

Perimenstrual increase in bronchial hyperreactivity in premenopausal women: Results from the population-based SAPALDIA 2 cohort

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Background: Studies on perimenstrual asthma are inconsistent, and different methodologies limit comparisons.

Objective: To investigate cyclic variations in bronchial hyperreactivity (BHR) to methacholine in premenopausal women in a population-based cohort and assess effect modification by oral contraceptives (OCs).

Methods: Day of menstruation cycle at the time of methacholine challenge was calculated in 571 menstruating women without hormonal treatment, age 28 to 58 years, on the basis of questionnaire data from the Swiss cohort study on Air Pollution And Lung Disease In Adults (SAPALDIA) cohort 2001/2002. A window of risk was defined 3 days before and after the first day of menstruation. Logistic and linear regression analyses were performed adjusting for main predictors of BHR and stratifying for asthma status. The impact of OCs was studied in the same sample enlarged by 130 women taking OCs.

Results: The prevalence of BHR was 13% (fall of $\geq 20\%$ in FEV₁ up to a maximal cumulative dose of 2 mg), and 6% had asthma. A total of 143 women had undergone methacholine challenge within the risk window. We observed a significant increase in BHR within the window of risk (odds ratio [OR], 2.3; 95% CI, 1.27-4.29). A cyclic association pattern was confirmed by trigonometric functions. Effect modification by asthma status and oral contraceptive use was found, with lower OR in subjects without asthma and OR < 1 in women using OCs.

Conclusion: The data provide evidence of a systematic variation in BHR during the menstruation cycle, supporting the hypothesis of a hormonal influence. OCs appear to have a

protective effect. Cyclicality of BHR could be of clinical importance in view of future medication recommendations and timing of respiratory function tests in women. (J Allergy Clin Immunol 2010;■■■:■■■-■■■.)

Key words: Asthma, bronchial hyperreactivity, epidemiology, menstruation, methacholine challenge test, oral contraceptives, premenstrual

The influence of female sex hormones on asthma and asthma exacerbations has been discussed widely, and various approaches have been adopted to investigate the hormonal hypothesis. Understanding hormonal influences on asthma exacerbations could lead to improved symptom management and decrease the disease burden considerably.

Epidemiologically, the hypothesis is supported by a clear positive association of asthma incidence and puberty in females.^{1,2} It is further strengthened by reports of change in severity of asthma symptoms in pregnancy^{3,5} and an increase in symptoms in the end luteal phase of the menstrual cycle. The latter, perimenstrual or premenstrual asthma (PMA), was first described by Frank et al in 1931.⁶ Studies on PMA have reported a prevalence of up to 40%.⁶ However, studies investigating objective parameters, such as forced expiratory volume in 1 second (FEV₁),⁷⁻¹¹ peak expiratory flow,^{8-10,12,13} bronchial hyperreactivity (BHR),⁷⁻¹¹ or emergency department visits,¹⁴⁻¹⁶ have been largely inconsistent. The role of exogenous sex hormones for asthma is still inconclusive, with studies reporting both improvement and worsening of symptoms as well as increased asthma incidence.¹⁷⁻²³ Most previous studies have been conducted in asthmatic outpatient populations. Even if symptoms of clinical importance might only be seen in a patient population, one should expect to find an impact of endogenous sex hormones also on the lung physiology of healthy individuals. We therefore aimed to study the effect of the menstrual cycle, specifically of the perimenstrual period, on BHR in a population-based cohort of the Swiss cohort study on Air Pollution And Lung Disease In Adults (SAPALDIA) and investigate the potential effect modification of asthma status and oral contraceptive (OC) use.

METHODS

Study population

The analyses are based on 704 women from the second assessment of the SAPALDIA cohort who complied with the eligibility criteria in 2002 (Fig 1). The methodology of SAPALDIA has been described in detail previously.^{24,25} In short, the study population was recruited in 1991 as a population-based,

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Abbreviations used

BHR:	Bronchial hyperreactivity
BMI:	Body mass index
CRP:	C-reactive protein
FEV ₁ :	Forced expiratory volume in 1 second
OC:	Oral contraceptive
OR:	Odds ratio
PMA:	Premenstrual asthma
SAPALDIA:	Swiss cohort study on Air Pollution And Lung Disease In Adults

random sample of adults ($N = 9651$; 18–60 years) from 8 study areas in Switzerland, representing a broad range of environmental conditions. The overall response rate to the second survey in 2002 was 86% ($N = 8047$), and 70% ($N = 6528$) agreed to participate in the health examinations. In both SAPALDIA 1 and 2, the interview and medical tests were conducted by trained fieldworkers at the field centers. In the second assessment, the Women's Health Questionnaire of the European Community Respiratory Health Study was introduced.²⁶ The women's questionnaire asked for the first day of the last menstruation preceding the SAPALDIA assessment as well as for the cycle length and other reproductive information. Women who reported menstruating ($N = 1482$) constituted the menstruation card study population and were given a menstruation card on which they should report the first day of their next menstruation. Data on lifestyle and health characteristics were taken from the main questionnaire.²⁴ Respiratory function was measured with the same spirometers, meeting American Thoracic Society performance criteria, in both SAPALDIA 1 and 2. A quality assessment in 2001 demonstrated that measurements of lung volumes by the 8 spirometers were comparable to one another.²⁷ BHR was assessed by methacholine challenge (Provocholine Roche, Nutley, NJ). Increasing concentrations of methacholine (0.39, 1.56, 6.25, and 25.0 mg/mL solutions in a phosphate buffer without phenol) were administered through an aerosol dosimeter (mefar MB3; Anandic Medical Systems, Diessenhofen, CH) up to a maximal cumulative dose of 2 mg. Exclusion criteria for BHR were pregnancy or breast-feeding, recent myocardial infarction, severe cardiac failure, β -blocker medication, epilepsy, or a FEV₁/forced vital capacity lower than 70% of the predicted value ($N = 158$). Women were defined as having asthma if they reported having ever had asthma, irrespective of whether this was confirmed to them by a doctor.

Of a total 4180 female participants participating in SAPALDIA 2, 3151 filled out the women's questionnaire. Exclusion criteria for the current analysis were menopausal status ($n = 1099$), based on the Stages of Reproductive Aging Workshop definition²⁸; undefined menopausal status ($N = 30$); pregnancy or lactation ($N = 30$); and the intake of OCs ($N = 213$) or hormone replacement therapy ($N = 297$). Of the 1482 eligible women having agreed to report the starting date of the next menstruation following their examination, 790 sent back the menstruation cards (53% response rate). Fifteen questionnaires were discarded because of inconsistencies of reported menstruation dates and cycle lengths. Missing information on age at menarche was imputed with the study population mean age of menarche. Of the women still available, 617 were eligible for and willing to participate in the methacholine test. After exclusion of 43 tests for qualitative reasons and 3 for missing baseline spirometry results, 571 participants were available for the main analysis.

In a second step, to study the impact of OC use on the hypothesized association, we enlarged the main study sample by women currently using OCs and complying with the eligibility and exclusion criteria ($N = 130$).

Exposure variable

A binary exposure variable was created based on the day of the menstrual cycle on which the participants underwent the methacholine challenge test. We defined a window of risk of 3 days before to 3 days after the first day of menstrual cycle. The binary variable took the value 1 if the examination fell within this window of risk and 0 otherwise. The day of menstrual cycle was

derived by subtracting the date of the first day of the next menstruation after the SAPALDIA examination, as reported prospectively by the menstruation card, from the date of examination. Thus, a value of 0 indicates that the next menstruation was just starting on the examination day. If the examination took place during menstruation, the first day of the current menstruation was taken, providing values between 0 and 7 days.

Outcome variable

Nonspecific bronchial responsiveness was assessed by bronchial challenge with methacholine chloride in participants able to produce satisfactory spirometry and fulfilling health criteria. Participants were excluded if they had had a myocardial infarction in the last 12 months, were taking medication for heart disease, had epilepsy, were pregnant, were lactating, and/or were receiving treatment with any β -blockers including eye drops.

Methacholine (Provocholine; Methapharm Inc, Brantford, Ontario, Canada) was administered by MEFAR aerosol dosimeters (Anandic Medical Systems, Diessenhofen, Switzerland) starting with inhalation of physiological sodium chloride followed by increasing concentrations of methacholine up to a cumulative dose of 2 mg. The dosimeter was triggered automatically at the beginning of the inhalation, and the subjects were instructed to hold their breath at full inspiration for 4 seconds. Between 1 and 2 minutes after the end of each inhalation, 2 FEV₁ maneuvers were performed, and the maneuver with the highest FEV₁ was recorded. Women were defined as having BHR if the methacholine challenge test resulted in a fall of $\geq 20\%$ of FEV₁ up to a cumulative dose of at most 2 mg (8.37 μmol). Furthermore, the methacholine responsiveness was determined for each subject by calculating an individual dose-response slope similar to the one proposed by O'Connor et al.²⁹ This slope was defined as the ratio between the percentage decline in FEV₁ from its maximal value measured during the test and the total cumulative dose of methacholine administered. An increase in slope corresponds to an increase in bronchial reactivity.³⁰ Because the distribution of the slopes was skewed, data were log-transformed to obtain a more symmetrical distribution. Before transformation a small constant was added (+0.01) to prevent 0 values.

Statistical methods

Women with and without methacholine challenge test and nonresponders and responders to the menstruation diary cards were compared by basic descriptive statistics (ANOVA for qualitative data and χ^2 for quantitative data). Multivariable analyses involved logistic and linear regression models that were derived in a backward selection process involving likelihood ratio tests (significance level, 0.2) and starting from the following initial set of variables: age, age², smoking status, body mass index (BMI), physical activity, baseline FEV₁, FEV₁², asthma status, atopy, C-reactive protein (CRP), respiratory infection before examination, respiratory medication within last 24 hours before examination, irregular menstruation, number of pregnancies, and age at menarche. Having imputed 20 missing data points on age of menarche, we also introduced a dummy variable to adjust for potential confounding by the imputation. Study center was introduced as a random effect in both linear and logistic regression models. The final regression model included age, smoking status, BMI, baseline FEV₁, reported asthma status, age at menarche, and study center. Regularity of menstruation has been described as effect modifier in other studies. Therefore, albeit regularity of menstruation did not result in an improvement of the model, we ran a sensitivity analysis excluding women with irregular menstruation and cycle lengths >32 or <24 days.

The logistic regression model was used to assess association between the binary outcome "hyperreactivity" and the binary exposure variable. Accordingly, results were expressed as odds ratios (ORs). Potential interactions between the binary exposure variable and asthma, age, BMI, smoking status, and age at menarche were tested by likelihood ratio tests (significance level, 0.2), and stratified analyses were run if there was evidence of an interaction. Linear regression models were used for the continuous outcome "logarithmized slope." Results of these analyses were expressed as geometric mean ratios. To describe potential periodical patterns, we introduced a cycle parameter "u" defined as the proportion of time of the menstrual cycle having

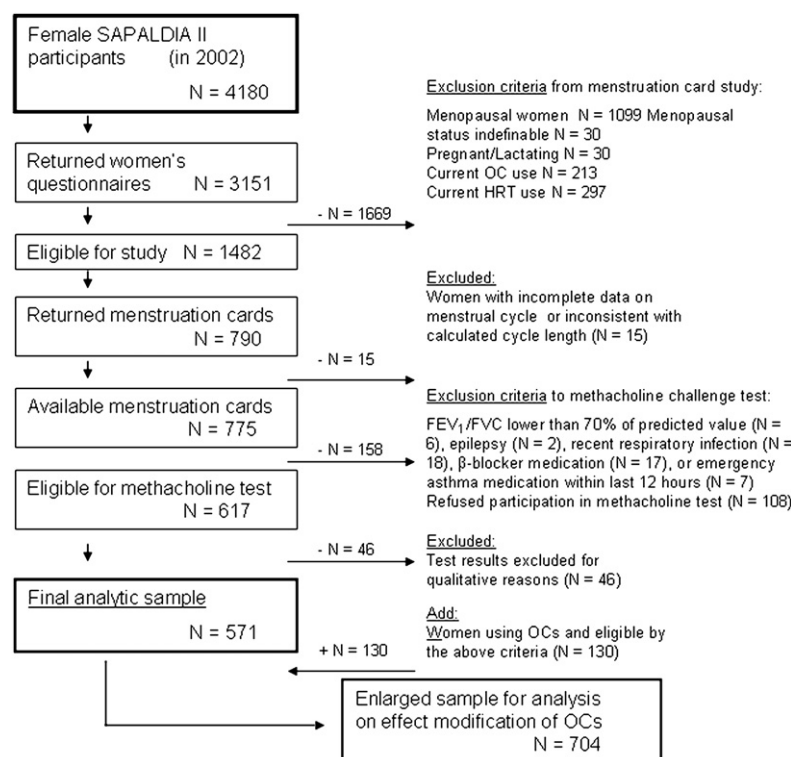


FIG 1. Study sample: flow chart. FVC, Forced vital capacity; HRT, hormone replacement therapy.

elapsed, on the day of examination, since the beginning of the last menstruation (eg, if a woman was examined 21 days after the start of the last menstruation and her menstrual cycle lasted 28 days, the cycle parameter u was set to 0.75). We then used trigonometric polynomials of order up to 3 to test for the presence of such patterns. These involved the functions $\sin(k\pi u)$, $\cos(k\pi u)$ with $k = 2, 4$, and 6 . For the graphical representation of such patterns, we used periodical linear splines with knots at $u = 0, 0.2, 0.4, 0.6, 0.8$, and 1 . To satisfy the periodicity condition, these splines were forced to take on the same value at 0 and 1 .

Further, a sensitivity analysis was run to investigate a potential modification by exogenous hormones. For this analysis, women currently using OCs and complying with the defined eligibility and exclusion criteria ($N = 130$) were re-included in the sample. We used the same logistic regression model as in the main analysis, additionally adjusted for OC use. Interaction was tested by likelihood ratio test, and stratified analyses were conducted.

Ethical review board

The SAPALDIA 2 study was approved by the local ethical commissions of each study center.

RESULTS

The main study sample consisted of 571 premenopausal women age 28 to 58 years (Table I). The only significant differences between women who sent back the menstruation card and those who did not were the regularity of menstruation and age. Two thirds of the women who had not returned the menstruation card had not reported on the regularity of menstruation in the reproductive questionnaire (67% nonresponders vs 7% responders), and among those with the respective data, irregular menstruation was 2 times more frequent in women not sending back the card (41% nonresponders vs 22% responders). Responders were

significantly younger by a median 3 years. Other differences (eg, prevalence of hyperreactivity, BMI, or education) were non-significant after adjusting for age. The women in our sample had significantly higher FEV₁ values and significantly less often had asthma than women who did not participate in the BHR testing, which can be explained by the exclusion criteria of the methacholine challenge test.

The days of examination were fairly equally distributed across the women's menstrual cycle (Fig 2). Twenty-five percent ($n = 143$) had undergone the methacholine challenge test within the defined window of risk. Seventy-five women were diagnosed as hyperreactive in the methacholine challenge test, of whom 24 had asthma (53% of the subjects with asthma) and 51 of whom did not (10% of all subjects without asthma). Altogether, 45 women reported having asthma (8%). Of these, 80% said that this was diagnosed by a doctor. Two women with asthma (5%) reported experiencing increasing asthma symptoms the week before menses.

In the main analysis, logistic regression yielded a positive association between the window of risk and hyperreactivity (OR, 2.3; 95% CI, 1.27-4.29; Table II). Stratification by asthma status provided evidence of a more pronounced association between BHR and menstrual cycle day in women with asthma. The effect estimates were very high but unstable because of the small number of nonhyperreactive subjects with asthma examined in the window of risk (adjusted OR, 65.5; 95% CI, 2.1-2028; raw OR, 8.24; 95% CI, 0.87-389.2). In a further limited sample of doctor-diagnosed subjects with asthma ($N = 36$), the observed associations went in the same direction (results not shown). In women with neither a history of asthma nor current asthma, there was a consistently positive association that was, however, no longer

TABLE I. Characteristics of study sample, overall and by BHR status

	BHR		Total (N = 571)	P value*
	No (N = 496)	Yes (N = 75)		
Age (y), mean (SD)	42 (6.13)	42 (6.28)	42 (6.15)	.717
Civil status (%)				
Married	65	63	65	.907
Divorced/separated	11	9	10	
Widowed	2	3	2	
Single	23	25	23	.907
Educational status (%)†				
Low	18	13	17	
Medium	63	64	63	
High	20	23	20	.584
Smoking status (%)				
Never	47	41	46	
Former	27	23	26	
Current	26	36	27	.195
Physical activity (%)‡				
Low	35	35	35	
Medium	41	40	41	
High	24	25	24	.978
BMI, mean (SD)	23.7 (4.36)	23.5 (3.66)	23.6 (4.28)	.753
Respiratory health				
FEV ₁ (L), mean (SD)	3.1 (0.46)	2.9 (0.42)	3.08 (0.46)	.001
Asthmatic (reported) (%)	4	32	8	<.001
Recent respiratory infection# (%)	15	15	15	.878
Atopy (%)§	32	50	34	.002
CRP (%)	1.4 (2.88)	1.1 (1.19)	1.4 (2.72)	.368
Reproductive characteristics				
Age of menarche, mean years (SD)	13.4 (1.58)	13.8 (1.56)	13.5 (1.58)	.043
No. of pregnancies, mean (SD)	2.3 (0.87)	2.2 (0.78)	2.3 (0.87)	.476
Menstrual cycle regularity (%)				
Regular	78	84	79	
Never regular	9	6	9	
Lately irregular	12	10	12	.472

* χ^2 Test for categorical data, ANOVA for quantitative data.

†Defined as highest degree of education achieved (low, mandatory schooling; medium, secondary education; high, tertiary education).

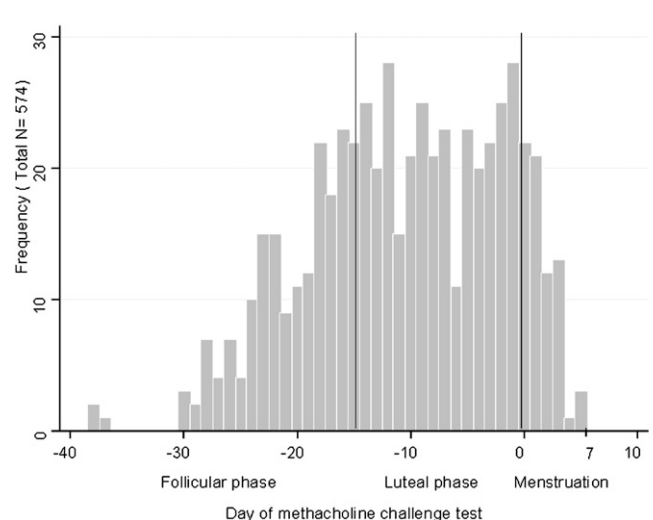
‡Based on frequency of physical activities per week causing sweating or breathlessness.

§Atopy defined as Phadiatop positivity (Kabi Pharmacia).

#Infection within the last 3 weeks before examination.

significant ($P = .072$). Linear regression analysis was consistent with the results found in logistic regression. The cyclicity of the association across the menstrual cycle can be seen in Fig 3. This pattern suggests that besides the perimenstrual increase, there is another slightly weaker increase in hyperreactivity in the periovulatory phase. There was no evidence of a modification of the observed cyclic patterns by age, BMI, age at menarche, regularity of menstruation, or age.

In a second step, we examined the potential modification by exogenous sex hormones (Table III). For this, the main sample was enlarged by 130 women taking OCs currently and otherwise eligible for analysis. The logistic analysis in the enlarged sample resulted in a reduction of the effect estimate; however, the association between the window of risk and hyperreactivity remained significant. There was evidence for interaction between the

**FIG 2.** Distribution of day of methacholine challenge in relation to first day of menstruation: menstrual cycle day on day of methacholine challenge test; 0 corresponds to the first day of menstruation.

window of risk and OC use ($P = .05$). The stratified analysis yielded an OR below 1 for women taking OCs; however, most probably because of power, this association is not statistically significant (OR, 0.054; 95% CI, 0.140-2.083).

DISCUSSION

We investigated the hypothesis of a hormonal influence on airway reactivity in a population-based cohort, including subjects with asthma as well as subjects without asthma. Our analysis yields a significant association between the day of menstrual cycle and BHR in premenopausal women. This cyclicity remained significant in subjects with asthma after stratification, and in subjects without asthma, the results were suggestive of a positive association indicating a biological mechanism not primarily related to the disease status.

The inclusion of women taking OCs in the sample provided evidence of an attenuation of the effect.

Most studies on PMA have examined symptom increase in outpatients with asthma.^{7,9,31} In these populations, the prevalence of PMA has been reported to be between 6% and 36% if self-reported^{7,31} and 23% to 40% if based on symptom scores.^{7,12,13,32} The prevalence of self-reported premenstrual increase of symptoms in female subjects with asthma in this study sample is 5%. It has been reported that women are not necessarily aware of PMA before they are directly approached on this issue or filling out symptom scores and diaries.³³ This might explain the relatively low rate in our study. Furthermore, women with severe asthma are treated more frequently in outpatient clinic settings and present with PMA more often.^{6,33} They may also be more sensitive to changes in their daily symptoms across the cycle, introducing recall and selection bias. Women with severe asthma were excluded from the methacholine testing in SAPALDIA; thus, the obtained results may be an underestimation of the prevalence of premenstrual symptoms as well as of the association between menstrual cycle and BHR. In fact, because of the exclusion criteria, the analytic sample included only 45 subjects with

TABLE II. Association between time of menstrual cycle (window of risk*) and BHR: results of logistic and linear regression models†

	Binary outcome: BHR		
	Exact OR	95% CI	P value‡
Unadjusted OR			
All (N = 571)	1.60	0.907 2.770	.086
Stratified by asthma status			
Without asthma (N = 526)	1.669	0.850 3.183	.128
With asthma (N = 45)	8.235	0.874 389.24	.051
	Adjusted OR	95% CI	P value‡
Logistic regression model‡:			
binary exposure:			
methacholine test			
within			
window of risk*			
Nonexposed (N = 428;	1		
hyperreactive, N = 50)			
Exposed (N = 143;	2.34	1.270 4.292	.060
hyperreactive, N = 25)			
Stratified by asthma status‡:			
Without asthma, exposed§	1.853	0.945 3.632	.072
(N = 135;			
hyperreactive,			
N = 18)			
With asthma, exposed#	65.48	2.1142028.27	.017
(N = 8; hyperreactive,			
N = 7)			
	Continuous outcome: log slope of airway reactivity		
	Geometric mean ratio	95% CI	P value‡
Linear regression model*:			
binary exposure:			
methacholine test			
within			
window of risk†			
Nonexposed (N = 428;	1		
hyperreactive, N = 50)			
Exposed (N = 143;	1.146	0.950 1.392	.169
hyperreactive, N = 25)			

‡ χ^2 for significance.*Adjusted for age, BMI, smoking status, asthma status, baseline FEV₁, age at menarche, and study center as random effect.

†-3 to +3 days of first day of menstruation.

‡Adjusted for age, BMI, smoking status, baseline FEV₁, age at menarche, and study center (random effect).

§Excluding participants reporting ever having asthma and doctor-diagnosed asthma.

#Participants reporting ever having asthma and doctor-diagnosed asthma.

asthma, of whom all presented a mild level of asthma status. Non-diagnosed asthma may have introduced misclassification, possibly resulting in an overestimation of the association for women without asthma. To reduce this potential bias, we defined asthma status on the basis of reported asthma history instead of current asthma symptoms. The participation rate was relatively low, although it was mainly reduced by a low participation of women with irregular menstruation. Furthermore, the questionnaire was self-administered, increasing the nonparticipation. Nevertheless, to our knowledge, this is the largest study sample used to date to investigate cyclic variation of airway responsiveness to date. Further strengths of the study are (1) the prospective assessment of beginning of menstruation, (2) the availability of standardized

lung function measurements, (3) additional objective data on atopic status and CRP, and (4) detailed data on general health and reproductive characteristics.

Our analysis supports evidence of a menstrual cyclicity of bronchial reactivity. It yielded a significantly higher chance of BHR shortly before and after the first day of menstruation (OR, 2.3). This result is consistent with earlier studies on perimenstrual hyperreactivity by Tan et al,^{10,34} but contrary to the studies by Pauli et al,⁸ Juniper et al,⁷ and Shames et al.⁹ These studies were of small sample size and inconsistent in the timing of the methacholine challenge test within the cycle. In subjects with asthma, the OR was very large already in the raw data. All but 1 participant with asthma examined within the window of risk were hyperreactive. We assume that a larger asthmatic sample would provide a weaker but still significantly positive association. After exclusion of subjects with asthma, the impact of the time of the menstrual cycle was no longer significant but still suggestive of a positive association. Hence, our results suggest a biological mechanism not primarily related to disease status but strongly amplified by the presence of asthma.

To describe the form of the cyclic association between BHR and day within the menstrual cycle, we used a periodical linear spline model. The resulting polygonal line suggested the presence of an additional increase in the periovulatory phase. A periovulatory increase in asthma symptoms has been described by Zimmerman et al,¹⁶ who recorded a higher frequency of emergency department visits in the periovulatory phase.

There have been conflicting publications on the role of OCs in PMA, with some authors describing the absence of PMA with OC use^{6,35} and others finding no difference in the prevalence of PMA with respect to OC use.^{6,13,22} Including women taking OCs into the study sample resulted in a reduction of the effect estimate. There is evidence of interaction between cycle day and OC use, and the stratified analysis resulted in an OR of BHR below 1 and thus in the protective direction. Stratified analyses were limited in power, however. To our knowledge, our analysis is the first in a population-based cohort with objective data on airway function providing evidence of an attenuation of the cyclic association by OCs. Most publications describing a protective effect are intervention studies or case reports.^{19,30,36} The effect of OCs on respiratory symptoms has been associated with asthma severity or asthma status,^{21,23,37} a hypothesis that we could not investigate in our sample because of the relatively small number of subjects with asthma and similar severity.

The definition of the window of risk was based on clinical reports of PMA and the known major changes of sex hormone levels during the female menstruation cycle. Most authors have hypothesized that the steep decrease in progesterone and estradiol levels at the end of the luteal phase might be responsible for PMA. Progesterone, reaching about 50% of its maximum level 2 to 3 days before the first day of menstruation, is mainly held responsible for the initiation of menstruation and the inflammatory processes involved.³⁸ Methacholine acts through direct stimulation of the bronchial smooth muscles inducing contraction,³⁹ and progesterone has been demonstrated to reduce bronchial smooth muscle contractility.⁴⁰ The observed increase in hyperreactivity may also be related to an increase in cellular inflammation during the luteal phase, reaching a maximum shortly before and during menstruation.^{41,42} Luteal peaks of exhaled nitric oxide and higher sputum eosinophil counts provide additional evidence for a hormonal role on airway inflammation.⁴³⁻⁴⁵ However, which

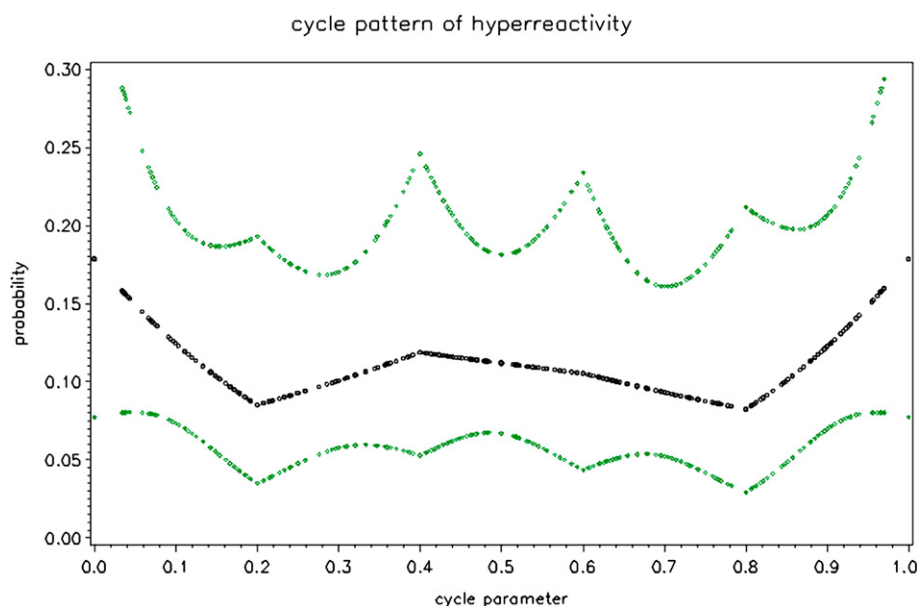


FIG 3. Cyclic pattern of hyperreactivity across the menstrual cycle in women with regular cycles of >24 or <32 days (N = 366). Adjusted for age, BMI, smoking status, asthma, baseline FEV₁, age at menarche, and study center (random effect); 0 and 1 correspond to the first day of menstruation, 0.5 to midcycle. *Green dotted lines, CI; black dotted line, estimated probability of hyperreactivity.*

TABLE III. Modification of cyclic pattern of BHR by OC use*

Logistic regression	Binary outcome: BHR			
Binary exposure: methacholine test within window of risk†	OR	95% CI	P value	
Unadjusted exact OR*	1.36	0.818	2.230	.210
Model*‡				
Unexposed (N = 530; hyperreactive, N = 69)		1		
Exposed (N = 171; hyperreactive, N = 29)	1.68	0.988	2.85	.055
Model‡ + adjustment for OC use	1.71	1.003	2.904	.049
Model*‡ + interaction term§	1.90	1.223	4.090	.009
Model*‡ stratified by OC use				
Strata: no OC use (exposed, N = 143; hyperreactive, N = 25)	2.33	1.270	4.292	.006
Strata: OC use (exposed, N = 28, hyperreactive, N = 4)	0.54	0.140	2.083	.371

*Sample including 571 women currently not taking OCs and 130 women taking OCs (N = 701: exposed, N = 530; unexposed, N = 171).

†-3 to +3 days of first day of menstruation.

‡Adjusted for smoking status, BMI, age, age at menarche, FEV₁, and asthma status.

§Interaction term for OC use and exposure variable P = .05.

hormone constellation or pathophysiological mechanisms lead to PMA remains unclear.

Individual reaction of women during the late luteal phase to methacholine and the cycle to cycle variability found by other authors^{12,28} suggests that next to sex hormones, additional factors must play a role, either further sensitizing the airways or modifying the hormonal effects. We tested various factors that might represent such a higher sensitization, such as atopy, CRP, or recent respiratory infection, without evidence for any modification of the result. Age showed a negative association to hyperreactivity of borderline significance. Other studies report

patients with PMA to be older than subjects with asthma without PMA.^{9,33} Older women might have been underrepresented because of the higher nonparticipation rate. Furthermore, we investigated additional reproductive characteristics as covariates and potential modifying factors. Cycle irregularity has been proposed to increase the risk of PMA.⁶ This was not the case in our study sample. Neither adjusting for nor excluding women with irregular cycles resulted in a noteworthy change of association, but we probably had an underrepresentation of women with cycle irregularity in the analytic sample. Therefore, our results should not be generalized to women with irregular menses. Given previous literature on irregularity, we may assume that the underrepresentation of women with irregular menstruation either did not bias the result or resulted in an underestimation of the effect. In our analysis, age at menarche is a highly significant covariate, without evidence of interaction. The model supports, if any, an unexpected direction of association, with later menarche associated with a higher risk of hyperreactivity. Early age at menarche and related metabolic states, such as obesity, have so far been associated with a greater severity of asthma⁴⁶ and with lower FEV₁.^{17,47}

Our data provide evidence of a systematic variation of BHR during the menstruation cycle with an increase in the perimenstrual period. The menstrual cyclicity of airway reactivity was found in women with as well as without asthma, suggesting a biological mechanism not primarily related to asthma. The risk of responsiveness was considerably lower in women using OCs. Menstrual cyclicity may be of clinical importance in view of future diagnosis and treatment recommendations. In screening and diagnostic testing, the day of menstrual cycle might have to be considered to reduce misdiagnosis. In view of treatment, assessing a perimenstrual increase in hyperreactivity could lead to cyclic adaptation of medication prescriptions.

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Clinical implications: Menstrual cyclicality of BHR may be of importance for future screening and diagnostic testing recommendations. In women with menstrual cyclicality, an adaptation of medication prescriptions might prove useful.

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