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GESTATIONAL AGE AT BIRTH AND RISK OF GASTRIC ACID-RELATED DISORDERS IN YOUNG ADULTHOOD

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Abstract

Purpose—Preterm birth is associated with gastric acid-related disorders in infancy, but no studies have examined this association beyond early childhood. We used antisecretory medication data to explore whether preterm birth is associated with gastric acid-related disorders in young adulthood.

Methods—National cohort study of 626,811 individuals born in Sweden in 1973–1979, followed up for antisecretory (proton pump inhibitor and H2-receptor antagonist) medication prescriptions from all outpatient and inpatient pharmacies nationwide in 2005–2009 (ages 25.5–37.0 years). We excluded individuals with congenital anomalies, and examined potential confounding by other comorbidities identified on the basis of oral anti-inflammatory or corticosteroid medication prescription.

Results—Gestational age at birth was inversely associated with antisecretory medication prescription in young adulthood. Adjusted odds ratios for ≥1 antisecretory medication prescription/year were 3.38 (95% CI, 1.73–6.62) for individuals born at 22–27 weeks, 1.38 (95% CI, 1.19–1.60) for those born at 28–34 weeks, and 1.19 (95% CI, 1.06–1.32) for those born at 35–36 weeks, relative to those born full-term (37–42 weeks). Exclusion of individuals who were prescribed oral anti-inflammatory or corticosteroid medications (≥1/year) had little effect on these results.

Conclusion—These findings suggest that low gestational age at birth may be independently associated with an increased risk of gastric acid-related disorders in young adulthood.

Keywords

gastric acid; gastroesophageal reflux; gestational age; premature birth

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INTRODUCTION

Preterm birth is associated with an increased risk of gastroesophageal reflux disease (GERD) in infancy.(1–2) Previous studies have also reported an association between preterm birth and an increased risk of esophageal adenocarcinoma (3) or gastric cardia adenocarcinoma (4) in later life. The mechanism is unknown but may involve increased susceptibility of immature epithelium to the carcinogenic effects of gastric acid in preterm infants, and/or a longer-term increased risk of GERD among these individuals.(3–4) To our knowledge, no studies to date have examined whether preterm birth is associated with an increased risk of GERD or other gastric acid-related disorders beyond early childhood. Such information would advance the understanding of etiologies of these conditions, as well as potential mechanisms underlying an association between preterm birth and esophageal adenocarcinoma or other complications of GERD in later life.

We conducted a national cohort study to explore whether preterm birth is associated with gastric acid-related disorders in young adulthood. Using nationwide pharmacy data in Sweden, we examined the association between gestational age at birth and antisecretory (proton pump inhibitor and H2-receptor antagonist) medication prescription among young adults (ages 25.5–37.0 years), while adjusting for potential confounders and examining the effect of comorbidities. We hypothesized that low gestational age at birth would be independently associated with increased antisecretory medication prescription in young adulthood.

METHODS

Study Population

We identified 685,733 singleton live births in the Swedish Birth Registry that occurred from 1973 through 1979. Of this total, 11,208 individuals (1.6%) died and 36,415 (5.3%) emigrated (determined by the absence of a Swedish residential address in census data) prior to the follow-up period (2005–2009). We excluded 7,763 other individuals (1.1%) who had significant congenital anomalies (i.e., other than undescended testicle, preauricular appendage, congenital nevus, or hip dislocation), 1,591 (0.2%) who had missing information for gestational age at birth, and 238 (<0.1%) who had missing information for birthweight. To remove possible coding errors, we also excluded 1,707 others (0.2%) who had a reported birthweight more than four standard deviations above or below the mean birthweight for gestational age and sex based on a Swedish reference growth curve.(5) A total of 626,811 individuals (91.4% of the original cohort) remained for inclusion in the study. This study was approved by the Ethics Committee of Lund University in Malmö, Sweden.

Antisecretory Medication Ascertainment

The study cohort was followed up for all outpatient and inpatient antisecretory medication prescriptions from July 1, 2005 through December 31, 2009, the first 4.5 years that the Swedish national pharmacy registry was kept. This registry, maintained by the Swedish National Board of Health and Welfare, includes a record of each medication prescribed by a health care provider and dispensed to a patient by any outpatient or inpatient pharmacy throughout Sweden.(6–13) For inpatients, the registry includes all medications prescribed and dispensed to a patient upon discharge from the hospital. All medications are categorized according to the Anatomical Therapeutic Chemical (ATC) Classification System developed by the WHO Collaborating Centre for Drug Statistics Methodology.(14) We obtained information for all prescriptions of antisecretory medications, which include H2-receptor antagonists (ATC code A02BA) and proton pump inhibitors (ATC code A02BC). These data were linked to the Swedish Birth Registry using an anonymous identification number,

(15) and were modeled as ≥1 or <1 antisecretory prescriptions per year on average during the follow-up period. The evaluation of multiple antisecretory prescriptions is expected to improve the positive predictive value for GERD, because GERD is usually a chronic, relapsing condition requiring long-term management.(16)

To examine potential confounding by comorbidities, we also obtained information for all prescriptions of oral anti-inflammatory medications (ATC code M01) and oral corticosteroids (ATC code H02). These medications may be prescribed more commonly among individuals who were born preterm and are also associated with gastroduodenal injury, hence they are an alternative indication for prescribing antisecretory medications for prevention or treatment of these adverse effects.(17–19)

Gestational Age at Birth Ascertainment

The exposure of interest was gestational age at birth, which was based on maternal report of last menstrual period and obtained from prenatal and birth records in the Swedish Birth Registry. This was modeled as a categorical variable (22–27, 28–34, 35–36, 37–42, ≥43 weeks) to allow for a non-linear effect. Cutpoints were preselected to allow sufficient numbers in each category for analysis.

Other Study Variables

We also obtained demographic information from the Swedish Birth Registry and census data that may be associated with preterm birth and with the subsequent risk of GERD or related disorders.(20) The following were included as adjustment variables:

Age. Modeled as a continuous variable by infant's date of birth.

Sex. Male or female.

Fetal growth. Measured as the number of standard deviations from the mean birthweight for gestational age and sex based on a Swedish reference growth curve,(5) categorized into six groups (<−2; −2 to <−1; −1 to <0; 0 to <1; 1 to <2; ≥2 SD) to allow for a non-linear effect. This was included to assess whether an association between gestational age at birth and antisecretory medications is independent of fetal growth.

Maternal marital status. Married/cohabiting, never married, divorced/widowed, or unknown.

Maternal education. Compulsory high school or less (≤9 years), practical high school or some theoretical high school (10–11 years), theoretical high school and/or college (≥12 years), or unknown.

Family income. Calculated as the annual family income divided by the number of people in the family, using a weighted system whereby small children were given lower weights than adolescents and adults. The final variable was categorized in quartiles.

Statistical Analysis

Generalized estimating equations were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between gestational age at birth (22–27, 28–34, 35–36, 37–42, ≥43 weeks) and antisecretory prescriptions (≥1/year vs. <1/year) in young adulthood, using full-term birth (37–42 weeks) as the reference category. Analyses were conducted first unadjusted and then adjusted for covariates. To examine and control for confounding by certain comorbidities, we repeated the adjusted analysis after excluding individuals who were prescribed oral anti-inflammatory medications (≥1/year: n=31,613; 5.0%) or oral corticosteroids (≥1/year: n=10,459; 1.7%). Robust standard errors were used

in all models to account for correlation among siblings. We explored first-order interaction effects between gestational age at birth and each of the covariates using a likelihood ratio test. All statistical tests were 2-sided with an α-level of 0.05. All analyses were conducted using Stata version 11.0.(21)

RESULTS

Of the 626,811 individuals in this cohort, 24,907 (4.0%) were born preterm (<37 weeks), including 165 (0.03%) born at 22–27 weeks, 7,414 (1.2%) born at 28–34 weeks, and 17,328 (2.8%) born at 35–36 weeks. Compared with full-term infants, preterm infants were more likely to be male, and their mothers were more likely to be unmarried, have low educational attainment, or have low family income (Table 1; $P<0.001$ for each of these comparisons using Kruskal-Wallis test).

Low gestational age at birth was associated with a higher prevalence of antisecretory medication prescription (≥1/year) (Table 2; $P_{trend}<0.001$). A total of 10,808 individuals (1.7%) from the entire cohort were prescribed ≥1 antisecretory medication/year, including 5.5% of those born at 22–27 weeks, 2.4% of those born at 28–34 weeks, and 2.0% of those born at 35–36 weeks, compared with 1.7% of those born full-term (37–42 weeks). A similar trend was found after excluding individuals who were prescribed oral anti-inflammatory medications (≥1/year) or oral corticosteroids (≥1/year) ($P_{trend}<0.001$).

Adjusted odds ratios for ≥1 antisecretory medication prescriptions/year were 3.38 (95% CI, 1.73–6.62) for individuals born at 22–27 weeks, 1.38 (95% CI, 1.19–1.60) for those born at 28–34 weeks, and 1.19 (95% CI, 1.06–1.32) for those born at 35–36 weeks, relative to those born full-term (37–42 weeks) (Table 3). A significant inverse linear trend was found across the full range of gestational ages ($P_{trend}<0.001$). Among all individuals born preterm (<37 weeks) combined, there was a modestly increased odds of antisecretory prescription relative to those born full-term (adjusted OR, 1.26; 95% CI, 1.15–1.37). Exclusion of individuals who were prescribed oral anti-inflammatory medications (≥1/year) or oral corticosteroids (≥1/year) had little effect on any of these results (Table 3).

Table 4 presents adjusted odds ratios for the association between model covariates and antisecretory medication prescription in young adulthood among the entire study cohort. After adjusting for the other variables included in the model (see Table 4 footnote), significant predictors of antisecretory prescription included female sex, lowest fetal growth, low family income, or having a mother who was unmarried or with low educational attainment. No first-order interactions were found between gestational age at birth and any of the model covariates at the $P<0.05$ level (data not shown).

DISCUSSION

Low gestational age at birth was associated with increased antisecretory medication prescription in young adulthood among individuals born in Sweden in 1973–1979. After excluding congenital anomalies and adjusting for confounders, young adults who were born extremely preterm (22–27 weeks) had more than 3 times the odds of antisecretory medication prescription relative to those who were born full-term. Exclusion of other comorbidities identified on the basis of oral anti-inflammatory or corticosteroid prescription had little effect on these results. These findings suggest that preterm birth, especially extreme preterm birth, may be independently associated with an increased risk of gastric acid-related disorders in young adulthood. Additional studies are warranted to confirm these findings and to identify whether they are specifically due to GERD or other related conditions.

These findings suggest possible mechanisms for a previously reported association between preterm birth and esophageal adenocarcinoma(3) or gastric cardia adenocarcinoma(4) in later life. A Swedish case-control study reported that 3,364 individuals born at gestational ages <35 weeks or with low birthweight had a 7-fold (95% CI, 1.98–18.6) increased risk of esophageal adenocarcinoma (a known complication of GERD) in adulthood, relative to age-matched controls.(3) Another Swedish study of 67 esophageal adenocarcinoma cases and 93 gastric cardia adenocarcinoma cases reported that gestational age at birth was inversely associated with risk of gastric cardia adenocarcinoma (P_{trend}=0.001) and non-significantly inversely associated with risk of esophageal adenocarcinoma (P_{trend}=0.07).(4) Potential mechanisms for these findings include increased susceptibility of immature epithelium to the carcinogenic effects of gastric acid in preterm infants, and/or an increased risk of GERD in later life.(3–4) The current study's findings are consistent with an increased risk of GERD or related disorders at least into young adulthood among individuals who were born preterm. Additional research is needed to confirm this association, as well as the long-term risk of esophageal adenocarcinoma and other potential complications.

To our knowledge, this is the first study to explore the association between preterm birth and the risk of gastric acid-related disorders beyond early childhood. One study of 727 preterm infants reported a GERD prevalence of 26.7% at ages 1–2 years, and those with GERD had lower gestational ages at birth on average than those without GERD (30.5 and 32.0 weeks, respectively), although there was no comparison group of full-term infants.(2) Other small studies have explored the natural history of GERD, without examining gestational age at birth. Some of these reported that >95% of infants with a history of regurgitation had marked improvement or resolution of symptoms by 1 to 2 years of age.(22–23) Others based on survey data reported that GERD persisting into later childhood is a risk factor for GERD in adulthood.(24–27) However, none of these examined the potential effect of gestational age at birth on the risk of GERD beyond early childhood.

Transient lower esophageal sphincter relaxations (TLESRs) are the predominant mechanism of GERD in infants and children,(28–30) as in adults.(31) A study of 36 preterm and term infants reported a similar prevalence and frequency of TLESRs in infants with or without GERD symptoms, but symptomatic infants had a higher proportion (16.5% vs. 5.9%) of TLESRs accompanied by acid reflux.(28) It is therefore hypothesized that GERD in infancy may be due to anatomic or sensory variations that facilitate acid reflux during TLESR rather than TLESR frequency,(28) although these variations are still not well-characterized in either preterm or term infants.

A limitation of the current study is the use of antisecretory medication prescriptions as a surrogate measure for GERD and other gastric acid-related disorders. This approach is unable to identify specific indications, or conditions that are treated without prescription medications or untreated. The medical consultation rate for adults with GERD has been reported to be approximately 30% per year,(32–33) with estimates ranging from 5.4%(34) to 56.0%.(35) Young adults who were born preterm may be more likely to be prescribed antisecretory medications as a result of comorbidities. In this study, we excluded individuals with congenital anomalies. We also examined potential confounding due to oral anti-inflammatory or corticosteroid prescription because they are common independent indications for prescribing antisecretory medications, but this had little effect on our results. Other clinical data were unavailable and residual confounding by comorbidities or health care utilization is possible.

Strengths of this study included its large population-based cohort design and the ability to examine these associations with good statistical power across the full range of gestational ages. We used nationwide medication data from all outpatient and inpatient pharmacies from

all health care settings throughout Sweden, thus avoiding bias that may result from self-reporting or from the sole use of hospital-based data. Information on sociodemographic factors and medications used for relevant comorbidities enabled evaluation and adjustment for these confounding effects.

In summary, this national cohort study suggests that low gestational age at birth may be independently associated with an increased risk of gastric acid-related disorders in young adulthood. Additional epidemiologic and clinical studies are warranted to confirm these findings, potential mechanisms, and the risk of esophageal adenocarcinoma and other complications throughout the life course.

Acknowledgments

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Abbreviations

ATC	Anatomical Therapeutic Classification
CI	confidence interval
GERD	gastroesophageal reflux disease
OR	odds ratio
TLESR	transient lower esophageal sphincter relaxation
WHO	World Health Organization

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Table 1

Infant and maternal characteristics by gestational age at birth (1973–1979)

	Gestational Age, n (%)				
	22–27 weeks (N=165)	**28–34 weeks (N=7,414)**	**35–36 weeks (N=17,328)**	**37–42 weeks (N=583,248)**	**≥43 weeks (N=18,656)**
Sex					
Male	90 (54.5)	4,199 (56.6)	9,680 (55.9)	298,967 (51.3)	9,348 (50.1)
Female	75 (45.4)	3,215 (43.4)	7,648 (44.1)	284,281 (48.7)	9,308 (49.9)
Maternal Marital Status					
Married/cohabiting	119 (72.1)	5,075 (68.4)	12,194 (70.4)	440,303 (75.5)	13,436 (72.0)
Never married	23 (13.9)	983 (13.3)	2,050 (11.8)	54,509 (9.4)	2,107 (11.3)
Divorced/widowed	20 (12.1)	1,201 (16.2)	2,807 (16.2)	81,862 (14.0)	2,891 (15.5)
Unknown	3 (1.8)	155 (2.1)	277 (1.6)	6,574 (1.1)	222 (1.2)
Maternal Education					
Compulsory HS or less (≤9 years)	49 (29.7)	2,321 (31.3)	5,295 (30.6)	154,640 (26.5)	5,420 (29.0)
Practical HS or some theoretical HS (10–11 years)	76 (46.1)	3,433 (46.3)	7,902 (45.6)	271,371 (46.5)	8,710 (46.7)
Theoretical HS and/or college (≥12 years)	37 (22.4)	1,467 (19.8)	3,782 (21.8)	148,993 (25.6)	4,251 (22.8)
Unknown	3 (1.8)	193 (2.6)	349 (2.0)	8,244 (1.4)	275 (1.5)
Family Income					
Lowest quartile	51 (30.9)	2,089 (28.2)	4,563 (26.3)	134,100 (23.0)	4,489 (24.1)
Second quartile	35 (21.2)	1,833 (24.7)	4,480 (25.9)	150,154 (25.7)	4,717 (25.3)
Third quartile	42 (25.5)	1,850 (25.0)	4,310 (24.9)	149,836 (25.7)	4,813 (25.8)
Highest quartile	37 (22.4)	1,642 (22.1)	3,975 (22.9)	149,158 (25.6)	4,637 (24.9)

Abbreviation: HS = High school.

Table 2

Antisecretory medication prescription (≥1/year) in young adulthood (ages 25.5–37.0 years) by gestational age at birth (1973–1979)

Gestational Age (weeks)	All Individuals (N=626,811) n (%)	After Exclusions[a] (N=586,551) n (%)
22–27	9 (5.5)	7 (4.4)
28–34	178 (2.4)	132 (1.9)
35–36	351 (2.0)	260 (1.6)
<37	538 (2.2)	399 (1.7)
37–42	9,932 (1.7)	7,482 (1.4)
≥43	338 (1.8)	241 (1.4)
All	10,808 (1.7)	8,122 (1.4)

[a]Excluding individuals who were prescribed oral anti-inflammatory medications (≥1/year: n=31,613; 5.0%) or oral corticosteroids (≥1/year: n=10,459; 1.7%).

Table 3

Odds ratios for association between gestational age at birth (1973–1979) and antisecretory medication prescription (≥1/year) in young adulthood (ages 25.5–37.0 years)

Gestational Age (weeks)	Unadjusted	Adjusted[a]	Adjusted After Exclusions[b]
22–27	3.32 (1.70, 6.47)	3.38 (1.73, 6.62)	3.34 (1.57, 7.11)
28–34	1.41 (1.22, 1.64)	1.38 (1.19, 1.60)	1.34 (1.12, 1.59)
35–36	1.19 (1.07, 1.33)	1.19 (1.06, 1.32)	1.16 (1.03, 1.32)
<37	1.27 (1.16, 1.39)	1.26 (1.15, 1.37)	1.23 (1.11, 1.36)
37–42	Reference	Reference	Reference
≥43	1.07 (0.95, 1.19)	0.97 (0.87, 1.09)	0.94 (0.82, 1.07)

[a] Adjusted for age, sex, fetal growth, maternal marital status, maternal education, and family income.

[b] Excluding individuals who were prescribed oral anti-inflammatory medications (≥1/year: n=31,613; 5.0%) or oral corticosteroids (≥1/year: n=10,459; 1.7%).

Table 4

Adjusted odds ratios[a] for association between model covariates and antisecretory medication prescription (≥1/year) in young adulthood (ages 25.5–37.0 years)

	OR (95% CI)	*P* value
Sex		
Male	Reference	
Female	1.56 (1.50–1.62)	<0.001
Fetal Growth (SD)		
<−2	1.31 (1.18–1.45)	<0.001
−2 to <−1	1.09 (1.03–1.16)	0.02
−1 to <0	1.03 (0.98–1.08)	0.22
0 to <1	Reference	
1 to <2	1.00 (0.94–1.06)	0.96
≥2	0.97 (0.87–1.07)	0.53
Maternal Marital Status		
Married/cohabiting	Reference	
Never married	1.08 (1.01–1.15)	0.02
Divorced/widowed	1.23 (1.17–1.30)	<0.001
Unknown	0.72 (0.51–1.01)	0.06
Maternal Education (years)		
Compulsory HS or less (≤9)	1.35 (1.27–1.44)	<0.001
Practical HS or some theoretical HS (10–11)	1.22 (1.16–1.29)	<0.001
Theoretical HS and/or college (≥12)	Reference	
Unknown	1.57 (1.16–2.13)	0.003
Family Income		
Lowest quartile	1.30 (1.23–1.38)	<0.001
Second quartile	1.11 (1.05–1.18)	<0.001
Third quartile	1.08 (1.02–1.15)	0.007
Highest quartile	Reference	

Abbreviation: HS = High school.

[a]The model included gestational age at birth, birth date (as a continuous variable), sex, fetal growth, maternal marital status, maternal education, and family income.