Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

CHEST

Original Research

ASTHMA

A Prospective Study of Respiratory Viral Infection in Pregnant Women With and Without Asthma

Vanessa E. Murphy, PhD; Heather Powell, MMedSc(ClinEpid); Peter A. B. Wark, BMed, PhD; and Peter G. Gibson, MBBS

Background: **Respiratory viral infections are common in pregnancy, but their health impact, especially in asthma, is unknown. The objective of this study was to assess the frequency, severity, and consequences of respiratory viral infection during pregnancy in women with and without asthma.**

Methods: **In this prospective cohort study, common cold symptoms were assessed during pregnancy in 168 women with asthma and 117 women without asthma using the common cold questionnaire and by self-report. Nasal and throat swabs were collected for suspected infections and tested by polymerase chain reaction for respiratory viruses. Pregnancy and asthma outcomes were recorded.**

Results: **Pregnant women with asthma had more prospective self-reported and questionnaire-detected common colds than pregnant women without asthma (incidence rate ratio, 1.77; 95% CI, 1.30-2.42; $P < .0001$). Retrospectively reported common colds in early pregnancy and post partum were increased in women with asthma compared with women without asthma. The severity of cold symptoms was also increased in women with asthma (total cold score median, 8; interquartile range [5, 10] in women with asthma vs 6 [5, 8] in control subjects; $P = .031$). Among women with asthma, having a laboratory-confirmed viral infection was associated with poorer maternal health, with 60% of infections associated with uncontrolled asthma and a higher likelihood of preeclampsia.**

Conclusions: **Pregnant women with asthma have more common colds during pregnancy than pregnant women without asthma. Colds during pregnancy were associated with adverse maternal and pregnancy outcomes. Prevention of viral infection in pregnancy may improve the health of mothers with asthma.**

CHEST 2013; 144(2):420–427

Abbreviations: ACQ = Asthma Control Questionnaire; CCQ = common cold questionnaire; IQR = interquartile range; IRR = incidence rate ratio; MAP = Managing Asthma in Pregnancy; PCR = polymerase chain reaction; RR = relative risk

Pregnant women, especially those with asthma, experience significant problems associated with respiratory viral infections.[1] The outcomes from pandemic 2009 influenza A(H1N1) were more severe in pregnant women and people with asthma,[2] and retrospective studies report more infections in pregnant women with asthma than those without asthma.[3,4] The effects of viral infection may be more severe among pregnant women with asthma, with a 10-fold increased risk of respiratory-related hospitalization during the influenza season described for pregnant women with

Manuscript received August 6, 2012; revision accepted February 19, 2013.

Affiliations: From the Centre for Asthma and Respiratory Diseases (Drs Murphy, Wark, and Gibson and Ms Powell), University of Newcastle and Hunter Medical Research Institute; and John Hunter Hospital (Ms Powell and Drs Wark and Gibson), Newcastle, NSW, Australia.

Funding/Support: This study was funded by the University of Newcastle, Asthma Foundation of NSW, and the National Health and Medical Research Council of Australia (NHMRC) [Grant 455593]. Dr Murphy was the recipient of an NHMRC Australian Research Training Fellowship (part-time). Dr Gibson is an NHMRC Practitioner Fellow.

Correspondence to: Vanessa E. Murphy, PhD, Centre for Asthma and Respiratory Diseases, Level 2, W Wing, Hunter Medical Research Institute, c/- University of Newcastle, University Dr, Callaghan, NSW 2308, Australia; e-mail: vanessa.murphy@newcastle.edu.au

DOI: 10.1378/chest.12-1956

asthma compared with women without asthma.[1] Respiratory viral infections are reported to be a significant cause of asthma exacerbations during pregnancy[5] and may be associated with adverse outcomes, such as low birth weight.[6]

The characteristics and mechanisms of these effects are not well understood. Among nonpregnant women with asthma, susceptibility to respiratory viral infection is not increased, but colds are more severe with more lower respiratory tract symptoms, which are longer lasting.[7] However, pregnant women may be more susceptible to viral infection because of a pregnancy-related impairment in antiviral interferon responses[8,9] or deficiencies in epithelial cell function, overproduction of mucus, or alveolar macrophage dysfunction.[10]

We hypothesized that during pregnancy, women with asthma experience more frequent and more severe respiratory viral infections than pregnant women without asthma. We assessed these effects prospectively during pregnancy by assessing common colds by self-report and using the common cold questionnaire (CCQ) and polymerase chain reaction (PCR) testing and retrospectively in early pregnancy and post partum.

Materials and Methods

Study Design

Pregnant women with and without asthma were recruited from April 2007 to November 2009 (Fig 1) at the antenatal clinic of John Hunter Hospital, Newcastle, Australia. Written informed consent was obtained and ethics approval granted by the University of Newcastle and Hunter New England Area Health Service Research Ethics Committees (approval number 07/02/21/3.06). Women between 12 and 20 weeks' gestation who were > 18 years of age were included. Exclusion criteria were the presence of a chronic medical disease (other than asthma), drug or alcohol dependence, and an inability to attend study visits or perform spirometry. Control subjects had never received a diagnosis of asthma, whereas women with asthma had a doctor's diagnosis of asthma and asthma symptoms or therapy in the prior 3 months.

Women completed monthly clinical visits and were telephoned fortnightly (e-Appendix 1, e-Fig 1). The majority (157 of 168, 93%) of the women with asthma also commenced participation in the Managing Asthma in Pregnancy (MAP) study.[11,12] Regardless of coparticipation in MAP, all women, with and without asthma, had the same schedule of study visits and telephone contacts and were eligible for additional visits based on the same criteria (current common cold). Some women consented to donate blood for in vitro studies of responses to viral infection.[8,9]

Clinical Measures

At each visit and telephone contact, asthma symptoms over the past 7 days were collected by self-report and using the Asthma Control Questionnaire (ACQ7).[13] Exacerbations were assessed by direct questioning and defined as those requiring medical intervention (hospital admission, ED presentation, unscheduled doctor visit, or the use of oral corticosteroids).

Common colds were assessed by direct questioning (self-report: "Do you currently have a cold?") and using the CCQ (e-Fig 2)[14] at each contact. The CCQ assessed nine symptoms over four domains (general: fevers, chills, muscle pains; nasal: watery eyes, runny nose, sneezing; throat: sore throat; chest: cough, chest pain), which were scored as none (0), mild (1), moderate (2), or severe (3).[14] A cold was "probable" when symptoms were moderate in at least two domains or mild in at least three domains. Unless otherwise indicated, a common cold was defined as instances wherein the CCQ indicated a "probable cold." Common cold severity was assessed by the total CCQ score (possible score, 0-27) and by the proportion of colds with a score ≥ 10.[14] Baseline scores are given in e-Table 1. Colds in early pregnancy and post partum were retrospectively assessed by self-report at the first study visit and 6 months post partum, respectively. Subjects with a current cold (women with and without asthma) or current asthma exacerbation were offered additional visits either at home or hospital within 48 h. If a new cold was reported 14 days after a previous report, it was considered a separate clinical event.[7]

Virus PCR Testing

Nasal and throat swabs were collected from women with common colds. Viruses were identified using real-time quantitative PCR for rhinovirus, enterovirus, respiratory syncytial virus A and B, influenza A and B, coronavirus, and human metapneumovirus.[15]

Statistical Methods

Statistical analysis was performed using Stata 11 (StataCorp LP). Results are presented as mean ± SD or median (interquartile range [IQR]) with Student *t* test and Wilcoxon rank sum tests as appropriate and Wilcoxon signed rank test for paired data. The χ^2 test was used to compare proportions. Two-sided tests with $P < 05$ were considered significant, with the exception of data on the frequency of common colds and PCR-positive colds ($P < .025$, because this outcome was assessed by two similar methods). The rate difference between the groups for colds was compared using a Poisson regression model adjusted for BMI, atopy, and parity, with a robust option when data were overdispersed. Secondary outcomes were cold severity (analyzed as panel data using Stata's xtreg with random effects and adjusted for baseline CCQ score, BMI, atopy, and parity), impact of colds on asthma, and impact of colds on pregnancy outcomes. We assessed the relationship between PCR-positive colds in asthma and preeclampsia/pregnancy-induced hypertension with logistic regression, adjusting for smoking, parity, age, BMI, and multiple pregnancy. Receiver operator curve (ROC) analyses were used to evaluate different diagnostic cutoff levels for the CCQ score in PCR positive infections (e-Fig 3). Kaplan-Meier survival estimates were used to investigate the time to first cold (e-Fig 4).

Results

Subject Characteristics

Two hundred eighty-five pregnant women were recruited (168 with asthma, 117 control subjects) (Fig 1). Pregnant women with asthma had significantly higher BMI ($P < .002$), significantly worse lung function ($P < .05$), and were more likely to have atopy ($P < .0001$) than control subjects (Table 1, e-Appendix 2, e-Table 2).

Frequency of Common Colds During Pregnancy

Pregnant women with asthma had more questionnaire-detected common colds during pregnancy (71%) than pregnant women without asthma (46%; $P < .0001$;

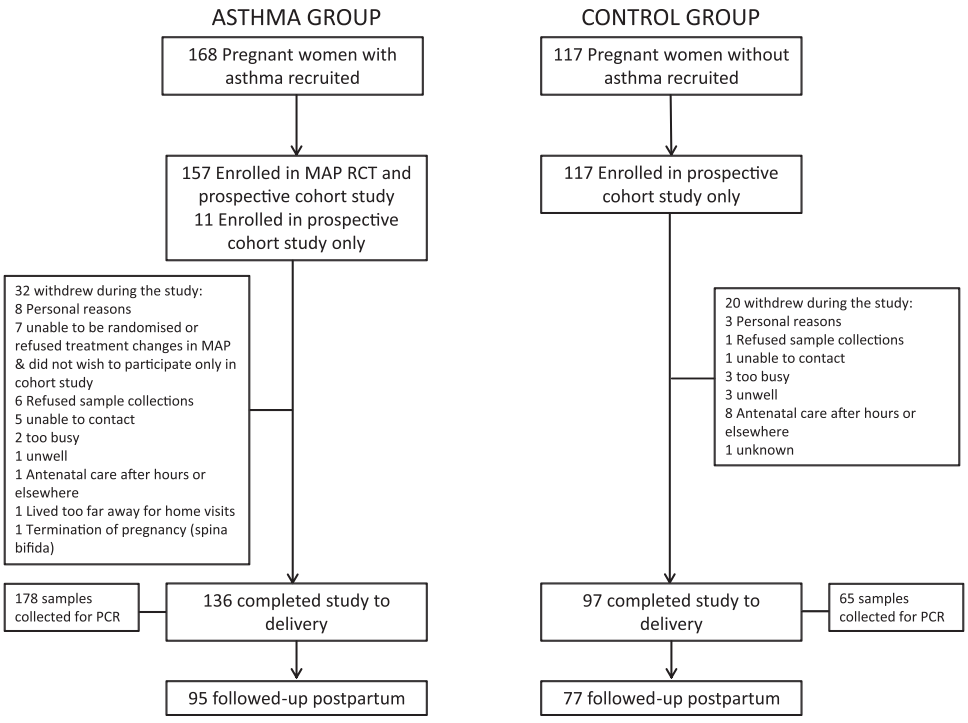

FIGURE 1. Recruitment, enrollment, and study completion. MAP = Managing Asthma in Pregnancy; RCT = randomized controlled trial.

relative risk [RR], 1.83; 95% CI [1.39, 2.41]) (Table 2). More women with asthma had multiple common colds than women without asthma (33% vs 16%; $P = .0028$; RR, 1.25; 95% CI [1.09, 1.42]). There were 223 common cold events in the asthma group and 83 in the control group (e-Table 3). The rate of common cold events adjusted for follow-up time, atopy, parity, and maternal BMI was significantly higher in the asthma group compared with the control group (Fig 2) (incidence rate ratio [IRR], 1.77; 95% CI [1.30, 2.42]; $P < .0001$). The control group had the same proportion of common colds detected in the second and third trimesters, whereas the asthma group had significantly more common colds detected in the second compared with the third trimester (Table 2) ($P < .0001$), despite longer follow-up times for the third trimester. In addition to questionnaire-detected colds, women with asthma also self-reported more colds prospectively during pregnancy and retrospectively in early pregnancy and post partum (e-Table 4).

Nasal and/or throat swab samples were collected from 80% of common cold events (20% were not collected because of refusal by the participant or lack of a clinical visit at the time of the event), within a median time from symptom onset of 3.5 days (IQR, 3-7 days) in the control group and 4 days (IQR, 2-7 days) in the asthma group (e-Table 5). Thirty-one percent of women with asthma and 18.8% of women without asthma had one or more PCR-positive colds during pregnancy (RR, 1.18; 95% CI [1.03, 1.34], asthma vs control) (Fig 3, Table 3), but this did not reach our significance level of $P < .025$ ($P = .0305$). There were 26 PCR-positive cold events in the nonasthmatic control group and 60 PCR-positive cold events in the asthma group (e-Table 5). There was no significant difference in the rate of PCR-positive colds between groups (adjusted for follow-up time, atopy, parity, and maternal BMI; IRR, 1.18; 95% CI [0.72, 1.94]; $P = .505$) (Table 3). The number of second trimester PCR-positive colds was higher than the number of third trimester colds in the asthma group ($P = .0442$) but not in the control group ($P = .4524$) (e-Table 5). In addition to questionnaire-detected colds, women with asthma also self-reported more colds prospectively during pregnancy and retrospectively in early pregnancy and post partum (e-Table 4).

Severity of Common Colds During Pregnancy

The median total CCQ score was higher among common cold events in the asthma group (median, 8; IQR [5, 10]) compared with the control group (median, 6; IQR [5, 8]) and was statistically significant when baseline values were adjusted for (xtreg, coefficient 1.16; 95% CI [0.11, 2.21]; $P = .031$) (e-Table 6). However, in PCR-positive colds, the total CCQ score was not different between groups (e-Table 6) (xtreg, coefficient 0.86; 95% CI [−1.13, 2.85]; $P = .397$).

Table 1—*Subject Characteristics*

Characteristic	Control Group (n = 117)	Asthma Group (n = 168)	*P* Value
Maternal age,[a] y	29.6 (4.6) Range, 18-38	28.5 (5.6) Range, 18-43	.086
Gestational age at recruitment,[a]wk	16.6 (2.3) Range, 12.6-21.3	16.9 (2.4) Range, 11.7-21.9	.193
Gravidity[b]	2 (1, 2)	2 (1, 3)	.010
Parity[b]	1 (0, 1)	1 (0, 2)	.016
Para 0[c]	49 (41.9)	56 (33.3)	.178
Maternal atopy[c]	51 (45.9) n = 111	115 (71.9) n = 160	< .0001
Maternal BMI[b]	25.2 (22.8, 28.7) n = 116	27.7 (24.4, 32.1) n = 165	.0005
Smoking status			…
Never[c]	66 (56.4)	80 (47.6)	…
Ex[c]	32 (27.4)	52 (31.0)	…
Current[c]	18 (15.4)	35 (20.8)	.245
Smoking pack-y[b]	3.0 (0.9, 6.0)	4.0 (1.5, 7.0)	.070
Prebronchodilator spirometry	n = 117	n = 142	…
FEV_1[a]	3.29 (0.42)	2.96 (0.52)	< .0001
% Predicted FEV_1[a]	102.9 (11.1)	93.8 (14.6)	< .0001
FVC[b]	3.93 (3.52, 4.24)	3.72 (3.34, 4.18)	.030
% Predicted FVC[b]	107.6 (98.0, 116.2) n = 116	103.0 (74.5, 112.6)	.037
No ICS treatment[d]	…	120 (71.4)	…
ICS treatment[d]	…	15 (8.9)	…
ICS/LABA treatment[d]	…	33 (19.6)	…
ICS dose (among ICS users), BDP equivalents μg/d	…	800 (650, 1,000) n = 47	…
ACQ7	…	0.86 (0.29, 1.57)	…
Influenza vaccine for current season[c]	10 (8.5)	16 (9.5)	.8407

Data were collected at the first study visit. ACQ7 = Asthma Control Questionnaire (7 item); BDP = beclomethasone dipropionate; ICS = inhaled corticosteroid; IQR = interquartile range; LABA = long-acting β-agonist.
[a]Mean (SD), Student *t* test.
[b]Median (IQR), Wilcoxon rank sum test.
[c]No. (%), χ^2 test.
[d]No. (%).

Impact of Colds on Asthma

One-third of the PCR-positive viral infections were associated with exacerbation requiring medical intervention and a further one-third with loss of control (e-Tables 7, 8). Total CCQ score significantly correlated with ACQ score (Spearman $r = 0.3187$, $P = .0131$, Spearman rank correlation) (e-Fig 5).

Among the subgroup of women with asthma participating in the MAP study, those randomized to fractional exhaled nitric oxide-based management (n = 69) were significantly less likely to report common colds (63.8% vs 82.2%; RR, 0.492; 95% CI [0.274, 0.881]) or PCR-positive colds (23.2% vs 42.5%; RR, 0.749; 95% CI [0.592, 0.948]) compared with those randomized to clinical guidelines-based management (n = 73).

Impact of Colds on Neonatal Outcomes

In the control group, women with at least one PCR-positive cold had babies of significantly lower birth weight ($P = .0274$) and length ($P = .0236$) compared with control subjects with PCR-negative colds (Table 4). Women with asthma with PCR-positive colds had significantly increased odds of preeclampsia or pregnancy-induced hypertension when adjusted for known preeclampsia risk factors (maternal smoking, age, BMI, parity, multiple pregnancy; OR, 8.48; 95% CI [1.41, 51.11]; $P < .02$) (Table 4) compared with women with asthma with PCR-negative colds.

Discussion

Pregnant women with asthma have more common colds during pregnancy than pregnant women without asthma, both by self-report and questionnaire. The severity of symptoms was higher in subjects with asthma with common colds than control subjects, when adjusted for baseline differences. Although PCR-positive colds were of similar severity in the two groups, virus-confirmed colds in subjects with asthma frequently resulted in exacerbations and were associated with perinatal effects.

Previous studies in nonpregnant adults with asthma have suggested that subjects with asthma are no more

Table 2—*Frequency of Common Colds During Pregnancy*

Cold Measures	Control (n = 117)	Asthma (n = 168)	Effect Size	*P* Value
Subjects with ≥ 1 cold (probable by CCQ) during pregnancy[a]	54 (46)	120 (71.4)	RR, 1.83; 95% CI (1.39, 2.41)	< .0001
Subjects with > 1 common cold during pregnancy[a]	19 (16.2)	55 (32.7)	RR, 1.25; 95% CI (1.09, 1.42)	.0028
No. of colds per person[b]	0 (0, 1)	1 (0, 2)	...	< .0001
	Range, 0-6	Range, 0-8		
No. of common cold events/person-wk[c]	0.035	0.067	IRR, 1.77; 95% CI (1.30, 2.42)	< .0001
Cold events by season			...	...
Summer[d]	13 (15.7)	33 (14.8)		
Autumn[d]	24 (28.9)	53 (23.8)		
Winter[d]	26 (31.3)	75 (33.6)		
Spring[d]	20 (24.1)	62 (27.8)		

Seasons were Australian summer (December-February), autumn (March-May), winter (June-August), spring (September-November). CCQ = common cold questionnaire; IRR = incidence rate ratio; RR = relative risk. See Table 1 legend for expansion of other abbreviation.
[a]No. (%), χ^2 test, RR.
[b]Median (IQR), Mann-Whitney test.
[c]IRR, Poisson regression, adjusted for atopy, parity, and BMI.
[d]No. (%).

susceptible to respiratory tract infections than subjects without asthma.[7] The evidence in the present study suggests that in pregnancy, women with asthma may be more susceptible to common colds than women without asthma but that cold symptoms associated with PCR-positive colds are similar to those in women without asthma. In a large prospective study, 14.4% of women had a common cold during pregnancy, with one-half of these colds medically recorded.[16] The CCQ we used identified more common colds than self-report, and not all of these were virus-positive by laboratory testing. The prospective nature of our study likely contributed to a high rate of reporting of common colds. It is possible that confounding by symptoms of rhinitis may have contributed to a high proportion of women with questionnaire-detected colds.

Common colds were more likely to occur in the second trimester than the third trimester in the asthma group only. Bánhidy et al[16] found that there was a lower prevalence of the common cold in the eighth and ninth months of pregnancy compared with the first 7 months; however, it was unclear if follow-up time and early deliveries had been accounted for. Asthma exacerbations also peak in the late second trimester.[5,17] Further evidence is required to determine if this is due to a pregnancy-specific rise in susceptibility to infection.

One-third of PCR-positive colds were associated with exacerbations requiring medical intervention. In previous studies, 60% of cases with a positive virus identification were associated with asthma exacerbation,[18] whereas cold severity was predictive of subsequent asthma worsening.[19] Viral infection is a significant asthma trigger, possibly because of the inflammatory pathways activated during infection. Understanding the relationship between viral infection and asthma[20] is important, as preventing viral infection could also prevent exacerbations. We have evidence that improved asthma management through fractional exhaled nitric oxide monitoring is associated with a reduction not only in exacerbations[11] but also in PCR-positive viral infections.

Pregnant women with asthma who had PCR-positive colds were more likely to have preeclampsia than

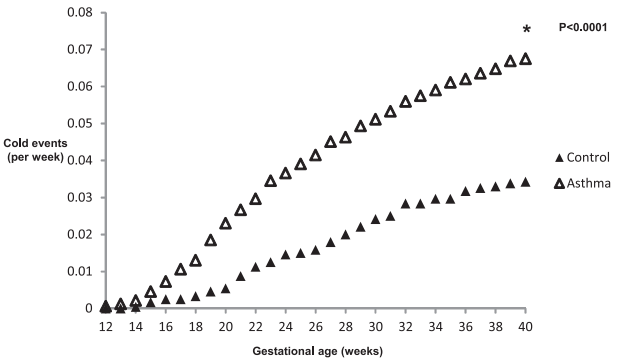

FIGURE 2. Cumulative common colds adjusted for total person-weeks per group in the asthma (△) and control (▲) groups over the course of pregnancy (*incidence rate ratio, 1.77; 95% CI [1.30, 2.42]).

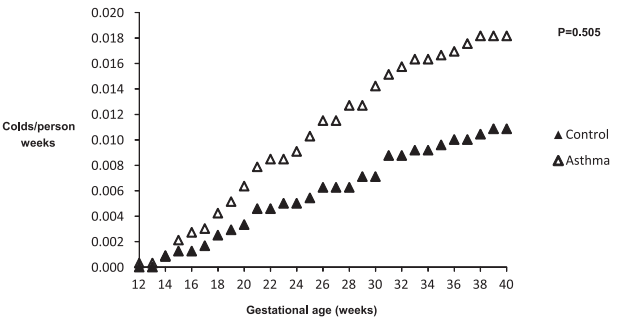

FIGURE 3. Cumulative polymerase chain reaction-positive colds adjusted for total person-weeks per group in the asthma (△) and control (▲) groups over the course of pregnancy (incidence rate ratio, 1.18; 95% CI [0.72, 1.94]).

Table 3—*Frequency of PCR-Positive Colds During Pregnancy*

Cold Measures	Control (n = 117)	Asthma (n = 168)	Effect Size	*P* Value
Subjects with ≥ 1 PCR-positive cold[a]	22 (18.8)	52 (31.0)	RR, 1.18; 95% CI (1.03, 1.34)	.0305
Subjects with multiple PCR-positive cold events[a]	3 (2.6)	8 (4.8)	…	.5254
PCR colds per person-weeks[b]	0.0108	0.0182	IRR, 1.18; 95% CI (0.72, 1.94)	.505
Influenza A[c]	1 (3.4)	5 (7.7)	…	…
Influenza B[c]	2 (6.9)	3 (4.6)	…	…
Human RV[c]	13 (44.8)	25 (38.5)	…	…
Human EV[c]	1 (3.4)	6 (9.2)	…	…
CoV[c]	3 (10.3)	9 (13.8)	…	…
RSV A[c]	0 (0)	1 (1.5)	…	…
RSV B[c]	4 (13.8)	1 (1.5)	…	…
Human MPV[c]	5 (17.2)	15 (23.1)	…	…
Total viruses detected	29	65	…	…
Multiple infection	RV + MPV	RV + EV	…	…
	RSV B + MPV	RV + CoV	…	…
	RSV B + MPV	CoV + MPV	…	…
	…	RSVA + RV	…	…
	…	FluA + MPV	…	…

CoV = coronavirus; EV = enterovirus; FluA = influenza A; MPV = metapneumovirus; PCR = polymerase chain reaction; RSV = respiratory syncytial virus; RV = rhinovirus. See Table 1 legend for expansion of other abbreviations.

[a]No. (%), χ^2 test, RR.

[b]IRR, Poisson regression adjusted for atopy, parity, and BMI.

[c]No. (% of all viruses detected).

women without PCR-positive colds, consistent with studies suggesting an association between maternal infection (bacterial or viral) and the risk of preeclampsia, possibly due to changes in the maternal immune system.[21] Pregnant women with asthma are at increased risk of preeclampsia compared with pregnant women without asthma.[22-25] No previous reports have linked asthma, preeclampsia, and viral infection during pregnancy. It

Table 4—*Impact of PCR-Positive Colds on Pregnancy Outcomes in the Control Group and the Asthma Group*

	Control Group			Asthma Group		
Pregnancy Outcomes	PCR− Colds (n = 24 Pregnancies and Babies)	PCR+ Colds (n = 22 Pregnancies and Babies)	*P* Value	PCR− Colds (n = 53 Pregnancies, n = 55 Babies)	PCR+ Colds (n = 52 Pregnancies, n = 52 Babies)	*P* Value
Gestational age,[a] wk	40.8 (39.7, 41.3) n = 22	39.9 (38.7, 41.0) n = 22	.1555	39.9 (38.6, 40.5) n = 54	39.6 (38.4, 40.3) n = 52	.6265
Preterm delivery of infant (< 37 completed wk)[b]	0 of 22	3 of 22 (13.6)	.2316	9 of 54 (16.7)	4 of 52 (7.7)	.2661
Birth weight,[a] g	3,600 (3,384, 3,885) n = 22	3,130 (2,790, 3,673) n = 22	.0274	3,520 (3,180, 3,875) n = 51	3,280 (3,010, 3,520) n = 51	.0605
Low birth weight (< 2,500 g)[b]	0 of 22	4 of 22 (18.2)	.1157	5 of 51 (9.8)	4 of 51 (7.8)	.727
Birth length,[a] cm	52 (51.5, 53.5) n = 15	51 (49, 51.9) n = 18	.0236	51 (49, 53) n = 45	50.5 (49, 52) n = 44	.2622
Birth head circumference,[a] cm	34.5 (33.5, 35.5) n = 21	34 (33, 35) n = 20	.0974	34.5 (33.5, 35.4) n = 51	34 (33, 35) n = 51	.3348
Apgar at 1 min[a]	9 (8, 9) n = 21	8 (8, 9) n = 21	.5328	9 (7, 9) n = 50	9 (6, 9) n = 51	.8501
Apgar at 5 min[a]	9 (9, 9) n = 22	9 (9, 9) n = 22	.5561	9 (9, 9) n = 50	9 (9, 9) n = 51	.4819
Maternal preeclampsia[b]	0	1 (4.5)	.3177	0	6 (11.5)	.0355
Maternal pregnancy-induced hypertension[b]	0	1 (4.5)	.3177	2 (3.8)	5 (9.6)	.4338
Maternal gestational diabetes	0	0	…	2 (3.8)	4 (7.7)	.6741
Still birth	0	0	…	1 (1.9)	0	.3241
Neonatal intensive care admission[b]	3 (13.6)	2 (9)	.6348	8 (4.8)	7 (13.5)	.8416
Congenital anomaly[b]	0	1 (4.5)	.3177	0	0	…

Note: Data not available on all infants due to delivery at other hospitals. See Table 1 and 3 legends for expansion of abbreviations.

[a]Median (IQR) Wilcoxon rank sum test.

[b]No. (%), χ^2 test.

is possible that inflammation associated with the response to viral infection and/or asthma exacerbation may contribute to the underlying endothelial dysfunction in preeclampsia.

There are limitations to our study. The CCQ is an unvalidated tool, which limits the conclusions we can make using this instrument, particularly since the CCQ is not validated to distinguish between viral infections and rhinitis. There was the possibility of recall bias for colds assessed retrospectively, although for the majority of pregnancy we collected data prospectively. The pregnant women with asthma had higher parity than pregnant women without asthma, which might increase their exposure to virus infections from other children.[26,27] However, we adjusted for this as well as other confounders, such as atopy and BMI (a known risk factor for exacerbations in pregnancy[28]), when considering the rate of colds. Our sample collection time was not ideal, with swabs collected within a median of 3 to 4 days from symptom worsening. We contacted women fortnightly by phone and sent mobile phone text reminders every other week to try to increase participation and offered home visits during colds. The CCQ covers only 2 days of the past 14, and since we did not administer it daily, it is possible colds were missed. The number of PCR-positive colds experienced by women with asthma, when adjusted for follow-up time, was not significantly different from the control group. This may be due to a lack of power, since only a proportion of common colds were tested in the laboratory, or rhinitis-like symptoms and cough may be amplified by asthma or pregnancy themselves, resulting in more colds being detected that were not true infections. Although we found second trimester colds to be more frequent than third trimester colds, it is possible that rhinitis of pregnancy may have contributed to this finding.

Conclusions

Common colds were more frequently reported among pregnant women with asthma compared with women without asthma. They occurred more often in the second trimester than the third, perhaps explaining the greater exacerbation risk at this time. There was an impact on maternal health, with one-third of infections associated with exacerbations requiring medical intervention. Prevention of respiratory viral infections may improve asthma outcomes during pregnancy.

Acknowledgments

Author contributions: Dr Murphy takes responsibility for the content of the manuscript, including the data and analysis.
Dr Murphy: contributed to study conception and design, analysis and interpretation of data, and writing the manuscript and gave final approval to the version to be published.
Ms Powell: contributed to analysis and interpretation of data and revision of the article for important intellectual content and gave final approval to the version to be published.
Dr Wark: contributed to acquisition of data and revision of the article for important intellectual content and gave final approval to the version to be published.
Dr Gibson: contributed to study conception and design, interpretation of data, and revision of the article for important intellectual content and gave final approval to the version to be published.
Financial/nonfinancial disclosures: The authors have reported to *CHEST* that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.
Role of sponsors: The sponsor had no role in the design of the study, the collection and analysis of the data, or in the preparation of the manuscript.
Other contributions: We thank Kelly Steel, BNursing; Karen McLaughlin, Dip App Sci (Nursing), BNursing, Post Grad Dip Midwifery; Rebecca Oldham, Advanced Dip Pathology testing, B Ed (Sci); Linda Howell, B Nursing; Joanne Smart, Ass Dip DMR; Noreen Bell, RN; and Sandra Dowley for assistance with clinical assessments and data collection; Lakshitha Gunawardhana, B Biotech (Hons); Alan Hsu, PhD; Kristy Parsons, B Biomed Sci; Rebecca Forbes, PhD; and Katherine Baines, PhD, for laboratory testing; and the midwives and staff of the antenatal clinic at John Hunter Hospital for their assistance during subject recruitment.
Additional information: The e-Figures and e-Tables can be found in the "Supplemental Materials" area of the online article.

References

1. Hartert TV, Neuzil KM, Shintani AK, et al. Maternal morbidity and perinatal outcomes among pregnant women with respiratory hospitalizations during influenza season. *Am J Obstet Gynecol*. 2003;189(6):1705-1712.
2. Jain S, Kamimoto L, Bramley AM, et al; 2009 Pandemic Influenza A (H1N1) Virus Hospitalizations Investigation Team. Hospitalized patients with 2009 H1N1 influenza in the United States, April-June 2009. *N Engl J Med*. 2009;361(20):1935-1944.
3. Minerbi-Codish I, Fraser D, Avnun L, Glezerman M, Heimer D. Influence of asthma in pregnancy on labor and the newborn. *Respiration*. 1998;65(2):130-135.
4. Clifton VL, Engel P, Smith R, Gibson P, Brinsmead M, Giles WB. Maternal and neonatal outcomes of pregnancies complicated by asthma in an Australian population. *Aust N Z J Obstet Gynaecol*. 2009;49(6):619-626.
5. Murphy VE, Gibson P, Talbot PI, Clifton VL. Severe asthma exacerbations during pregnancy. *Obstet Gynecol*. 2005; 106(5 pt 1):1046-1054.
6. Murphy VE, Clifton VL, Gibson PG. Asthma exacerbations during pregnancy: incidence and association with adverse pregnancy outcomes. *Thorax*. 2006;61(2):169-176.
7. Corne JM, Marshall C, Smith S, et al. Frequency, severity, and duration of rhinovirus infections in asthmatic and non-asthmatic individuals: a longitudinal cohort study. *Lancet*. 2002;359(9309):831-834.
8. Forbes RL, Gibson PG, Murphy VE, Wark PA. Impaired type I and III interferon response to rhinovirus infection during pregnancy and asthma. *Thorax*. 2012;67(3):209-214.
9. Forbes RL, Wark PA, Murphy VE, Gibson PG. Pregnant women have attenuated innate interferon responses to 2009 pandemic influenza A virus subtype H1N1. *J Infect Dis*. 2012;206(5): 646-653.
10. James KM, Peebles RS Jr, Hartert TV. Response to infections in patients with asthma and atopic disease: an epiphenomenon or reflection of host susceptibility? *J Allergy Clin Immunol*. 2012;130(2):343-351.
11. Powell H, Murphy VE, Taylor DR, et al. Management of asthma in pregnancy guided by measurement of fraction of

exhaled nitric oxide: a double-blind, randomised controlled trial. *Lancet*. 2011;378(9795):983-990.
12. Powell H, McCaffery K, Murphy VE, et al. Psychosocial outcomes are related to asthma control and quality of life in pregnant women with asthma. *J Asthma*. 2011;48(10):1032-1040.
13. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J*. 1999;14(4):902-907.
14. Powell H, Smart J, Wood LG, et al. Validity of the common cold questionnaire (CCQ) in asthma exacerbations. PLoS One 2008;3(3):e1802.
15. Wark PA, Bucchieri F, Johnston SL, et al. IFN-gamma-induced protein 10 is a novel biomarker of rhinovirus-induced asthma exacerbations. *J Allergy Clin Immunol*. 2007;120(3):586-593.
16. Bánhidy F, Acs N, Puhó E, Czeizel AE. Pregnancy complications and delivery outcomes of pregnant women with common cold. *Cent Eur J Public Health*. 2006;14(1):10-14.
17. Stenius-Aarniala BS, Hedman J, Teramo KA. Acute asthma during pregnancy. *Thorax*. 1996;51(4):411-414.
18. Beasley R, Coleman ED, Hermon Y, Holst PE, O'Donnell TV, Tobias M. Viral respiratory tract infection and exacerbations of asthma in adult patients. *Thorax*. 1988;43(9):679-683.
19. Walter MJ, Castro M, Kunselman SJ, et al; National Heart, Lung and Blood Institute's Asthma Clinical Research Network. Predicting worsening asthma control following the common cold. *Eur Respir J*. 2008;32(6):1548-1554.
20. Nicholson KG, Kent J, Ireland DC. Respiratory viruses and exacerbations of asthma in adults. *BMJ*. 1993;307(6910):982-986.
21. Rustveld LO, Kelsey SF, Sharma R. Association between maternal infections and pre-eclampsia: a systematic review of epidemiological studies. *Matern Child Health J*. 2008;12(2):233-242.
22. Murphy VE, Namazy JA, Powell H, et al. A meta-analysis of adverse perinatal outcomes in women with asthma. *BJOG*. 2011;118(11):1314-1323.
23. Martel MJ, Rey E, Beauchesne MF, et al. Use of short-acting beta2-agonists during pregnancy and the risk of pregnancy-induced hypertension. *J Allergy Clin Immunol*. 2007;119(3):576-582.
24. Martel MJ, Rey E, Beauchesne MF, et al. Use of inhaled corticosteroids during pregnancy and risk of pregnancy induced hypertension: nested case-control study. *BMJ*. 2005;330(7485):230.
25. Rudra CB, Williams MA, Frederick IO, Luthy DA. Maternal asthma and risk of preeclampsia: a case-control study. *J Reprod Med*. 2006;51(2):94-100.
26. Johnston SL, Pattemore PK, Sanderson G, et al. The relationship between upper respiratory infections and hospital admissions for asthma: a time-trend analysis. *Am J Respir Crit Care Med*. 1996;154(3 pt 1):654-660.
27. Lain SJ, Roberts CL, Warning J, Vivian-Taylor J, Ford JB. A survey of acute self-reported infections in pregnancy. *BMJ Open*. 2011;1(1):e000083.
28. Hendler I, Schatz M, Momirova V, et al; National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Association of obesity with pulmonary and nonpulmonary complications of pregnancy in asthmatic women. *Obstet Gynecol*. 2006;108(1):77-82.