Clinical Study Report Synopsis

Drug Substance	PPIs and H_2RAs
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Association between acid-suppressing drug use during pregnancy and asthma in the offspring

Study dates:	Retrospective observational cohort study covering the period January 1996 – December 2010
Phase of development:	Therapeutic use
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Study centre(s)

UK

Objectives

- To estimate the relative risk of asthma in children associated with maternal use of proton pump inhibitors (PPIs) during pregnancy.
- To estimate the relative risk of asthma in children associated with maternal use of histamine 2 receptor antagonists (H_2RAs) during pregnancy.
- To identify other potential risk factors associated with the development of asthma in children.

Study design

A retrospective, observational cohort study performed using data from The Health Improvement Network (THIN) primary care database in the UK.

Identification of female participants

Women aged 18–45 years between 1 January 1996 and 31 December 2010, and who had completed pregnancies during this period, were identified from THIN. Using the family identification number and date of birth recorded in THIN, 126 659 completed pregnancies were linked to 129 790 live-born infants.

Cohorts of women exposed and unexposed to H_2RAs and PPIs

Exposure to acid-suppressing drugs during pregnancy was defined as the presence of at least one prescription of H_2RAs or PPIs anytime between the last menstrual period (LMP) date and the delivery date. PPIs and H_2RAs were considered separately, and exposure was categorized according to pregnancy trimester. Women exposed to acid-suppressing drugs during the pre-pregnancy period (90 days before the LMP date) but not during pregnancy were also identified.

A cohort of 3045 women with at least one prescription for PPIs or H_2RAs during pregnancy was identified, corresponding to 3154 infants in the exposed cohort. These exposed women were matched (same calendar quarter at LMP date and same age at LMP data) to a sample of 10 000 unexposed women. In total, 10 233 infants were born in the unexposed cohort. In addition, 1135 infants whose mothers were exposed to acid-suppressing drugs during their pre-pregnancy period but not during pregnancy were identified.

Selection and follow-up of infants

Infants were included in the analysis if: they were registered with a practice at the time of the last THIN update; were at least one year old on the date of the last data collection for their practice; they were alive at one year of age; they were at least one year old on 1 January 2011; and they had no information gaps in their computer file. A total of 10 116 infants met these inclusion criteria: 2371 in the exposed cohort (2315 mothers) and 7745 in the unexposed cohort (7596 mothers). In the pre-pregnancy exposure cohort, 894 infants (884 mothers) met the inclusion criteria. Among infants in the exposed cohort, 816 (34.4%), 1414 (59.6%) and

141 (5.9%) had been exposed *in utero* to PPIs, H_2RAs and both drugs, respectively. In the pre-pregnancy exposure cohort, the corresponding numbers of infants were 600 (67.1%), 269 (30.1%) and 25 (2.8%). All 10 116 infants were followed up from one year of age until they met one of the following endpoint: asthma diagnosis; their sixth birthday; death; or the end of the study period (31 December 2011).

Asthma case ascertainment

A total of 823 potential asthma cases were identified from THIN records using an automated computer search for specific Read codes (571 in unexposed cohort, 65 among infants exposed to PPIs *in utero*, 173 among infants exposed to H_2RAs *in utero* and 14 among infants exposed to both drugs *in utero*). Asthma cases were ascertained by manual review of anonymized electronic medical records. A total of 763 infants with a confirmed asthma diagnosis were identified (93% confirmation rate); 526 (92%) in the unexposed cohort and 237 (94%) in the exposed cohort (60 [92%] exposed to PPIs, 164 [95%] exposed to H_2RAs and 13 [93%] exposed to both drugs). In the pre-pregnancy exposure cohort, 98 potential asthma cases were identified and 93 (95%) were confirmed after manual review.

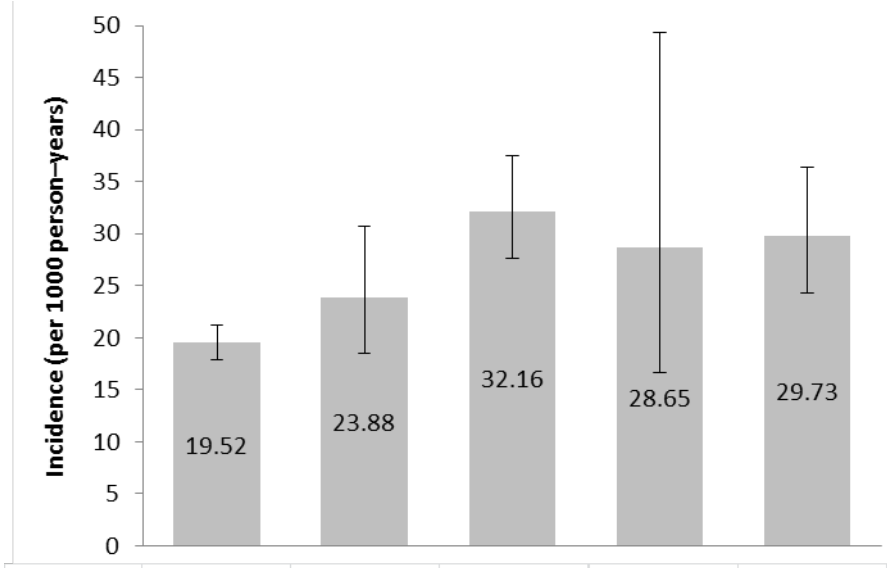
Data collection and analysis

The incidence of asthma in infants was calculated for each exposure category. Different Cox proportional hazard models were used to estimate the relative risk for infants to develop asthma according to their mothers' antenatal exposure to acid-suppressing drugs. Results are reported below for two models. Model A was adjusted for year of delivery and number of primary care physician (PCP) visits and referrals in the year before the LMP date. In addition to the aforementioned factors, model B was adjusted for maternal comorbidities (asthma, allergies, gastroesophageal reflux disease and peptic ulcer disease), use of non-steroidal anti-inflammatory drugs, antacids, antibiotics and antihistamines during pregnancy, and sex of infant. Cox proportional hazard models adjusted for year of delivery and number of PCP visits and referrals in the year before the LMP date were also used to identify other potential risk factors for asthma in infants.

Summary of results

Incidence of asthma

Crude incidences of asthma in infants according to their mothers' exposure to acid-suppressing drugs are shown in Figure 1. Incidence was highest in the cohort of infants exposed to H_2RAs *in utero* and lowest in the unexposed cohort. The crude incidence ratios for asthma associated with drug use during pregnancy were 1.22 (95% CI: 0.94–1.60) for PPIs, 1.65 (95% CI: 1.38–1.96) for H_2RAs and 1.47 (95% CI: 0.85–2.54) for both drugs. The incidence ratio for the pre-pregnancy exposure to acid-suppressing drugs relative to non-exposure was 1.52 (95% CI: 1.22–1.90).



Exposure	Non	PPIs	H_2RAs	PPIs+H_2RAs	Pre-pregnancy
No. of cases	526	60	164	13	93
Person-years	26 946	2513	5099	454	3128

Figure 1. Incidence of asthma in infants according to their mothers' exposure to acid-suppressing drugs. Whiskers represent 95% confidence intervals.
H_2RA; histamine 2 receptor antagonist; PPI, proton pump inhibitor.

Risk of asthma in infants associated with maternal exposure to acid-suppressing drugs

Hazard ratios for the risk of asthma in infants associated with PPI and H_2RA use during pregnancy are shown in Table 1. In both models, exposure to PPIs during pregnancy was not associated with an increased risk of asthma in infants. In contrast, use of H_2RAs at any time during the pregnancy and during the second semester was associated with a significantly increased risk of asthma in infants. A significantly increased risk was also observed in model A for exposure to H_2RAs during the third trimester of pregnancy. Exposure to PPIs in the year before pregnancy was associated with a significantly increased risk of asthma in infants in both models. Exposure to H_2RAs during the year before the pregnancy was only associated with a significantly increased risk of asthma in model A.

Table 1. Hazard ratios for asthma in infants associated with PPI or H_2RA use during pregnancy.

	Adjusted HR (95% CI) Model A[a]	Adjusted HR (95% CI) Model B[b]
Exposure during pregnancy[c]		
PPIs		
At any time	1.12 (0.88–1.44)	1.03 (0.76–1.40)
During the first trimester	1.16 (0.88–1.52)	1.07 (0.76–1.51)
During the second trimester	1.39 (0.89–2.18)	1.11 (0.60–2.05)
During the third trimester	1.04 (0.68–1.60)	0.69 (0.36–1.30)
During all three trimesters[d]	1.40 (0.72–2.72)	0.73 (0.23–2.31)
H_2RAs		
At any time	1.43 (1.20–1.70)	1.32 (1.05–1.64)
During the first trimester	1.16 (0.84–1.61)	1.15 (0.77–1.72)
During the second trimester	1.77 (1.34–2.33)	1.75 (1.25–2.47)
During the third trimester	1.38 (1.14–1.68)	1.20 (0.93–1.54)
During all three trimesters[d]	1.48 (0.76–2.85)	1.26 (0.51–3.08)
Exposure during the year before pregnancy[c]		
PPIs in the year before the LMP date	1.49 (1.18–1.89)	1.46 (1.08–1.98)
H_2RAs in the year before the LMP date	1.68 (1.23–2.30)	1.45 (0.96–2.19)

[a]Cox proportional hazard model adjusted for year of delivery and number of maternal PCP visits and referrals in the year before the LMP date.
[b]Cox proportional hazard model adjusted for year of delivery, number of maternal PCP visits and referrals in the year before the LMP date, maternal comorbidities (asthma, allergies, gastroesophageal reflux disease and peptic ulcer disease), maternal use of NSAIDs, antacids, antibiotics and antihistamines during pregnancy, and sex of infant.
[c]Relative to non-exposure.
[d]At least one prescription of the corresponding acid-suppressing drug per trimester.
CI, confidence interval; H_2RA, histamine 2 receptor antagonist; HR, hazard ratio; LMP, last menstrual period; NSAID, non-steroidal anti-inflammatory drug; PCP, primary care physician; PPI, proton pump inhibitor.

Other predictors of asthma in infants

Hazard ratios for risk factors potentially associated with the development of asthma in infants are summarized in Table 2. The strongest predictors of asthma in infants were pre-existing maternal multiple sclerosis, maternal use of β2-adrenergic receptor agonists during pregnancy and maternal allergies diagnosed during pregnancy.

Table 2. Hazard ratios for asthma associated with maternal life style, comorbidities and drug use during pregnancy.

	Adjusted HR (95% CI)[a]
Maternal life style	
BMI within 5 years of LMP date, kg/m^2	
15.00–19.99	1.05 (0.78–1.40)
20.00–24.99[b]	1(–)
25.00–29.99	1.18 (0.96–1.44)
≥ 30.00	1.07 (0.83–1.36)
Unknown	1.04 (0.87–1.25)
Smoking in the year after delivery	
Non smoker[b]	1 (–)
Current smoker	1.19 (0.95–1.51)
Former smoker	1.37 (1.08–1.73)
Unknown	0.98 (0.82–1.18)
Rural/Urban	
Urban[b]	1 (–)
Town	1.06 (0.84–1.34)
Village	0.78 (0.55–1.10)
Unknown	1.23 (1.02–1.47)
Number of PCPs in the year before the LMP date	
≤ 4[b]	1 (–)
5–9	0.97 (0.71–1.32)
10–19	1.11 (0.83–1.48)
≥ 20	1.56 (1.15–2.12)
Number of referrals in the year before the LMP date	
≤ 1[b]	1 (–)
2–4	1.14 (0.97–1.35)
5–9	1.24 (1.00–1.54)
≥ 10	1.07 (0.74–1.55)
Drug use during pregnancy[c]	
β2-Adrenergic receptor agonists	2.26 (1.87–2.71)
Asthma medications	1.58 (1.34–1.86)
Acetaminophen	1.41 (1.18–1.69)
Antacids	1.37 (1.18–1.58)
NSAIDs	1.20 (0.71–1.31)
Antihistamines	1.08 (0.89–1.32)
Antibiotics	1.04 (0.90–1.21)
Prokinetics	0.54 (0.33–0.89)

	Adjusted HR (95% CI)[a]
Maternal comorbidities[d]	
Allergies	
Pre-existing	1.10 (0.93–1.29)
Diagnosed during pregnancy	1.93 (1.24–2.99)
Asthma	
Pre-existing	1.55 (1.21–2.00)
Diagnosed during pregnancy	0.99 (0.76–1.28)
Autoimmune disease	
Pre-existing	1.78 (1.03–3.10)
Diagnosed during pregnancy	0.64 (0.09–4.57)
GERD	
Pre-existing	1.07 (0.79–1.44)
Diagnosed during pregnancy	1.17 (0.92–1.48)
Hay fever[e]	
Pre-existing	1.21 (0.96–1.52)
Multiple sclerosis[e]	
Pre-existing	2.66 (0.99–7.11)

[a]Cox proportional hazard model adjusted for year of delivery and number of maternal PCP visits and referrals in the year before the LMP date.
[b]Reference category.
[c]Relative to non-use.
[d]Relative to absence of comorbidity.
[e]No cases of newly-diagnosed disease during pregnancy
CI, confidence interval; GERD, gastroesophageal reflux disease; HR, hazard ratio; LMP, last menstrual period; NSAID, non-steroidal anti-inflammatory drug; PCP, primary care physician.