Original Article

Longitudinal Analysis of Lung Function in Pregnant Women with and without Asthma

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What is already known about this topic? Spirometry is a useful clinical asthma management tool, yet its utility in pregnancy is unclear.

What does this article add to our knowledge? Pregnancy and mild asthma have limited impact on spirometry.

How does this study impact current management guidelines? Spirometry can be used in clinical assessment and education during pregnancy.

BACKGROUND: Spirometry is commonly used to assess and monitor lung function. It may also be a useful tool to monitor maternal health during pregnancy. However, large studies examining lung function across gestation are limited. Also, whether spirometry values follow the same pattern during pregnancy in women with and without asthma is unknown.
OBJECTIVE: To investigate the effect of advancing gestation, and its interaction with asthma, on lung function in a large well-defined cohort of pregnant women.
METHODS: Data were obtained from prospective cohorts involving women with (n = 770) and without (n = 259) asthma (2004-2017), recruited between 12 and 22 weeks' gestation. Lung function (forced vital capacity [FVC], FEV_1, FEV_1:FVC%) was assessed periodically during pregnancy using spirometry. Multilevel mixed-effect regression models were used to assess changes in lung function over gestation.
RESULTS: Asthma had a significant effect on baseline lung function (FEV_1%, −9%; FVC%, −3%; FEV_1:FVC%, −4%). FVC% decreased with advancing gestation (−0.07%/wk; 95% CI, −0.10 to −0.04]), as did FEV_1%, but only among those without asthma (women without asthma: −0.14%/wk, 95% CI, −0.22 to −0.06%; compared with women with asthma: 0.02%/wk, 95% CI, −0.01 to 0.06). FEV_1:FVC% remained relatively stable for women without asthma (0.03%/wk; 95% CI, −0.08 to 0.02), but increased for women with asthma (0.06%/wk; 95% CI, 0.04 to 0.16).
CONCLUSIONS: Data suggest that advancing gestation negatively affects FVC% and FEV_1%. This is consistent with extrapulmonary restriction from advancing pregnancy. Yet, the presence of asthma altered the trajectories of FEV_1% and FEV_1:FVC%. Optimal asthma management during pregnancy might have opposed the negative effects of gestation on lung function. © **2020 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;■:■-■)**

Key words: *Pulmonary function tests; Pregnancy; Asthma; Gestation; Spirometry*

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Abbreviations used
ACQ6- 6-item Asthma Control Questionnaire
BMI- Body mass index
ECO- Exhaled carbon monoxide
FVC- Forced vital capacity
GLI12- Global Lung Index 2012
GWG- Gestational weight gain
NHANESIII- Third National Health and Nutrition Examination Survey

INTRODUCTION

Lung function has been associated with multiple disease outcomes,[1-6] in addition to being a key component in respiratory disease diagnosis and monitoring.[7] Spirometry is the most commonly used technique to assess lung function, with values compared with a relevant reference population to aid interpretation.[8] Several reference values exist, which account for age-, sex-, and ethnicity-related differences, including the third National Health and Nutrition Examination Survey (NHANESIII)[9] and the Global Lung Index 2012 (GLI12).[10] Existing reference data sets are based on healthy nonpregnant populations; thus, whether advancing gestation influences spirometric values, and therefore their interpretation in the context of pregnancy, is unclear.

Lung function may affect perinatal outcomes, with FEV_1 in women with asthma negatively associated with gestational hypertension, preterm birth, and fetal growth.[11,12] Notably, perinatal outcomes were not associated with other measures of asthma symptom control during pregnancy (ie, symptoms, activity limitation, sleep loss) in this study,[11] although an earlier study has suggested that daily asthma symptoms are related to risk of intrauterine growth restriction.[13] This highlights the significance of monitoring lung function during pregnancy, particularly in women with asthma, who are at increased risk of adverse perinatal outcomes and in whom the course of asthma is unpredictable during pregnancy.[14-17]

Existing lung function reference values derived from cross-sectional studies of healthy nonpregnant individuals do not elucidate whether spirometry indices change during pregnancy; hence, research examining the impact of advancing gestation on lung function, and therefore the utility of spirometry and its interpretation, during pregnancy is needed. Hormonal and physiological adaptations that occur during pregnancy may affect maternal lung function, notably the lower chest wall circumference and subcostal angle of the rib cage increase and the diaphragm elevates.[18] However, a lack of adequately designed large-scale prospective studies of spirometry in pregnancy limits our understanding regarding the pattern of lung function during pregnancy. Previous studies are limited by sample size, study design/methodological flaws, including statistical methods, number of data collection points and methods, and/or lack of inclusion of both asthmatic patients and controls.[19-27] Hence, longitudinal changes in lung function during pregnancy are yet to be examined in a large cohort of women, with and without asthma.

This study aimed to examine the effect of advancing gestation, and its interaction with asthma, on FEV_1, forced vital capacity (FVC), and FEV_1:FVC% in pregnancy.

METHODS

Population

Data were collected from 4 prospective cohorts of pregnant women, recruited between 12 and 22 weeks' gestation and followed until delivery, via the antenatal clinics of several Australian hospitals (2004-2017).[28-31] As previously described, women without respiratory disease served as healthy controls; women with asthma were defined as having a physician diagnosis plus recent symptoms/medication use. Ethics approval was obtained for all studies and written informed consent obtained before participation (see this article's Online Repository text at www.jaci-inpractice.org).

Measurements

Baseline weight and height were measured and body mass index (BMI) calculated (kg/m^2) and categorized as not overweight (<25.0 kg/m^2), overweight (25.0-29.9 kg/m^2), and obese (≥ 30.0 kg/m^2). Gestational weight gain (GWG) was calculated in a subset with repeat weight measurements. Current medication use (self-report), smoking status and tobacco exposure (self-report and exhaled carbon monoxide [ECO], measured with piCO Smokelyzer Breath CO Monitor [Bedford, UK]), and Asthma Control Questionnaire score[32] were recorded at recruitment and throughout the study period; asthma was classed as "controlled" (6-item Asthma Control Questionnaire [ACQ6] score <1.5) or "uncontrolled" (ACQ6 score ≥ 1.5).[33] Self-reported medication adherence was recorded at each visit, as the % doses missed in the previous week.

Lung function was assessed using spirometry (*Phase II*: Spirotac IV, Vitalograph, Buckingham, UK; Managing Asthma in Pregnancy study/Viral Exacerbations in Pregnancy study and Breathing for Life Trial: EasyOne Spirometer, NicheMedical, North Sydney, Australia). FVC and FEV_1 were measured by a trained respiratory research nurse or research midwife according to American Thoracic Society/European Respiratory Society guidelines, expressed as a percentage of predicted values (NHANESIII[9]), and FEV_1:FVC ratio (%) calculated.

Statistical analysis

Analysis was performed using SAS version 9.4 (SAS Institute, Inc, Cary, NC). Data are presented as mean $\pm$ SD or n (%). Multilevel mixed-effect regression models were used to analyze lung function changes (FVC%, FEV_1%, FEV_1:FVC%), with gestational age (fixed effect) used as the time scale[34] and an interaction term for Gestational age $\times$ Asthma to determine whether the trend differed by asthma status. Random participant-level intercepts accounted for repeated measures on participants, and random slopes were included to model heterogeneity in trends; random intercepts and slopes were allowed to be correlated. Restricted maximum likelihood was used for parameter estimation. Models were adjusted for potential confounders (maternal age, smoking status, ECO measurement, and BMI category at baseline), and their interaction with asthma status; thus, participants with nonmissing confounders comprised the analysis sample. Potential confounders were considered for removal in an augmented backward selection approach, if they did not improve the model fit compared with the full model with all confounders (measured by a decrease in Akaike information criterion or nonsignificant Wald *P* value), and if their removal did not alter the regression coefficient for the trend (the "change in estimate" approach). Model assumptions were assessed using histograms and residual plots. Additional (sensitivity) analyses were performed to assess the influence of each GWG and asthma control status. Significance was accepted when *P* was less than .05.

TABLE I. Baseline characteristics of pregnant women with and without asthma

Characteristic	Control (n = 259)	Asthma (n = 770)	*P* value
Maternal age (y), mean ± SD	29.3 ± 4.9	29.0 ± 5.4	.330
Gestational age (wk), mean ± SD	19.3 ± 5.3	17.7 ± 2.9	<.001
Parity, median (interquartile range)	0 (0-1) n = 258	1 (0-2) n = 598	.001
Ethnicity, n, %			.202
White	240 (92.7)	677 (87.9)	
Indigenous*	4 (4.5)	33 (4.3)	
Asian	3 (1.2)	16 (2.1)	
Hispanic	—	5 (0.7)	
African	—	3 (0.4)	
Other	3 (1.2)	6 (0.8)	
Unknown	9 (3.5)	30 (3.9)	
BMI, mean ± SD†	27.6 ± 6.2	29.4 ± 7.5	<.001
BMI categories, n (%)			.002
Not overweight‡	114 (44.0)	245 (31.8)	
Overweight	77 (29.7)	240 (31.2)	
Obese	72 (27.8)	289 (37.5)	
Current smoker, n (%)	25 (9.8) n = 256	138 (18.3) n = 756	.001
Ex-smoker, n (%)	81 (32.0) n = 253	207 (27.8) n = 746	.195
ECO, mean ± SD	3 ± 5	4 ± 6 n = 748	.009
FVC% predicted, mean ± SD	99.0 ± 11.5 n = 254	95.8 ± 13.0 n = 660	<.001
FEV_1% predicted, mean ± SD	97.5 ± 10.9 n = 254	90.9 ± 13.8 n = 666	<.001
FEV_1/FVC%, mean ± SD	83.4 ± 5.3 n=255	80.5 ± 7.5 n = 661	<.001
No. of visits during pregnancy, mean ± SD	3.2 ± 2.1	4.5 ± 1.7	<.001

*Indigenous included Aboriginal, Torres Strait Islander, and Maori.
†Data missing n = 3 in asthma cohort and n = 3 in nonasthma cohort.
‡Fourteen women (7 in both control and asthma groups) had a BMI <18.5 kg/m^2 (range, 16.6-18.4 kg/m^2) and were combined with women with a "healthy" BMI at baseline as "not overweight."

RESULTS

A total of 1029, predominately White (89% [n = 917]), women were included, of whom 259 (25%) were healthy controls and 770 (75%) had asthma (Table I). The mean number of visits during pregnancy was 4.1 ± 1.9, with recruitment at a mean 18.1 ± 3.7 weeks' gestation. Most were overweight (31% [n = 317]) or obese (35% [n = 361]) at baseline; 29% [n = 288] were ex-smokers and 16% [n = 163] current smokers.

At baseline, women with asthma had a median ACQ6 score of 1.0 (0.33-1.83), with 37% (n = 282) classed as "uncontrolled"[33] and 37% (n = 283) taking inhaled corticosteroid at a median dose of 500 μg (400-1000). Of the 283 women using inhaled corticosteroid medication, most (69% [n = 196]) were using an inhaled corticosteroid/long-acting beta-agonist combination. Most women with asthma (95% [n = 730]) used short-acting beta-agonist medication.

The regression analysis data sets for the outcome variables FVC%, FEV_1%, and FEV_1:FVC% included 921 participants (90%) with 1 or more outcome assessment and nonmissing maternal age, smoking status, ECO measurement, and BMI category at baseline (Table II). Figure 1 depicts lung function trajectories by asthma status (see also Figure E1 in this article's Online Repository at www.jaci-inpractice.org).

Women with, versus without, asthma had 2.7% lower FVC% at baseline (P = .004). The interaction term indicated that the difference in FVC% trends was not statistically significant by asthma status (0.05%/wk; 95% CI, −0.03 to 0.14; P = .215) and as such was removed from the model, with results showing FVC% decreased for both groups by 0.07%/wk (P < .001; Table II).

Baseline FEV_1% was 9% lower in women with, versus without, asthma (P < .001). The interaction term indicates differential trends in FEV_1% during gestation (P < .0001) where those without asthma had a significant decrease in FEV_1% (0.14%/wk; 95% CI, 0.06 to 0.22; P < .0001; Table II) and those with asthma had a nonsignificant increase of 0.02%/wk (95% CI, −0.01 to 0.06; P = .055).

Women with, versus without, asthma had 4.2% lower FEV_1:FVC% at baseline (P < .001). The interaction term (P = .002) indicates that FEV_1:FVC% trends during gestation differed for those without asthma (decrease of 0.03%/wk; 95% CI, −0.08 to 0.02; P = .299; Table II) and those with asthma (increase of 0.06%/wk; 95% CI, 0.04 to 0.08; P < .0001).

Sensitivity analyses

GWG was calculated for the 490 (48%) women with repeat weight measurements (controls: n = 93 [36%]; those with asthma: n = 397 [52%]). Median GWG did not differ between groups (0.50 kg/wk, interquartile range, 0.40-0.68, vs 0.48 kg/wk, interquartile range, 0.31-0.65, P = .23). The inclusion of weight at each visit changed the estimates marginally (but not the direction), with an increase in baseline FVC (asthma and controls) and an increase in the interaction term for FEV_1; however, the number of observations reduced by approximately 46%, reducing the power of the models (see Online Repository text and Table E1 in this article's Online Repository at www.jaci-inpractice.org). Notably, the effect of baseline obesity on reducing FEV_1 became statistically significant, whereas the positive effect of obesity on FEV_1/FVC became nonsignificant, after adjusting for weight at

TABLE II. Mixed model regression coefficients for FVC% predicted, FEV_1% predicted, and FEV_1:FVC% across gestation in women with and without asthma (n = 921)

	FVC% predicted (3229 observations)		FEV_1% predicted (3247 observations)		FEV_1:FVC (3229 observations)	
Variable	**Estimate**	***P* value**	**Estimate**	***P* value**	**Estimate**	***P* value**
Constant	**96.51 (92.08 to 100.94)**	**<.001**	**95.64 (90.65 to 100.63)**	**<.001**	**89.06 (86.54 to 91.58)**	**<.001**
Asthma	**−2.63 (−4.42 to −0.83)**	**.004**	**−8.82 (−11.58 to −6.06)**	**<.001**	**−4.19 (−5.88 to −2.51)**	**<.001**
Gestational age (wk)	**−0.07 (−0.10 to −0.04)**	**<.001**	**−0.14 (−0.22 to −0.06)**	**<.001**	−0.03 (−0.08 to 0.02)	.299
Asthma × Gestational age*	—	—	**0.16 (0.08 to 0.25)**	**<.001**	**0.09 (0.03 to 0.14)**	**.002**
Maternal age at study entry	0.07 (−0.08 to 0.21)	.362	**0.19 (0.05 to 0.33)**	**.009**	**−0.18 (−0.24 to −0.10)**	**<.001**
Smoking status at study entry		.0935		.037		.0403
Never smoker	Reference		Reference		Reference	
Ex-smoker	−1.02 (−3.31 to 1.28)	.386	−2.51 (−4.83 to −0.19)	.034	−1.31 (−2.45 to −0.17)	.024
Current smoker	1.52 (−0.24 to 3.27)	.090	0.75 (−1.05 to 2.54)	.415	−0.74 (−1.59 to 0.11)	.086
ECO (ppb)	0.04 (−0.03 to 0.12)	.273	−0.05 (−0.12 to 0.02)	.134	−0.09 (−0.14 to −0.05)	<.001
BMI category at study entry		0035		.2607		.0006
Not overweight†	Reference		Reference		Reference	
Overweight	−1.01 (−2.93 to 0.91)	.303	−0.73 (−2.70 to 1.24)	.466	0.24 (−0.69 to 1.17)	.610
Obese	**−3.10 (−4.94 to −1.26)**	**.001**	−1.57 (−3.45 to 0.31)	.102	**1.60 (0.71 to 2.49)**	**<.001**

ppb, Parts per billion.
Bold indicates statistical significance ($P < .05$).
*The interaction term for gestational age and asthma was not significant for FVC% predicted (0.05; 95% CI, −0.03 to 0.14; $P = .215$), and the results from the FVC model without the interaction term are presented.
†Includes underweight (n = 14; range, 16.64-18.5 kg/m^2) and healthy weight.

each visit. These results suggest that the analysis findings that were presented for the larger cohort, without adjusting for GWG, are potentially understating the differences in lung function observed between women with and without asthma during pregnancy.

The ACQ6 score was calculated at baseline and at each visit throughout pregnancy for women with asthma. Using a linear mix-model, the within-person change in the ACQ6 score was calculated at less than 1% over 40 weeks' gestation. The inclusion of asthma control (uncontrolled and controlled, based on an ACQ6 score cutoff point of 1.5) during pregnancy changed the estimates only slightly (but not the direction), particularly for FVC (increase in baseline values). There was a significant difference between baseline values for lung function between uncontrolled and controlled asthma (as well as each compared with no asthma), and a significant interaction term with gestational age for both uncontrolled and controlled asthma; however, the rate of change over gestation did not differ between uncontrolled and controlled asthma (see Online Repository text and Table E2 in this article's Online Repository at www.jaci-inpractice.org). This suggests that asthma control during pregnancy did not significantly impact lung function trajectory in this population with predominantly mild asthma.

In exploring the effect of asthma control on lung function trajectories, controlling for medication adherence, the number of observations dropped dramatically (∼25% of total), which drastically reduced the power of the models (data not shown); thus, this variable was not included in the final models.

DISCUSSION

This study examined the effects of advancing gestation, and its interaction with asthma, on lung function, using repeat spirometry measures from a large cohort of well-characterized pregnant women with and without asthma. FVC% and FEV_1% declined with advancing gestation; however, although FVC% declined at the same rate in women with and without asthma, the trajectories for FEV_1% and FEV_1:FVC% differed by asthma status. FEV_1% remained relatively stable in women with asthma, whereas FEV_1:FVC% increased marginally. Conversely, FEV_1% decreased significantly for women without asthma. Results translate to lung function changes of between −5.6% and +2.4% over 40 weeks' gestation; thus, advancing gestation impacts spirometry indices, although of seemingly limited clinical importance, and is altered by the presence of mild asthma.

Before our study, the trajectory of lung function over the course of pregnancy had not been adequately described. Our results indicate that advancing gestation impacts lung function, totaling a 5.6% decrement in FEV_1% and 2.8% decrement in FVC% over 40 weeks' gestation; FEV_1:FVC% was unaffected. Similarly, a Brazilian study of 120 healthy women observed a statistically significant decline in FVC% (∼4%) and FEV_1% (∼3.5%), from the first to third trimester, whereas FEV_1:FVC% remained stable.[25] In contrast, Grindheim et al[20] reported a 3.1% *increase* in FVC% from 15 to 36 weeks' gestation (4 measurements) in 87 nonsmoking women without asthma, with no change detected in FEV_1% or FEV_1:FVC%. Alternatively, gestational age did not affect spirometry indices in a study of 20 women with, and 20 women without, asthma; there was no significant difference within either group, across the 3 measurements (16, 25, and 35 weeks).[27] Similarly, a study of 51 healthy women did not detect a difference across trimesters in FEV_1, FVC, or their ratio.[23] However, these studies are largely limited by sample size.[20,23,27] Our results suggest that pregnancy-induced changes in lung function occur, in line with extrapulmonary lung restriction caused by an enlarging uterus as pregnancy progresses; however, the clinical importance is questionable.

As expected, asthma was associated with significantly lower baseline lung function compared with controls, with the greatest effect on FEV_1%, particularly in those with uncontrolled asthma at baseline. Interestingly, there was a significant interaction effect between asthma and gestational age on FEV_1% and FEV_1:FVC

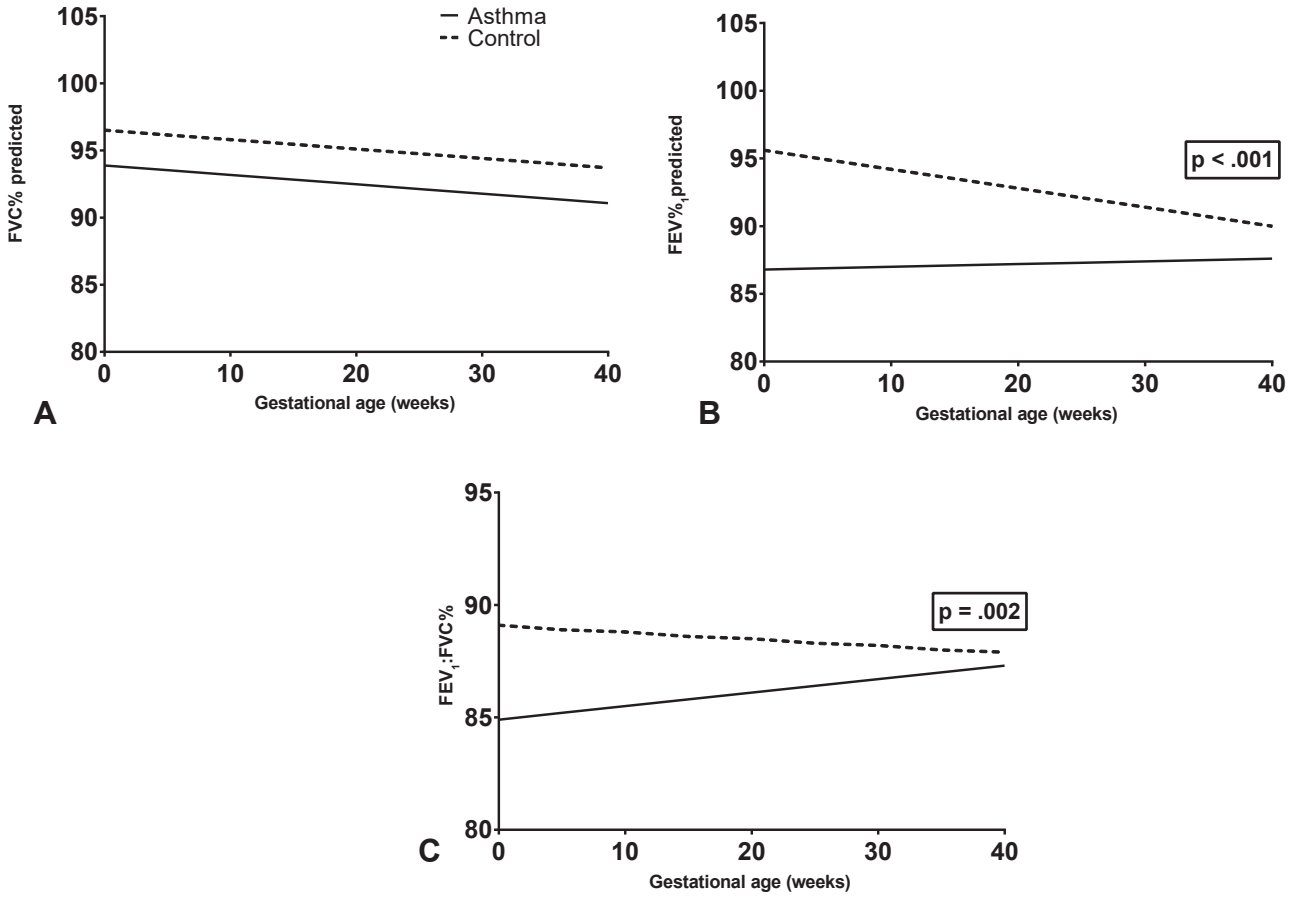

FIGURE 1. Lung function changes during pregnancy among women without asthma (*dashed*) and women with asthma (*solid line*). (**A**) FVC % predicted. (**B**) FEV_1% predicted. (**C**) FEV_1:FVC%. Displayed *P* values are from the interaction term Gestational age × Asthma in mixed model.

%, but not FVC%, such that FEV_1:FVC% marginally increased in women with asthma over the course of pregnancy, whereas FEV_1% declined in controls. Only 1 previous study has examined the interaction effect between asthma and gestational age on lung function.[27] This longitudinal study reported significantly higher FEV_1% and FEV_1:FVC% in women with asthma (n = 20) versus controls (n = 20) (∼3% difference) at 35 weeks' gestation, but not at 16 and 25 weeks.[27] Similar to our findings, authors reported a significant Group × Time effect on FEV_1% ($P = .04$) and FEV_1:FVC% ($P = .01$) in mixed-effect models; however, the strength and direction of these associations were not reported, limiting comparisons with our results.[27] Another study measured spirometry at approximately 18, 28, and 29 weeks' gestation in nonsmoking women with asthma and allergic rhinitis.[35] No significant change in FEV_1% or spirometry classification ("normal," "mild/moderate obstruction," "small airway obstruction") was observed; however, this study was limited by its small sample of 42 women (n = 22 at the third assessment), a relatively narrow assessment period, and no healthy control group.[35] In our large cohort, using statistical methods that account for the increase in precision through taking repeated measures during pregnancy, and controlling for key confounders, we were able to detect a statistically significant interaction effect between asthma status and gestational age on spirometry parameters. Although information on medication adherence was collected, its inclusion in the models dramatically reduced the sample size and was therefore not included in the present analyses; however, given the impact of medication adherence on asthma management, the collection of this variable should be an important consideration for further research in this area.

The observed positive interaction effect between asthma and gestational age on lung function may reflect the fact that participants received active asthma management during pregnancy, suggesting that optimal asthma management, and/or use of asthma medications, modifies the negative impact of advancing gestation on lung function. Indeed, participants were not instructed to withhold asthma medications before assessment; thus, results may reflect recent asthma medication use, specifically bronchodilators. Moreover, analyses did not account for changes in medication use or adherence throughout pregnancy, due to a reduction in power of the models; however, sensitivity analyses including asthma control (ACQ6) revealed no difference in lung function trajectories during pregnancy between patients with "controlled" and "uncontrolled" asthma. This may be expected in our population given that a less than 1% total change in ACQ6 score over pregnancy was observed. The effect may differ in women whose asthma is not actively managed throughout pregnancy, or whose asthma control fluctuates significantly and/or who are nonadherent to their asthma medication. Further research is needed to explore these aspects.

Although it is well established that lung function deficits are associated with obesity, this has been examined during pregnancy in only 1 previous study that specifically excluded women with asthma.[20] In their study of 87 women, Grindheim et al[20] found no effect of pregestational BMI more than 25 kg/m^2, nor excessive GWG, on FEV_1, FVC, or peak expiratory flow during pregnancy.[20] In contrast, our results demonstrate that an elevated BMI alone can contribute to an altered lung function trajectory during pregnancy, in women with and without asthma. Obesity in early pregnancy was a significant negative predictor of FVC% (−3.1%), compared with a BMI less than 25 kg/m^2, having a marginally greater influence than asthma (−2.6%). A limitation of our study is that data on prepregnancy BMI were not available for our cohort. Nevertheless, the high rates of obesity in women of child-bearing age and the notably higher prevalence in pregnant women with asthma[36] mean that our findings are highly relevant to this population group. GWG was not available for approximately half of our sample, limiting our ability to explore the effect of this modifiable factor; yet, although reduced in power, our sensitivity analysis suggests that GWG may be an important factor to consider in future studies.

Monitoring lung function during pregnancy may be relevant to perinatal outcomes, as well as asthma outcomes. Early work by Schatz et al[12] detected a direct relationship between mean FEV_1% during pregnancy and infant birth weight ($r = 0.11$; $P < .04$) in 352 women with asthma. A lower maternal FEV_1% was associated with a 3-fold increased odds of birth weight in the lowest quartile (<3150 g), and women with a mean FEV_1% less than 90%, versus greater than or equal to 90%, were 2.5 times more likely to have an infant with low ponderal index.[12] A second study by Schatz et al reported a weak, but statistically significant, correlation ($r = 0.08$; $P < .001$) between average FEV_1% during pregnancy and infant birth weight in 2123 women with asthma, whereas no relationship between birth weight and mean asthma symptoms, sleep disturbance, or activity limitation during pregnancy existed,[11] supporting the utility of spirometry. Mean FEV_1% was also significantly lower (by 2.2%-2.4%) for women who developed gestational hypertension, delivered preterm, or had a low-birthweight infant, compared with women without this outcome.[11] However, whether these associations are observed in women without respiratory disease remains unknown.

A major strength of this study is the relatively large sample of well-defined women, with and without asthma, with repeat spirometry measures collected prospectively during pregnancy. Previous studies were limited by methodological design; were of small sample size, reducing statistical power; collected few repeat lung function measurements and/or during a narrow time frame; and/or did not include women with and without asthma to assess the disease impact.[19-27] Furthermore, evaluation of an interaction effect between asthma status and gestational age had not been adequately examined before our study.

The same reference equation was used within the prospective cohorts included in this analysis, allowing assessment of within-participant changes. However, the use of NHANESIII, not GLI12[37] reference values, may be deemed a limitation. Previous studies demonstrate good agreement in FEV_1, FVC, and FEV_1:FVC predicted values between GLI12 and alternatives, including NHANESIII.[8,10,37] Our in-house comparison between NHANESIII and GLI12 values for the spirometry results obtained in our population sample also demonstrated a strong agreement (correlation coefficients: FEV_1%, 0.98; FVC%, 0.97).

A limitation in the interpretation of the results is the possibility that women with asthma had previously performed spirometry and therefore performed the technique better; however, because the quality of all spirometry tests was evaluated against guidelines, a training effect within the asthma group should not be present within our population (although could be present over time within both groups). In addition, the definition of asthma was participant report of physician diagnosis and recent history of medication and/or symptoms; we did not perform pre- and post—short-acting beta-agonist spirometry to confirm asthma diagnosis, nor is provocation testing for research acceptable in pregnancy. Although this is representative of the population in the antenatal clinics, the absence of spirometric confirmation of asthma may have led to contamination of the asthma group with women without asthma. If so, the effect of asthma on lung function in pregnancy would be diluted; therefore, our results would *underestimate* the effect of asthma. Furthermore, it is unclear whether any participants were affected by respiratory infections or asthma exacerbation on the date of testing.

The inclusion of ECO and smoking status in the models strengthened the coefficient of primary interest; hence, both variables were retained. However, interpretation of the effect of smoking on lung function in the models is limited given the collinearity between these 2 variables. Lastly, our cohort received regular contact and active asthma management during pregnancy, which may limit the generalizability of results. Although the sensitivity analysis did not show an effect of asthma control status on the interaction with gestational age, this may reflect the fact that most women had relatively mild asthma at baseline, that asthma control remained relatively unchanged throughout pregnancy (<1% change in ACQ6 score), and that all women received a form of asthma management. It is possible that an analysis of less well-controlled women would provide different results. Thus, further research examining the effect of asthma on lung function in pregnancy in women with more severe or poorly controlled asthma, and further elucidation of the effect of tobacco smoke exposure, is warranted.

CONCLUSIONS

FVC% and FEV_1% declined significantly over gestation, consistent with extrapulmonary restriction from an increasingly gravid uterus; FEV_1:FVC% was unaffected. FVC% declined at the same rate in women with and without asthma, yet, asthma status altered FEV_1% and FEV_1:FVC% trajectories. In women with asthma, FEV_1% remained relatively stable, whereas FEV_1:FVC% increased marginally, despite lower baseline values. This may reflect active asthma management during pregnancy, which raises the question of whether optimal asthma management can oppose the observed negative effects of advancing gestation on lung function. Research examining the difference between lung function measures collected during the pregnant and nonpregnant state would further elucidate the impact of pregnancy on lung function. This research provides evidence to support the use of spirometry in clinical assessment, and education, of pregnant women with asthma in the context of fractional exhaled nitric oxide/asthma symptom assessment.

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ONLINE REPOSITORY

METHODS

Data were collected from 4 prospective cohorts of pregnant women with asthma, conducted from 2004 to 2017: Phase II Asthma in Pregnancy Study (Phase II) (2004-2006),[E1] the Managing Asthma in Pregnancy study[E2] and the concurrent Viral Exacerbations in Pregnancy study (2007-2010),[E3] and the ongoing Breathing for Life Trial (2013-2017).[E4] Most participants were recruited via the antenatal clinic at the John Hunter Hospital (NSW Australia); a portion from the Managing Asthma in Pregnancy study was recruited at Maitland Hospital (NSW, Australia), and a portion from the Breathing for Life Trial recruited from 5 additional sites in Brisbane (QLD, Australia), Canberra (ACT, Australia), and Sydney (NSW, Australia).

Inclusion/exclusion criteria

Women 18 years or older, with physician-diagnosed asthma, plus asthma symptoms or asthma medication use in the past year, were enrolled between 12 and 22 weeks' gestation and followed regularly throughout their pregnancy until delivery. Women were excluded if they had a chronic lung disease other than asthma, were unable to perform spirometry, or had drug/alcohol dependence. Additional exclusion criteria for the Managing Asthma in Pregnancy study were more than 3 courses of oral corticosteroids in the past year, hospital admission for an asthma exacerbation in the past 3 months, or regular use of prednisolone/theophylline.[E2] Women were excluded from participation in the Breathing for Life Trial if they had used an oral corticosteroid consecutively for 14 days or more in the past 3 months.[E4]

Women without respiratory disease, between 12 and 22 weeks' gestation, served as healthy controls. Women were excluded as a control if they had a history of asthma, concomitant chronic illness, and drug or alcohol dependence, were unable to attend study visits, or were unable to perform spirometry.

RESULTS

Sensitivity analysis—GWG

For FVC% predicted, the baseline value increased for women without asthma (99.9% vs 96.5% in main analysis) and women with asthma (97.2% vs 93.9% in main analysis) when weight at each visit was included in the model (Table E1). The decline in FVC% over gestation marginally decreased to −2.4% (−2.8% in main analysis) and the Asthma × Gestational age interaction term in the FVC% predicted model increased but remained nonsignificant (−0.11; 95% CI, −0.005 to 0.23; $P = .06$). For FEV_1% predicted, the improvement in lung function over 40 weeks' gestation doubled in women with asthma (1.6% vs 0.8% in main analysis) when GWG was included as a confounder, and for women without asthma the decline increased by 1.6% (−7.2% vs −5.6% in main analysis). Also, by including GWG, obesity had a significant negative effect on FEV_1% predicted (−2.7%; $P = .045$). For FEV_1:FVC%, the effect of obesity was no longer significant when including GWG as a confounder (1.22%; $P = .079$).

Sensitivity analysis—Asthma control

There was a slight increase in baseline FVC (controlled asthma 97.2% and uncontrolled asthma 95.4%, vs 93.9% in main analysis; and controls 99.4% vs 96.5% in main analysis) when asthma control was included in the model (Table E2). For baseline FEV_1 and FEV_1/FVC, there was a slight decrease for uncontrolled asthma (85.0% and 83.9%, respectively) but a slight increase for controlled asthma (88.0% and 85.2%, respectively) versus the main analysis (FEV_1, 86.8%; FEV_1/FVC, 84.9%). The decline in FVC% over gestation marginally increased to −3.2% versus −2.8% in the main analysis, with no significant interaction term for Asthma (controlled or uncontrolled) × Gestational age. Also, by including asthma control, the negative effect of obesity was slightly reduced (3.0% vs 3.1% in main analysis). The decline in FEV_1 remained unchanged for women without asthma, when asthma control was included in the model; however, the improvement in FEV_1 increased in uncontrolled asthma (1.6% vs 0.8% in main analysis), whereas FEV_1 did not change over gestation for controlled asthma (0%). For FEV_1/FVC, the improvement reduced to 1.6% over gestation for controlled asthma and increased to 3.6% for uncontrolled asthma (compared with 2.4% in main analysis). However, there were no statistically significant differences in lung function trajectories between controlled and uncontrolled asthma.

TABLE E1. Mixed model regression coefficients for FVC% predicted, FEV_1% predicted, and FEV_1:FVC% across gestation in women with and without asthma including GWG as confounder

	FVC% predicted (n = 490, observations = 1731)		FEV_1% predicted (n = 490, observations = 1749)		FEV_1:FVC (n = 490, observations = 1731)	
Variable	**Estimate**	***P* value**	**Estimate**	***P* value**	**Estimate**	***P* value**
Constant	**99.87 (94.54 to 105.21)**	**<.001**	**96.08 (90.23 to 101.94)**	**<.001**	**89.38 (86.29 to 92.46)**	**<.001**
Asthma	**−2.66 (−4.49 to −0.83)**	**.004**	**−10.08 (−13.22 to −6.94)**	**<.001**	**−4.17 (−6.02 to −2.33)**	**<.001**
Gestational age (wk)	**−0.06 (−0.11 to −0.01)**	**.015**	**−0.18 (−0.28 to −0.07)**	**<.001**	−0.01 (−0.08 to 0.05)	.649
Asthma × Gestational age*	—	—	**0.22 (0.10 to 0.33)**	**<.001**	**0.08 (0.02 to 0.15)**	**.014**
Maternal age at study entry	0.03 (−0.11 to 0.18)	.640	**0.17 (0.02 to 0.32)**	**.027**	**−0.18 (−0.25 to −0.10)**	**<.001**
Smoking status at study entry						
Never smoker	Reference		Reference		Reference	
Ex-smoker	−0.29 (−2.68 to 2.10)	.812	−1.74 (−4.20 to 0.72)	.165	−1.18 (−2.44 to 0.09)	.068
Current smoker	1.51 (−0.28 to 3.30)	.098	0.70 (−1.14 to 2.54)	.456	−0.08 (−1.67 to 0.15)	.102
ECO (ppb)	−0.04 (−0.12 to 0.05)	.392	−0.13 (−0.22 to −0.04)	.006	−0.10 (−0.15 to −0.04)	<.001
BMI category at study entry						
Not overweight†	Reference		Reference		Reference	
Overweight	−0.59 (−2.65 to 1.46)	.572	−0.65 (−2.76 to 1.47)	.550	0.19 (−0.87 to 1.25)	.727
Obese	**−3.15 (−5.71 to −0.59)**	**.016**	**−2.68 (−5.30 to −0.06)**	**.045**	1.22 (−0.14 to 2.57)	.079
Weight (kg)	0.002 (−0.04 to 0.05)	.939	0.02 (−0.03 to 0.07)	.357	−0.003 (−0.03 to 0.02)	.831

ppb, Parts per billion.
Bold indicates statistical significance ($P < .05$).
*The interaction term for gestational age and asthma was not significant for FVC% predicted (0.11; 95% CI, −0.005 to 0.23; $P = .060$): the results from the FVC model without the interaction term are presented.
†Includes underweight (n = 14; range, 16.64-18.5 kg/m^2) and healthy weight.

TABLE E2. Mixed model regression coefficients for FVC% predicted, FEV_1% predicted, and FEV_1:FVC% across gestation in women with controlled asthma, uncontrolled asthma, and no asthma (n = 921)

	FVC% predicted (3226 observations)		FEV_1% predicted (3244 observations)		FEV_1:FVC (3226 observations)	
Variable	**Estimate**	***P* value**	**Estimate**	***P* value**	**Estimate**	***P* value**
Constant	**99.42 (94.83 to 104.01)**	**<.0001**	**95.67 (90.70 to 100.63)**	**<.0001**	**89.06 (86.55 to 91.58)**	**<.0001**
Asthma status						
No asthma	Reference		Reference		Reference	
Controlled (ACQ6 score <1.5)	**−2.16 (−3.95 to −0.37)**	**.018**	**−7.72 (−10.50 to −4.94)**	**<.0001**	**−3.83 (−5.55 to −2.11)**	**<.0001**
Uncontrolled (ACQ6 ≥1.5)	**−3.99 (−5.83 to −2.15)**	**<.0001**	**−10.64 (−13.72 to −7.56)**	**<.0001**	**−5.21 (−7.17 to −3.25)**	**<.0001**
Gestational age (wk)	**−0.08 (−0.11 to −0.05)**	**<.0001**	**−0.14 (−0.22 to −0.06)**	**.0004**	−0.03 (−0.08 to 0.02)	.299
Asthma × Gestational age*						
No asthma	Reference		Reference		Reference	
Controlled (ACQ6 score <1.5)	—	—	**0.14 (0.05 to 0.22)†**	**.002**	**0.07 (0.02 to 0.13)†**	**.009**
Uncontrolled (ACQ6 score ≥1.5)	—	—	**0.18 (0.08 to 0.28)**	**.001**	**0.12 (0.05 to 0.19)**	**.0004**
Maternal age at study entry	0.06 (−0.08 to 0.20)	.377	**0.19 (0.04 to 0.33)**	**.010**	**−0.17 (−0.24 to −0.10)**	**<.0001**
Smoking status at study entry						
Never smoker	Reference		Reference		Reference	
Ex-smoker	−0.90 (−3.19 to 1.38)	.438	−2.42 (−4.73 to −0.11)	.040	−1.32 (−2.46 to −0.18)	.024
Current smoker	1.52 (−0.23 to 3.26)	.089	0.71 (−1.08 to 2.50)	.436	−0.74 (−1.59 to 0.10)	.086
ECO (ppb)	0.05 (−0.02 to 0.13)	.161	−0.04 (−0.11 to 0.03)	.259	−0.09 (−0.14 to −0.05)	<.0001
BMI category at study entry						
Not overweight‡	Reference		Reference		Reference	
Overweight	−0.98 (−2.89 to 0.93)	.316	−0.70 (−2.66 to 1.26)	.484	0.25 (−0.68 to 1.18)	.593
Obese	**−3.00 (−4.84 to −1.17)**	**.001**	−1.45 (−3.33 to 0.42)	.129	**1.60 (0.72 to 2.49)**	**.0004**

ppb, Parts per billion.
Bold indicates statistical significance ($P < .05$).
*The interaction term for gestational age and asthma was not significant for FVC% predicted: the results from the FVC model without the interaction term are presented.
†Not statistically significantly different to uncontrolled asthma.
‡Includes underweight (n = 14; range, 16.64-18.5 kg/m^2) and healthy weight.

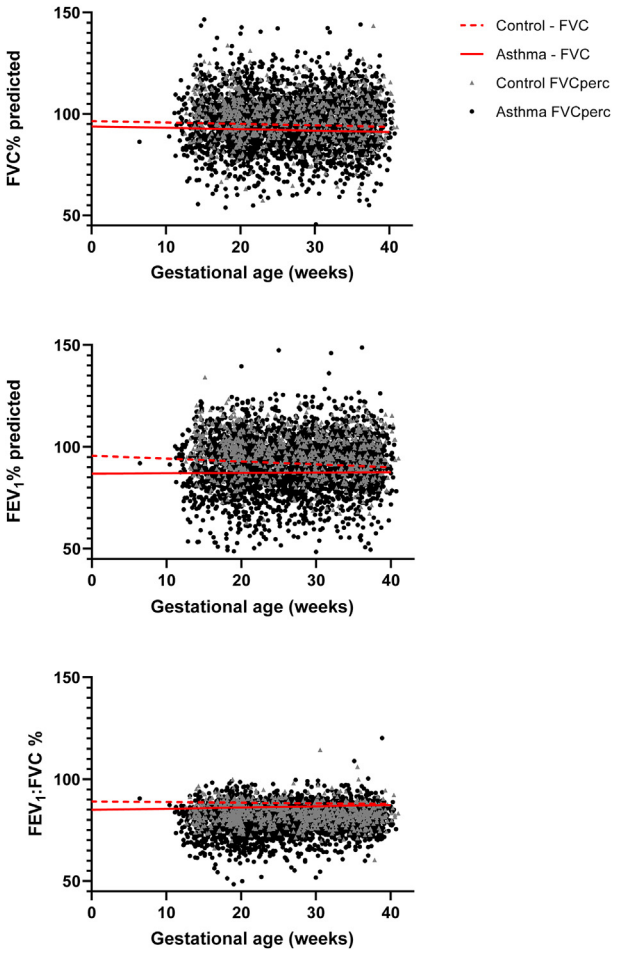

FIGURE E1. Changes in FVC% predicted, FEV1% predicted, and FEV1:FVC% during pregnancy among women without asthma (*dashed*) and women with asthma (*solid line*). Figures depict scatterplot of individual values and regression lines based on the coefficients of the variables "asthma," "gestational age," and, if significant, the interaction term of "Asthma × Gestational age" found in Table II.

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