12 times greater ($P = .064$) compared with unexposed mothers. Associations of asthma in offspring and H_2Bs or PPIs dispensed within the first, second, and third trimesters are shown in Figure 2.

Table 1. Maternal Characteristics

Maternal Characteristics	Not Exposed to H_2Bs/PPIs 94.5% (86 403)	Exposed to H_2Bs/PPIs 5.5% (5025)	*P* Value
Maternal age, years			
Mean ± SD (n)	32.3 ± 5.3 (85 884)	32.5 ± 5.7 (4995)	.037
Bedouin origin, % (n)	63.2% (54 447)	79.9% (3998)	< .001
Family status			
Married	71.9% (62 093)	72.0% (3617)	
Divorced	1.5% (1177)	1.4% (64)	
Widowed	0.2% (169)	0.2% (11)	
Single	17.9% (13 810)	19.1% (871)	.195
Gravidity,			
Median	3.00	4.00	< .001
Min, Max	1, 20	1, 20	
Parity,			
Median	3.00	4.00	< .001
Min, Max	1, 19	1, 18	
Asthma, % (n)	3.1% (2685)	5.6% (282)	< .001
Allergies, % (n)	0.6% (531)	0.7% (34)	.578
SES, % (n)			
Low	85.4% (58 570)	91.7% (3406)	
Intermediate	12.6% (8675)	7.3% (271)	
High	1.95% (1338)	1% (37)	< .0001
Lack of prenatal care, % (n)	26.7% (23 102)	24.7% (1,240)	.001

SES, socioeconomic status.

Among exposed mothers, 49.4% consumed famotidine (2485 mothers), 13% ranitidine (668 mothers), 0.7% cimetidine (36 mothers), 6.8% lansoprazole (346 mothers), 0.8% pantoprazole (43 mothers), and 38.7% omeprazole (1947 mothers). None of the mothers consumed esomeprazole. Subgroup analyses of the risk by each drug individually showed an increased risk associated with exposure to lansoprazole (RR, 1.70; 95% CI, 1.39–2.11; $P \leq .001$; Figure 2).

Sensitivity Analyses

Until 2005 all H_2Bs and PPIs were available only by prescription; after 2005 some H_2B and PPI formulations became available over the counter. To reduce a possible misclassification bias in assessment of true exposure to H_2Bs and PPIs by excluding medication purchases without prescription, we reevaluated the risk of asthma only in children born before 2005 and found similar results (RR, 1.09; 95%CI, 0.99–1.21; $P = .069$). The effect of other potential risk factors remained unchanged, as well.

In an attempt to refute the possibility of confounding by indication, we examined if maternal consumption of PPIs and H_2 blockers 2 years after birth was associated with asthma in children. We limited this analysis to mothers who did not take the medication in pregnancy and up to 2 years after delivery and to their children who did not receive PPIs and H_2 blockers. Contrary to our expectations, the RR equaled 1.29 ($P < .001$)—stronger than the estimate obtained for the period of gestation.

Table 2. Offspring Characteristics

Offspring Characteristics	Not Exposed to H_2Bs/PPIs 94.5% (86 403)	Exposed to H_2Bs/PPIs 5.5% (5025)	*P* Value
Birth weight, g			
Mean ± SD (n)	3142.6 ± 573.86 (86 395)	3155.3 ± 569.78 (5025)	.127
Age at the end of follow-up, years			
Mean ± SD (n)	8.00 ± 2.89 (86 403)	6.60 ± 2.50 (5025)	< .001
Male sex, % (n)	52.5% (45 381)	51.6% (2592)	.196
APGAR 1 minute < 5, % (n)	1.7% (1447)	1.8% (91)	.463
APGAR 5 minutes < 7, % (n)	0.7% (597)	0.7% (37)	.662
Term birth, % (n)	89.8% (77 576)	89.7% (4508)	.867
Cesarean section, % (n)	16.3% (14 099)	18.6% (936)	< .001
H2B or PPI dispensing, % (n)	0.3% (244)	0.6% (29)	< .001

Table 3. Association Between Prenatal Exposure to H_2 Blockers and/or Proton Pump Inhibitors and the Risk of Asthma Among Offspring

	Adjusted Relative Risk of Asthma in Offspring (95%CI)	*P* Value
Prenatal H_2B or PPI dispensing	1.09 (1.01–1.17)	.023
Maternal asthma	1.96 (1.83–2.12)	< .001
Maternal allergies	1.07 (0.88–1.30)	.456
Infertility treatments	1.22 (1.12–1.32)	< .001
Lack of prenatal care	0.68 (0.64–0.71)	< .001
Male sex	1.09 (1.04–1.13)	< .001
Maternal age, years	1.00 (0.99–1.00)	.363
Preterm delivery vs term	1.23 (1.15–1.32)	< .001
Low birth weight (<2500 g)	1.11 (1.04–1.18)	.001
Cesarean section delivery	1.17 (1.12–1.22)	< .001
Child H_2B or PPI dispensing (between age 0 and 2 years)	2.08 (1.80–2.40)	< .001
Prenatal antibiotic dispensing	1.33 (1.29–1.38)	< .001
Prenatal NSAID dispensing	1.08 (1.02–1.16)	.001
Prenatal Metoclopramide dispensing	1.09 (1.01–1.15)	.0125
Prenatal Insulin dispensing	1.24 (1.06–1.44)	.005
Child birth year	1.09 (1.08–1.09)	< .001

All the factors are adjusted to others as listed in the table.
NSAID, nonsteroidal anti-inflammatory drug.

Discussion

The main finding of this investigation provides evidence of a weak association between prenatal exposure to H_2Bs and PPIs and the development of asthma in children and suggests that the extent of exposure and specific medications contribute to disease development. The methodology used in our investigation was similar to the one applied previously in relation to the safety of drug exposure during pregnancy.[21] The population-based nature of the estimates adds to the validity of the findings in the current analyses.

The association of in utero exposure to H_2Bs and PPIs and the development of childhood asthma was first described by Dehlink et al,[3] who investigated exposure to gastric acid suppression drugs and allergic diseases and demonstrated an increased risk odds ratio (OR) of 1.51. A similar increase in childhood asthma following antenatal exposure to H_2Bs and PPIs was reported by Andersen et al.[22] In an analysis of a selected population, Hak et al obtained similar results in a small number of asthmatic children who had been exposed in utero and even prior to conception, to H_2Bs and PPIs.[1] In a study of asthma risk among children exposed to a variety of drugs in utero, Kallen et al reported increased risk associated with "drugs for gastroesophageal reflux" (drugs not specified). [23] Mulder et al described an association of prenatal exposure to PPIs and H_2Bs and an increased risk for the development of asthma and allergic conditions in offspring.[24] Potential risk factors involved in the purported association were not fully studied. Of note, the magnitude of the association between prenatal exposure to H_2Bs and PPIs and childhood asthma is consistent between the studies, within the range of 1.2–1.5 depending on the type of calculated index (OR or RR) and is similar to the one obtained in the present investigation.

Childhood asthma was marginally associated with exposure to H_2Bs and PPIs within 2 months before conception ($P = .064$) as well as with maternal exposure to medication 2 years after delivery (as found in the sensitivity analysis). This last finding was verified for mothers not exposed to the medications before, during, or within 2 year after pregnancy. Being biologically implausible, this probably spurious, relationship may be a result of an unidentified confounding factor. Similarly. Andersen et al showed that exposure to paracetamol within 30 days prior to the first menstrual period increased the risk of childhood asthma. This association was also found for 1 year after birth, and the authors could not rule out the noncausal explanations of their findings.[25]

Additional Factors Affecting Asthma in Childhood

Similarly to previous findings,[6,7] Bedouin-Muslim mothers purchased H_2Bs and PPIs more frequently compared with Jewish mothers, which may indicate a higher frequency of acid reflux in Bedouin-Muslim mothers or a less cautious pattern in consumption of drugs in pregnancy.

A statistically significant association was found between H_2B/ PPI exposure and maternal asthma (Table 1). As gastroesophageal reflux is of frequent occurrence in patients with asthma and has been considered a potential trigger for asthma symptoms, the use of antacids has been advocated in their treatment[26] and has become common practice among some clinicians, although evidence of a significant clinical benefit is lacking.[27]

The study results are consistent with previous findings in identification of the risk factors of childhood asthma

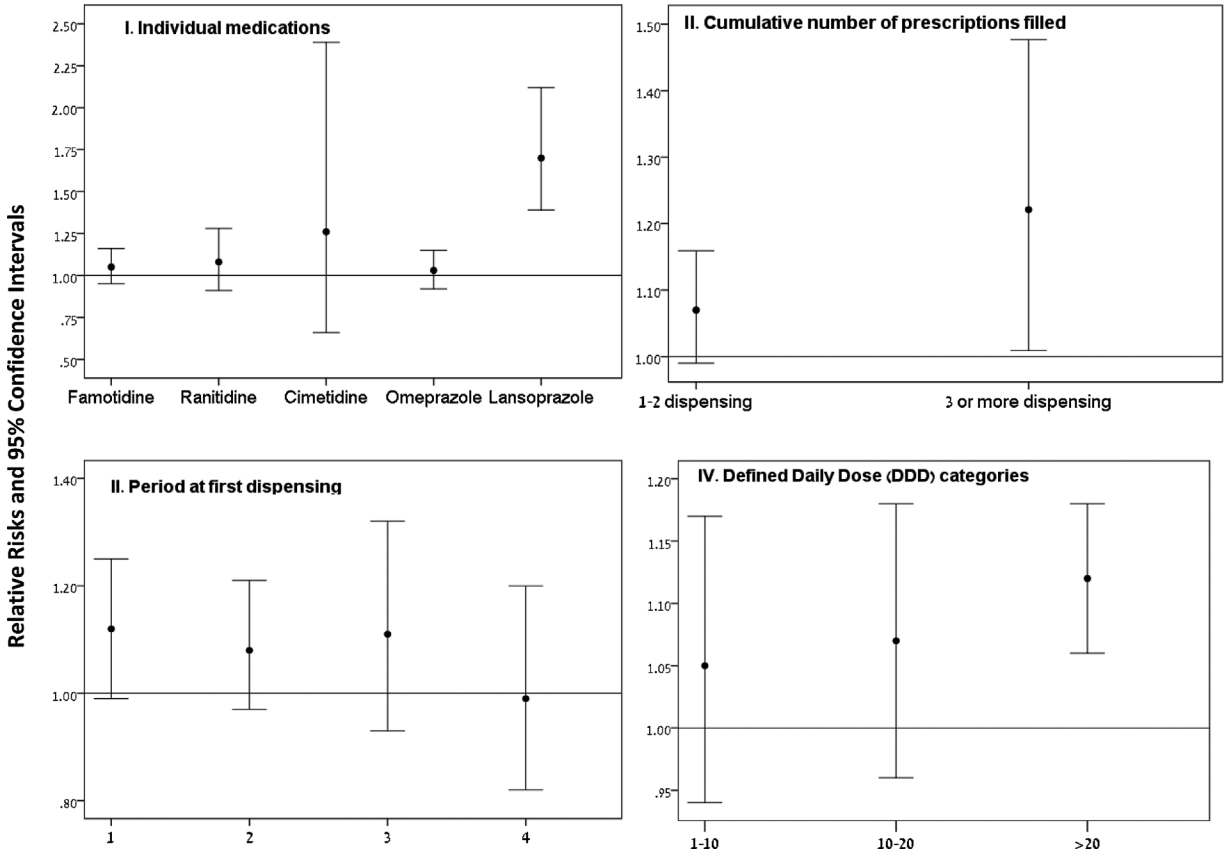

Figure 2. Relative risks (RRs) and 95% confidence intervals (CIs) of asthma in children by (I) individual medications; (II) period at first dispensing (1 = 2 months prior to conception, 2 = first trimester, 3 = second trimester, 4 = third trimester); (III) cumulative number of prescriptions filled (less than 3 and 3 or more prescriptions); (IV) defined daily dose (DDD) categories (<10, 10–20, and more than 20 DDD). (Number of women exposed to pantoprazole was not sufficient for this analysis (Graph I)).

development, other than H_2B/ PPI exposure, for example, preterm birth[28] and lower birth weight, maternal asthma,[29] male sex,[30] and delivery by cesarean section.[30] We also found that child exposure to H_2Bs/PPIs between ages 0 and 2 years was associated with asthma development, which could be explained by the same mechanism as in adults (ie, suppression of gastric-mediated breakdown of allergens in the stomach). The lack of prenatal care (LOPC) appeared to have a protective effect on asthma in childhood (RR, 0.68; $P = .001$); however, we consider this a spurious association in view of the fact that the asthma definition was based on the medication purchases in most of the cases. Specifically, as LOPC is negatively associated with medication purchases, it appeared that children born to mothers in the LOPC group experienced less asthma.

Limitations

The study has a number of limitations.

- The main possible bias in a study of this kind is confounding by indication, supported by a statistically significant association between maternal consumption of the medications 2 years after delivery and childhood asthma. This finding raises a question on the causality of the effect at study. We were not able to retrieve the exact indication for administering the H_2B and PPI medications from our databases. However, these medications can be taken for a variety of reasons, which possibly explains why the propensity score method failed to distinguish between the exposed and unexposed subjects.
- According to our findings, prenatal exposure to H_2Bs and PPIs appears significantly associated with asthma development in children with a relatively low risk, estimated at less than 1.30 in most of the subgroup analyses. The potential confounding effects of known prenatal factors associated with asthma in the offspring were largely controlled. However, over-the-counter purchase of medications (eg, paracetamol, folic acid and other vitamins, food additives) and factors such as paternal asthma, maternal body mass index, or smoking were not available or not

reliably reported and therefore not available for the analysis. Other residual confounding factors associated with asthma could exist, for example, exposure to environmental smoking and pollution, but it is likely that these were distributed equally between the exposure groups.

- In addition, our databases included medications dispensed only by "Clalit" pharmacies up to 2011, whereas after 2005 some H_2Bs and PPIs could be purchased over the .counter, which might have caused exposure misclassification bias. However, we assume that the missed exposures represent only a small proportion of consumption of H_2Bs and PPIs because of their higher cost. The risk estimate obtained in the sensitivity analysis on the data before 2005 remained unchanged.
- The study is prone to the misclassification bias frequent in pharmacoepidemiology, whereas exposure to a medication was based on dispensing records and not verified for actual consumption or dose. We assume this bias to be nondifferential.
- There is a possibility of misclassification of the outcome at study, which we tried to minimize by applying consumption of antiasthmatic medications in addition to hospitalization diagnoses. We used a strict prescription regime criterion to minimize the chance of asthma false-positive cases; however, some asthmatic children may have been excluded.

In an attempt to characterize our findings in terms of causality, we might apply the Bradford Hill criteria. Some of these, for example, consistency and dose response, were met in the study. However, others are more problematic in view of the absence of the experimental data or well-established biological plausibility, relatively small effect size, and possible biases in using the retrospectively collected database.

We therefore may conclude that there is a statistical, but not causal, association between exposure to H_2Bs or PPIs and asthma in childhood of a minor magnitude. An unidentified causative factor could not be ruled out.

In view of the low and most probably noncausal effect, we cannot recommend avoidance of acid-suppressing medications in pregnant mothers who require them for treatment.

More studies are needed to explore this risk in a prospective fashion.

Acknowledgments

The authors declare no conflicts of interest relevant to this study. M.Y.S. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. We thank members of the Computer Units of "Clalit" Southern District and of Soroka Medical Center.

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Declaration of Conflicting Interests

The authors have no conflicts of interest to disclose.

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