American Journal of Epidemiology Advance Access published December 15, 2005

American Journal of Epidemiology
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DOI: 10.1093/aje/kwj032

Original Contribution

Effect of Fetal Sex on Airway Lability in Pregnant Women with Asthma

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Received for publication May 11, 2005; accepted for publication September 13, 2005.

The authors investigated the association between sex of the fetus and maternal airway lability among pregnant women with asthma. Data were prospectively collected among 702 pregnant women with a diagnosis of asthma who were recruited in southern New England between 1997 and 2000 and followed through pregnancy. Peak expiratory flow lability, defined as percent daily maximum minus the minimum divided by the mean, was assessed at enrollment and at 21, 29, and 37 weeks' gestation. There was a −9.9 percent (95 percent confidence interval: −19.4, −0.4) difference in airway lability observed between women carrying female fetuses and those carrying male fetuses. This difference persisted throughout pregnancy. Among pregnant asthmatic women, carrying a female fetus is associated with worse maternal asthma, as assessed by greater airway lability, than is carrying a male fetus.

asthma; fetus; peak expiratory flow rate; pregnancy; sex

Abbreviation: PEF, peak expiratory flow.

Asthma is a common chronic illness estimated to affect 3.7–8.4 percent of pregnant women in the United States (1). Preliminary evidence (2–5) suggests increased severity of maternal asthma among women carrying female fetuses and supports earlier anecdotal reports of a fetal sex effect (6). We assessed the potential effect of fetal sex on maternal asthma longitudinally throughout pregnancy with repeated measurements, utilizing diurnal variation in peak expiratory flow (PEF), one of the defining features of asthma which increases with increasing asthma severity (7).

We hypothesized that female fetal sex, as compared with male fetal sex, is associated with worse maternal asthma during pregnancy, as measured by greater overall PEF lability in pregnancy (2, 3). Since male fetuses produce a surge of androgens at 12–16 weeks (8), we further conjectured that a protective effect enjoyed by women carrying male fetuses would be most notable during the fourth month of pregnancy.

MATERIALS AND METHODS

Study population

Between April 1997 and June 2000, 3,413 women were invited to participate in a study of asthma in pregnancy. Pregnant women were recruited while receiving prenatal care from 56 private obstetric practices and 15 clinics at six hospitals in southern New England (Bridgeport, Danbury, Hartford, and New Haven, Connecticut, and Springfield, Massachusetts). After accounting for refusals ($n = 531$), ineligibility at the home interview (usually related to enrollment after 24 weeks' gestation) ($n = 389$), miscarriages ($n = 73$), and nonparticipation for other reasons ($n = 41$), 2,379 women (69.7 percent) were enrolled in the study. Following enrollment, 174 women were excluded from analysis because of a stillborn fetus, molar pregnancy, a planned or spontaneous abortion ($n = 69$), multiple birth

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($n = 43$), loss to follow-up or withdrawal ($n = 60$), or inadequate information on asthma status ($n = 2$). Of the 2,205 singleton livebirths, 941 occurred among women who reported having ever received a physician's diagnosis of asthma.

The Human Investigation Committee of Yale University (New Haven, Connecticut) approved this study, and all respondents provided informed consent before participation.

Data collection

At enrollment, women were interviewed prior to 24 weeks' gestation, usually at home. The standardized questionnaire administered included in-depth questions about demographic factors, pregnancy history, height and weight, health care utilization, smoking, asthma history, activity limitations due to asthma, household exposures, and other chronic conditions during the year before pregnancy and the period since conception.

Women were trained at enrollment to assess their lung function using a hand-held self-recording peak flow meter (Vitalograph Ltd., Buckingham, United Kingdom). They were instructed to measure PEF for 10 days twice daily, once in the morning before taking asthma medications and once in the evening before bedtime, and to concurrently complete a daily symptom and medication diary. During each morning or evening session, the meter automatically recorded one PEF reading for the highest value of 2–5 attempts, with accuracy ± 3 percent or ± 0.05 liters, and ± 5 percent flow or ± 12 liters/minute, whichever was greater (10). Each PEF reading was recorded by the meter as ''good'' if time to peak flow was within 40–300 ms. This helped identify maneuvers performed with improper technique or insufficient initial effort.

We contacted women for follow-up telephone interviews at 20, 28, and 36 weeks' gestation to monitor asthma symptoms, medication use, and health care utilization by month of pregnancy since the last interview, and to capture changes in exposure to cigarette smoke. PEF was also assessed as described previously during two (selected randomly) of the three assigned follow-up times, using peak flow meters delivered by mail or in person to the women. Because of late enrollment, 29 women could not be monitored at 20 weeks' gestation.

A postpartum interview was conducted in the hospital ($n = 1{,}344$) or by telephone within 1 month of delivery ($n = 544$) for information on asthma symptoms, medication use, health care utilization, household exposures, and exposure to cigarette smoke. Data on pregnancy outcome were abstracted from hospital delivery records.

Measurements

Fetal sex (male or female) was assessed using information obtained from hospital delivery records. Amplitude percent mean was used to measure diurnal (within-day) variation of PEF as follows: $100 \times (PEF_{max} - PEF_{min})/PEF_{mean}$, calculated for each day (11). PEF_{max} was defined as the higher of the morning and evening readings, PEF_{min} as the lower reading, and PEF_{mean} as the average of the two.

Potential covariates for which data were obtained from maternal interviews included self-reported age, race/ethnicity, years of education completed, marital status, height, weight, smoking status (never, former, or current) during the year prior to pregnancy, asthma-related emergency visits during the year prior to pregnancy, and inhaled corticosteroid use assessed throughout pregnancy by month of pregnancy.

Data analysis

Only women with a physician's diagnosis of asthma ($n = 941$) were considered for analysis. Data included PEF measurements falling within 100–850 liters/minute, as recommended by the American Thoracic Society for the normal adult range assessed by peak flow monitors (12). Data were subset to readings of PEF lability, which included 2–10 days of readings in each time period, and to singleton livebirths. Results from tests that were not recorded as ''good'' (10) were excluded. A natural logarithmic transformation was applied to account for skewness in the outcome data. The final data set included 702 asthmatic women with information on fetal sex.

Longitudinal analysis of the effect of fetal sex over the course of pregnancy was conducted with linear mixed models using SAS PROC MIXED (SAS Institute, Inc., Cary, North Carolina), which allowed us to account for variance at three levels—between subjects, within subjects between peak flow measurement periods, and within periods between days (13). By accounting for between-day variance, we were able to address differences in variance related to differing numbers of days of PEF measurements obtained (mean no. of days = 5.0 (standard deviation, 2.8)). The restricted maximum likelihood method and Akaike's Information Criterion were used to select the appropriate covariance structure and random-effects terms for the model (13). The maximum likelihood method was then used to select the appropriate mean structure. We initially selected covariates for inclusion in our model from the literature and by a stepwise statistical procedure at significance levels of 0.15 for entry and 0.3 for removal.

Linear splines (14) with knots (two line segments of varying slopes) at various gestational ages were tested to explore possible changes in the response over time separately by fetal sex. Our final regression model included a constant linear slope with a linear spline with one knot. A nonparametric trend was calculated using LOESS for women with male and female fetuses, and these ''observed'' trends were compared with those ''predicted'' by linear splines. A random-intercepts model was chosen, which assumes that all variability in subject-specific slopes is attributable to group differences (13). We report the restricted maximum likelihood marginal estimates using an unstructured covariance structure, which provided the smallest Akaike Information Criterion values. Sensitivity analysis conducted with other covariance structures (simple, compound symmetry, first-order autoregressive, Toeplitz, exponential, Gaussian) did not demonstrate a substantive difference in the marginal estimates. Exploratory modeling and statistical analyses were performed in SAS, version 9.1 (SAS Institute, Inc.),

TABLE 1. Selected characteristics of pregnant women with asthma ($n = 631$) at study enrollment, by sex of the fetus, Connecticut and southern Massachusetts, 1997–2001

	Male fetus		Female fetus	
	Median or no.*	IQR† or %	Median or no.	IQR or %
Peak expiratory flow rate (liters/minute)	377.8	133.0	369.8	127.0
Diurnal variation of peak expiratory flow‡ (%)	7.82	12.66	8.45	13.78
Maternal age (years)				
<25	79	24.8	83	26.5
25–29	86	27.0	76	24.3
30–34	100	31.5	93	29.7
≥35	53	16.7	61	19.5
Maternal race/ethnicity				
Non-Hispanic White	212	66.7	201	64.2
Hispanic	24	7.5	39	12.5
Non-Hispanic Black	71	22.3	61	19.5
Other	11	3.5	12	3.8
Education				
Less than high school	50	15.7	53	16.9
High school	66	20.8	58	18.5
Some college	85	26.7	74	23.6
College or graduate school	117	36.8	128	40.9
Marital status				
Married	219	68.9	204	65.1
Unmarried	99	31.1	109	34.8
Height (inches)§				
<63	87	27.3	101	32.3
63–64	94	29.6	86	27.5
65–66	67	21.1	54	17.2
≥67	70	22.0	72	23.0
Prepregnancy weight (pounds)§				
<125	70	22.1	81	26.1
125–149	118	37.2	92	29.7
150–174	65	20.5	60	19.4
≥175	64	20.2	77	24.8
Smoking status¶				
Never smoker	180	56.8	172	54.9
Former smoker	110	34.7	106	33.9
Current smoker	27	8.5	35	11.2
Asthma-related emergency care¶				
Yes	28	9.0	33	10.8
No	285	91.0	272	89.2
Inhaled corticosteroid use				
Yes	37	11.6	32	10.2
No	281	88.4	281	89.8

* Totals may differ because of missing values.

† IQR, interquartile range.

‡ Diurnal variation of peak expiratory flow was defined as 100 × (maximum − minimum)/mean.

§ 1 inch = 25.4 mm; 1 pound = 0.45 kg.

¶ Assessed for the year prior to pregnancy.

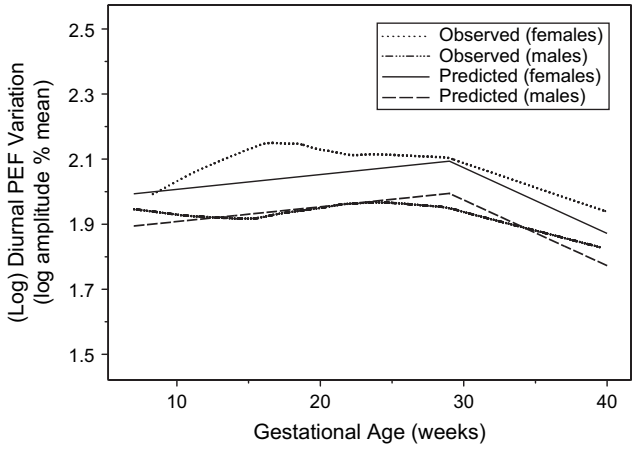

FIGURE 1. Log diurnal variation of peak expiratory flow (PEF) by gestational age and the sex of fetus, Connecticut and southern Massachusetts, 1997–2001. Diurnal variation of PEF (amplitude % mean) = 100 × (maximum − minimum)/mean.

and S-PLUS, version 6.2 (Insightful Corporation, Seattle, Washington).

RESULTS

Table 1 shows selected characteristics of participants at enrollment, by fetal sex. Participants ranged in age from 14 years to 48 years. The majority of participants were non-Hispanic White with some higher education. Slightly over half of the women were carrying male fetuses (51.0 percent). As expected, the median PEF rate was somewhat higher for women carrying male fetuses (377.8 liters/minute) than for those carrying female fetuses (369.8 liters/minute). The median untransformed diurnal variation of PEF also demonstrated greater asthma severity for women with female fetuses (8.45 percent) than for those with male fetuses (7.82 percent). As table 1 shows, none of the covariates differed substantially by fetal sex.

We fitted a longitudinal model that included linear splines to account for an observed change in slope that reflected a relative downturn (improvement) in airway lability at 29 weeks (figure 1). This pattern fitted by the linear splines agreed with the observed pattern obtained by the nonparametric LOESS trend. Cubic splines would have produced a smoother curve, but they did not improve the fit of the models over the use of linear splines, possibly because of the relatively small number of time points employed in the study. The association with fetal sex was attenuated slightly towards the null after adjustment for selected demographic variables (model 2 in table 2). In the model with full adjustment (model 3), there was a nearly 10 percent difference in airway lability observed between women carrying female fetuses and those carrying male fetuses, with greater lability being associated with female fetuses (percent difference for male fetuses versus female fetuses: −9.9, 95 percent confidence interval: −19.4, −0.4).

TABLE 2. Log diurnal variation of peak expiratory flow* among pregnant women with asthma ($n = 702$) and percent difference in log diurnal variation by gestational week with male fetuses versus female fetuses, Connecticut and southern Massachusetts, 1997–2001

Model and gestational age (weeks)	Male fetus		Female fetus		% difference	
	Estimate	95% CI†	Estimate	95% CI	Estimate	95% CI
Model 1‡						
14	1.93	1.85, 2.00	2.04	1.97, 2.12	−11.4	−20.9, −1.8
29	1.98	1.89, 2.06	2.09	2.00, 2.18	−11.4	−20.9, −1.8
37	1.83	1.72, 1.94	1.95	1.84, 2.06	−11.4	−20.9, −1.8
Model 2§						
14	1.93	1.85, 2.00	2.03	1.96, 2.11	−10.4	−19.8, −0.9
29	1.99	1.90, 2.07	2.09	2.00, 2.18	−10.4	−19.8, −0.9
37	1.84	1.73, 1.95	1.94	1.83, 2.05	−10.4	−19.8, −0.9
Model 3¶						
14	1.93	1.85, 2.00	2.03	1.95, 2.10	−9.9	−19.4, −0.4
29	1.99	1.91, 2.08	2.09	2.00, 2.18	−9.9	−19.4, −0.4
37	1.83	1.72, 1.94	1.93	1.82, 2.05	−9.9	−19.4, −0.4

* Diurnal variation of peak expiratory flow was defined as 100 × (maximum − minimum)/mean.
† CI, confidence interval.
‡ Longitudinal model including gestational age with a knot at 29 weeks.
§ Results were additionally adjusted for marital status, race/ethnicity, height, and prepregnancy weight.
¶ Results were additionally adjusted for inhaled corticosteroid use during pregnancy, any asthma-related emergency visits during the year prior to pregnancy, and smoking status during the year prior to pregnancy.

DISCUSSION

We observed evidence for an association between fetal sex and asthma severity during pregnancy, as assessed by PEF lability. There was a 10 percent improvement in airway lability for male fetuses compared with female fetuses that was observed throughout pregnancy.

There were several strengths to our study. In contrast with earlier studies (15), we utilized objective measures of PEF lability to estimate asthma severity. A recent analysis of factors associated with the course of asthma during pregnancy did not find an effect of fetal sex (16), but the authors relied upon participants' subjective overall assessment of asthma during pregnancy. Our results agree with those of Beecroft et al. (2), who assessed women during the second trimester, and demonstrate that a fetal sex effect is observable throughout pregnancy. We performed a longitudinal analysis using linear mixed models, which can effectively model the correlation structure between repeated outcome measures, accommodate time-dependent covariates, and handle missing and irregularly timed data (17).

A limitation of our study is that our measurements of PEF lability did not include labor and delivery. Our study was also less effective at measuring a sex effect during the first trimester, for which we had limited data. While we were unable to support our hypothesis that the sex difference would peak in the second trimester, the small size of the effect and the large amount of between- and within-subject variability inherent to the measurement of PEF lability may have made it difficult to model parametrically small changes in slope, which are suggested in the LOESS-smoothed curves (figure 1). Alternately, the lack of a statistically significant change in the fetal effect size over pregnancy may be real.

The mechanism for this putative effect of fetal sex on asthma severity during pregnancy remains uncertain. In developing male fetuses, testosterone is secreted from 8 weeks onward; testosterone level peaks at 12–16 weeks and then decreases to a low level in late gestation (8). There is evidence that testosterone potentiates β-adrenergic-mediated relaxation of bronchial tissue and inhibits response to histamine (18, 19). Hence, asthmatic women with male fetuses may experience a protective effect, particularly from the second trimester onward. Alternatively, recent studies suggest that sex-specific factors related to the presence of a female fetus may promote activation of inflammatory pathways associated with asthma in the maternal system (4, 5).

The overall pattern observed in our study—an improvement in maternal asthma followed by relative worsening around the 29th week and late pregnancy improvement—has been noted previously (20). Schatz et al. (20) suggested that net changes in the pulmonary corticosteroid effect could result from competitive binding to glucocorticoid receptors during pregnancy by progesterone and free cortisol, levels of which both increase dramatically towards the end of pregnancy.

In summary, sex hormones are thought to modulate asthma severity (22–24), but in-vitro studies, animal models, and clinical studies have offered conflicting evidence regarding effects of sex steroids on asthma (25–28). Further research with large sample sizes is needed to clarify these potential effects. Our finding of an effect of fetal sex on

maternal asthma builds upon previous case reports and cross-sectional studies. We utilized objective measures and longitudinal analyses that accounted for multiple sources of variance. Continued investigation of the effects of fetal sex on maternal asthma is warranted to clarify understanding of this widely prevalent disease.

ACKNOWLEDGMENTS

This work was supported by grants AI41040 and DA05484 from the National Institutes of Health. Additional support was received through the Kellogg Scholars in Health Disparities Program.

Conflict of interest: none declared.

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