

ORIGINAL ARTICLE

Asthma and Rhinitis

Determinants of low risk of asthma exacerbation during pregnancy

Z. Ali¹  | L. Nilas^{2,3} | C. S. Ulrik^{1,3}

¹Department of Pulmonary Medicine, Hvidovre Hospital, Hvidovre, Denmark

²Department of Gynaecology and Obstetrics, Hvidovre Hospital, Hvidovre, Denmark

³Institute of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

Correspondence

Zarqa Ali, Department of Pulmonary Medicine 253, Hvidovre Hospital, DK-2650 Hvidovre, Denmark.
Email: zarqa_ali@hotmail.com

Funding information

The Danish Lung Association; Amager and Hvidovre Hospital Research Foundation; Glaxo Smith Kline (GSK); Grosserer L.F. Foght's Foundation; Torben and Alice Frimodt's Foundation; The Unit of Science Research and Innovation; Global Excellence in Health

Summary

Background: Assessment of asthma control every 4–6 weeks during pregnancy is recommended to reduce risk of exacerbation, and by that improve outcome.

Objective: To identify determinants of pregnancies with low risk of asthma exacerbation.

Methods: All pregnant women enrolled into the Management of Asthma during Pregnancy (MAP) programme at Hvidovre Hospital since 2007. Assessment of asthma control, adjustment of treatment, spirometry and measurement of exhaled nitric oxide (F_{ENO}) were performed, and baseline characteristics and exacerbation history were collected at enrolment. Determinants of low-exacerbation risk pregnancies were identified by logistic regression analysis (stepwise backward elimination).

Results: In 1283 pregnancies, 107 exacerbations were observed. Multiple regression analysis revealed that no history of pre-pregnancy exacerbations ($P < .001$), no prescribed controller medication ($P < .001$), and clinically stable asthma at enrolment ($P = .002$) were significantly associated with low risk of exacerbation during pregnancy; with these combined characteristics, only two of 385 pregnancies were complicated by an exacerbation (OR 0.04, 95% CI 0.01–0.18, $P < .001$).

Conclusion and clinical relevance: Clinically stable asthma at enrolment, together with no history of previous exacerbations and no prescribed controller medication, is a determinant of low risk of an asthma exacerbation during pregnancy, which may guide clinicians in individualizing surveillance of asthma during pregnancy.

KEYWORDS

asthma, eosinophils, prevention

1 | INTRODUCTION

Asthma is a common chronic condition and affects up to 15% of pregnant women.^{1,2} Previous studies have shown that one-third of women with asthma report an improvement, one-third no change, and one-third worsening of their asthma during pregnancy.³ Exacerbations of asthma during pregnancy have been linked to increased risk of adverse pregnancy and perinatal outcomes, including pre-eclampsia, preterm delivery, low birth weight, and small for gestational age infants.^{4–6} Regular follow-up visits every 4–6 weeks, including assessment of lung function, have been

recommended for all pregnant women with asthma⁷ to reduce the risk of exacerbations and thereby the risk of pregnancy and perinatal complications for both mother and child.^{5,8} However, a substantial proportion of pregnant women with asthma does not experience exacerbations and may therefore not benefit from close follow-up.

It would, therefore, be helpful to have a tool to identify pregnancies with low risk of asthma exacerbation during pregnancy to assist clinicians in personalizing the intensity of asthma monitoring. However, our current knowledge of factors associated with low risk of asthma exacerbation is very limited.^{9,10}

The aim of this study was to identify determinants of pregnancies with low risk of asthma exacerbation during pregnancy, and by that identify pregnancies where the intensity of asthma monitoring during pregnancy may be reduced without having negative impact on pregnancy outcome.

2 | MATERIALS AND METHODS

2.1 | Material

The Management of Asthma during Pregnancy (MAP) programme was initiated in 2007, and participants for this study were consecutively recruited through the Department of Obstetrics and Gynaecology, Hvidovre Hospital, Denmark. The MAP study has been described in detail previously.¹¹⁻¹⁴

Inclusion criteria were as follows:

1. A diagnosis of asthma defined according to the GINA guidelines¹
2. Current treatment with at least rescue bronchodilator (GINA Step 1 therapy)
3. The first visit to the outpatient clinic at the Department of Pulmonary Medicine within the first 18 weeks of pregnancy.

The MAP programme includes scheduled follow-up visits every fourth week during pregnancy. At the first visit, baseline data, incl. case history, addressing the number and severity of any previous asthma exacerbations, tobacco exposure, and prescribed asthma medication was obtained. The importance of adherence with controller medication was addressed, and inhaler device technique checked. Lung function, that is spirometry, and fractional exhaled nitric oxide ($F_{E}NO$) were measured.

2.2 | Ethics statement

The study was performed in accordance with the Helsinki II declaration and the Danish legislation. The study was approved by the Research Ethics Committee of the Capital Region of Denmark (H-D-2007-0051) and the Danish Data Protection Agency (2007-41-0770).

2.3 | Definitions and methods

2.3.1 | Definitions

Asthma control was assessed based on daytime asthma symptoms, night-time awakenings due to asthma, use of rescue medication, and asthma-related activity limitation. Well-controlled, partly controlled and uncontrolled asthma was defined according to GINA.¹ Patients were classified as having clinically stable asthma provided they fulfilled the criteria for having well-controlled asthma together with normal lung function ($FEV_1 > 80\%$ predicted) and $F_{E}NO < 25$ p.p.b.

Smoking status was classified as current (minimum one cigarette per day), ex (stopped before or when the current pregnancy was confirmed) or lifelong non-smokers. Lifetime tobacco exposure was

estimated as pack-years: (number of cigarettes per day/20 × duration of smoking [years]). Environmental tobacco smoke (ETS) was defined as living with someone smoking at home (as smoking in workplaces, restaurants etc. is not allowed in Denmark).

Allergy is based on symptoms together with a positive skin prick test and/or allergen-specific immunoglobulin E.

2.3.2 | Spirometry

Spirometry was performed with the Vitalograph Pneumotrac spirometer and a computerized system (Spirotrac IV; Vitalograph, Buckingham, UK). The forced expiratory volume in the first second (FEV_1) from a maximum inspiration and forced vital capacity (FVC) were measured according to American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines.¹⁵ Due to the young age of the women, airflow limitation was defined as FEV_1/FVC below lower limit of normal (LLN) according to ATS/ERS pulmonary function interpretation guidelines.¹⁶

2.3.3 | Exhaled nitric oxide

Fractional exhaled nitric oxide ($F_{E}NO$) was measured with Ecomedics CLD 88sp analyzer and DENOX 88 at a controlled flow rate of 50 mL/s according to ATS guidelines.¹⁷ The mean value of two measurements in parts per billion (p.p.b.) was recorded.

2.3.4 | Outcome measures

Asthma exacerbations after enrolment into the MAP programme were defined as exacerbations requiring unscheduled doctor visit, hospital admission, treatment at the emergency department or/and a rescue course of systemic corticosteroids according to the official American Thoracic Society/European Respiratory Society guidelines.¹⁷

2.3.5 | Statistical analysis

Baseline data (collected at the first visit) were compared in pregnancies with and without asthma exacerbations by the Chi-square test using SAS Enterprise Guide 7.1. Results are presented in a forest plot with odds ratios (OR) and 95% confidence intervals (CI).

A multiple logistic regression with backward elimination was carried out, using the Proc Logistic procedure in SAS, with the following potential determinants for low risk of exacerbation during pregnancy: age (continuous variable), BMI < 25, clinically stable asthma, no history of pre-pregnancy exacerbations, no ETS, never-smokers, no prescribed controller medication, $FEV_1 \geq 80\%$ of predicted, $FEV_1/FVC \geq LLN$, and $F_{E}NO < 25$. The significant determinants from the multiple logistic regression were used to identify pregnancies with low risk of asthma exacerbation during pregnancy. The sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) were calculated as a measure of the diagnostic performance of the identified determinants. Furthermore, a receiver operating characteristic (ROC) curve of the combined significant

determinants was performed in SPSS software version 22 (SPSS Inc. Chicago, IL, USA), and the area under the curve (AUC) was calculated.

In all the statistical analyses, a two-tailed *P*-value of ≤ 0.05 was considered significant.

3 | RESULTS

Over the 9-year study period, 1283 pregnancies in 1208 women were eligible for the present analysis; baseline characteristics are given in Table 1. A total of 107 exacerbations were observed, and eight pregnancies (0.6%) were complicated by more than one exacerbation.

Only 5% (*n* = 40) of the pregnancies in women classified as having clinically stable asthma at the first visit were complicated by an asthma exacerbation during pregnancy, while the remaining 95% (*n* = 839) did not (*P* < .001). Among women with no history of pre-pregnancy exacerbations, 4% (*n* = 37) had an asthma exacerbation during pregnancy (*P* < .001). Furthermore, $F_{E}NO < 25$ p.p.b. was significantly associated with low risk of an asthma exacerbation (OR 0.51, 95% CI 0.33-0.79, *P* = .001) (Figure 1).

The multiple logistic regression analysis revealed that no history of pre-pregnancy exacerbations, no prescribed controller medication, and clinically stable asthma at the first visit were independent determinants of pregnancies with a low risk of an asthma exacerbation (Table 2). The sensitivity of the three significant determinants (pre-pregnancy exacerbations, prescribed controller medication, and clinically stable asthma) to identify pregnancies with risk of an asthma exacerbation during pregnancy was 98%, and the negative predictive value (NPV) was 99% (Table 3). Only two of 385 pregnancies characterized by these determinants were complicated by an asthma exacerbation (OR 0.04, 95% CI 0.01-0.18, *P* < 0.001). The ROC curve (AUC = 0.77, 95% CI 0.72-0.81) for the diagnostic performance of the three determinants combined to identify pregnancies with low risk of an asthma exacerbation during pregnancy is presented in Figure 2.

Furthermore, risk factors for exacerbation of asthma during pregnancy were $FEV_1 < 80\%$ predicted, $FEV_1/FVC < LLN$, $F_{E}NO > 25$ p.p.b., moderate/severe asthma, uncontrolled asthma, and previous exacerbations.

The results remained unchanged after exclusion of twin pregnancies and exclusion of all women contributing with more than one pregnancy to the data set.

4 | DISCUSSION

In the present study of a large sample of pregnant women with asthma, we found that women who presented with clinically stable asthma at the first visit, no history of pre-pregnancy exacerbations, and not being prescribed controller medication have a low risk of an asthma exacerbation during pregnancy.

TABLE 1 Baseline characteristics, obtained at the first visit to the pulmonary outpatient clinic, of 1283 pregnancies in women with asthma enrolled in the Management of Asthma during Pregnancy (MAP) programme

Characteristics	Pregnancies (1283)
Age (year)	31 ± 5 (17-44)
Allergy	411 (32)
Body mass index (BMI)	
BMI (kg/m ²)	26 ± 5 (16-65)
BMI < 25	646 (50)
Pregnancy	
Singleton	1247 (97)
Gemelli	36 (3)
Treatment	
Controller medication at the time of inclusion	521 (41)
Controller medication prescribed at the first visit	811 (63)
Pre-pregnancy history of exacerbations	379 (30)
Clinically stable asthma	879 (69)
Smoking status	
Environmental tobacco exposure	163 (13)
Never-smokers	946 (74)
Ex-smokers	279 (22)
Pack-years	7 ± 5
Current smokers	57 (4)
Pack-years	12 ± 7
Spirometry	
FEV_1 (L)	3.0 ± 0.5
FEV_1 % predicted	93.2 ± 12.9
$FEV_1 > 80\%$ predicted	1085 (85)
FEV_1/FVC ratio (%)	80.9 ± 6.9
$FEV_1/FVC > LLN^a$	1135 (88)
Fractional exhaled nitric oxide ($F_{E}NO$)	
$F_{E}NO$ (p.p.b.)	20 ± 17
$F_{E}NO$ (p.p.b.) < 25 p.p.b.	990 (77)

Data are given as mean ± SD with range in brackets or numbers with percentages in brackets.

Clinically stable asthma = having well-controlled asthma (according to GINA guidelines) together with normal spirometry and $F_{E}NO < 25$ p.p.b. at the time of enrolment.

^aLower limit of normal.

According to the current recommendations, regular monitoring of asthma every four to 6 weeks during pregnancy is recommended for all pregnant women with asthma,^{1,7} as the general paradigm is that the course of asthma during pregnancy is largely unpredictable.^{7,18,19} Despite these recommendations, this is not clinical practice in many, probably most, countries due to lack of resources to closely monitor all pregnant women with asthma. Furthermore, evidence is lacking that implementing this regimen improve pregnancy outcome nor is beneficial for all pregnant women with asthma. Identification of clinical

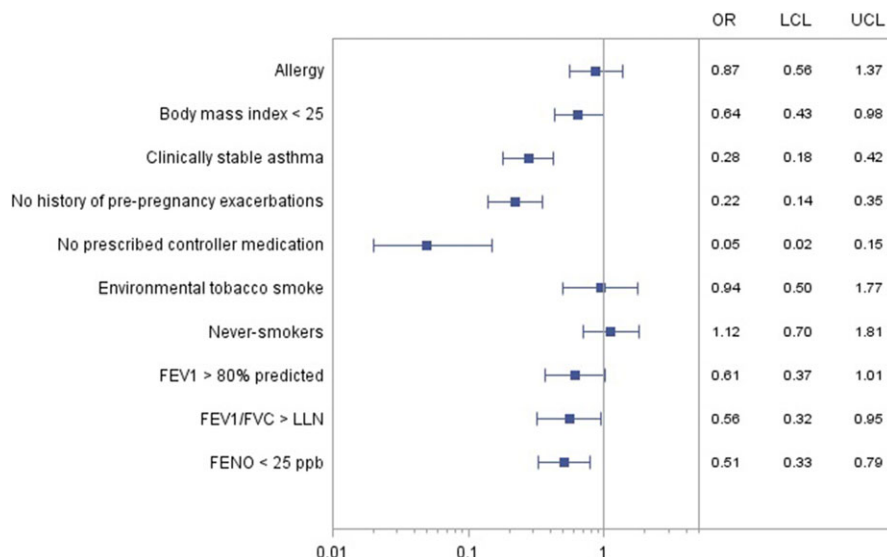


FIGURE 1 Determinants of low risk of asthma exacerbation during pregnancy (univariate analysis) in 1283 pregnancies among women enrolled in the Management of Asthma during Pregnancy (MAP) programme. The association is reported as odds ratio (OR) with upper (UCL) and lower (LCL) 95% confidence limits. Clinically stable asthma is defined as having well-controlled asthma (according to GINA guidelines) together with normal spirometry and FENO < 25 p.p.b. at the time of enrolment. LLN, lower limit of normal

TABLE 2 Determinants of pregnancies with low risk of an exacerbation among 1283 pregnancies in women enrolled in the Management of Asthma during Pregnancy (MAP) programme

	OR	95% CI	P-value
No prescribed controller medication	0.09	0.03-0.29	<.001
No history of pre-pregnancy exacerbations	0.37	0.24-0.58	<.001
Clinically stable asthma	0.51	0.33-0.79	=.002

Multiple logistic regression analysis with backward elimination: results are given as odds ratio (OR) with 95% confidence interval (CI) and P-value.

Clinically stable asthma defined as having well-controlled asthma (according to GINA guidelines) together with normal spirometry and FENO < 25 p.p.b. at the time of enrolment.

TABLE 3 The validity of the combined significant determinants (no pre-pregnancy history of exacerbations, no prescribed controller medication, and clinically stable asthma) to identify pregnancies with asthma exacerbation during pregnancy

	Exacerbation(s)	No exacerbation	
Test positive	97	801	PPV = 11%
Test negative	2	383	NPV = 99%
Sensitivity = 98%		Specificity = 32%	

Test positive = history of pre-pregnancy exacerbations, prescribed controller medication, and clinically unstable asthma.

Test negative = no history of pre-pregnancy exacerbations, no prescribed controller medication, and clinically stable asthma.

PPV=positive predictive value, NPV = negative predictive value.

Clinically stable asthma = having well-controlled asthma (according to GINA guidelines) together with normal spirometry and FENO < 25 p.p.b. at the time of enrolment.

characteristics associated with low risk of an asthma exacerbation during pregnancy could allow subgroups of women to be allocated to less intense follow-up, possibly by their general practitioner (GP) due to lack of resources. This is the first study providing GPs with tools to

pinpoint women with low risk of exacerbation during pregnancy, and by that allocate the limited resources to women with higher risk. Besides making resource allocation more reasonable, such an approach could reduce unnecessary anxiety that is associated with an intense follow-up in the majority of pregnant women with asthma.

Among those with all three identified determinants (no history of pre-pregnancy exacerbations, no prescribed controller medication, and clinically stable asthma), the probability of being exacerbation-free during pregnancy was 99% (NPV). The three determinants performed well with regard to correctly designate pregnancies as positive if they experienced an exacerbation (sensitivity 98%). A high sensitivity comes along with a low false negative rate, and it is often stated, that a test with high sensitivity has potential value in screening, as cases with disease rarely are missed.²⁰ On the other hand, the three determinants are not very specific and a high proportion of women who never will experience any asthma exacerbation during pregnancy would still be allocated to intense follow-up.

Some women with asthma stop or reduce their use of asthma controller medication in early pregnancy,²¹ often without consulting their doctor,²² and reduced adherence with controller medication during pregnancy is associated with increased risk of asthma-related emergency department visits.²³ The reason for abstaining controller medication is very likely to be fear of harmful effects of the drugs on the foetus.²⁴ Non-adherence to controller medication is, in general, a major risk factor for asthma exacerbations,²⁵ and the risk of having an exacerbation is reduced by more than 75% among women who are using controller medication regularly.²⁶ Asthma exacerbations during the first trimester of pregnancy increase the risk of congenital malformations.^{27,28} In our cohort, around 20% of the pregnant women not using controller medication at inclusion were prescribed such medication at the first visit. Optimizing medication, discussing the importance of adherence to treatment and a thorough asthma assessment with spirometry and F_eNO as early in pregnancy as possible is important to correctly identify women at low risk of an exacerbation. This would allow for an allocation of resources on

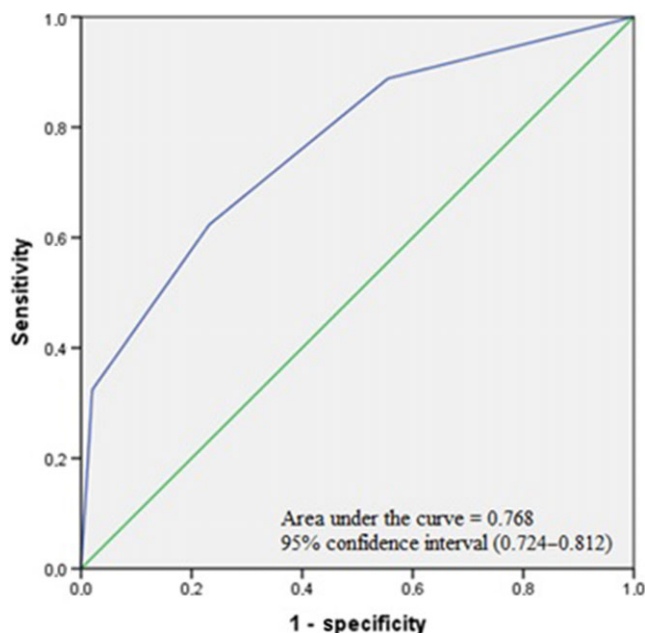


FIGURE 2 The receiver operating characteristic (ROC) curve illustrating the power of the three significant determinants, that is no history of pre-pregnancy exacerbations, no prescribed controller medication, and clinically stable asthma at the first visit, to identify pregnancies with low risk of an exacerbation among 1283 pregnancies in women enrolled in the Management of Asthma during Pregnancy (MAP) programme. Clinically stable asthma = having well-controlled asthma (according to GINA guidelines) together with normal spirometry and FENO < 25 p.p.b. at the time of enrolment

those who will benefit from an intense asthma-monitoring programme. This initial assessment can be performed either by a pulmonologist in an outpatient clinic or by a GP if the setting allows it. Pregnant women with no history of pre-pregnancy exacerbation, clinically stable asthma at the first visit, and no prescribed controller medication could have regular follow-up by the GP while the other women could have an intense follow-up every fourth week at the pulmonary outpatient clinic. However, before implementing this in a clinical practice, there is a need for further research in a prospective design to evaluate the incidence of exacerbation rate in women with regular follow-up compared to close follow-up.

It is well documented that active and passive tobacco smoke exposure is a major risk factor for worse asthma control, excessive decline in FEV₁, and impaired responses to ICS and oral steroids.^{29–32} Asthmatic women who are current smokers during pregnancy have more severe asthma exacerbations during pregnancy relative to women who are non-smokers.³³ However, this could also be explained by socio-economic status and low educational level as these factors are associated with both smoking during pregnancy^{34,35} and severe asthma exacerbations.³⁶ Furthermore, the combination of asthma and smoking also significantly increases the incidence of low birth weight neonates and preterm deliveries.³⁷ In the present study, we found no association between

never-smokers and a low risk of an asthma exacerbation during pregnancy, but relatively few of the women were smokers. In a smaller cohort of 500 pregnant women, Grarup et al¹³ have shown that passive tobacco exposure in women, enrolled in the MAP programme, is associated with an increased risk of episodes of uncontrolled asthma.

This large study is sufficiently powered to assess asthma exacerbations during pregnancy. Even though all pregnant women referred to give birth at Hvidovre Hospital were informed and invited to this study, there could be a selection bias in women responding to the invitation. The women enrolled in the MAP cohort are comparable to the background population of pregnant women with regard to age and marital status.¹¹ We have previously reported that the proportion of current smokers is lower in women participating in the MAP programme than the background population of pregnant women.¹¹ This uneven distribution could have influenced the results and affected the power to detect a difference regarding smoking. Additionally, as in other population studies, there is a risk of several types of bias including factors associated with lifestyle that are not easily measured. We have earlier found that a higher proportion of nulliparous women accept an invitation to participate in lifestyle interventional trials during pregnancy at our department.³⁸ A predominance of nulliparous women was also found in the present study, however, adjusting for parity did not change any results.

Furthermore, we were not able to adjust for confounders such as socio-economic status and marital status due to lack of data. Nevertheless, the present study has a high external validity, and in our view, the results can be generalized to the population. All pregnant women were seen by the same pulmonologist (CSU) which increases the data validity.

In conclusion, our study suggests that women presenting in early pregnancy with no history of pre-pregnancy exacerbations, no prescribed controller medication, and clinically stable asthma at the first visit are associated with low risk of an asthma exacerbation during pregnancy. This may assist clinicians in identifying women that do not need an intense monitoring during pregnancy.

ACKNOWLEDGEMENTS

The Danish Lung Association, Amager and Hvidovre Hospital Research Foundation, Glaxo Smith Kline (GSK), Grosserer L.F. Foght's Foundation, Torben and Alice Frimodt's Foundation, The Unit of Science Research and Innovation, and Global Excellence in Health (Capital Region of Denmark) have financially supported this research.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Z. Ali  <http://orcid.org/0000-0003-2411-7177>

REFERENCES

- Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention www.ginasthma.com [updated 2016].
- Wilson DH, Adams RJ, Tucker G, Appleton S, Taylor AW, Ruffin RE. Trends in asthma prevalence and population changes in South Australia, 1990-2003. *Med J Aust*. 2006;184:226-229.
- Schatz M, Harden K, Forsythe A, Chilingar L, Hoffman C, Sperling W, et al. The course of asthma during pregnancy, post partum, and with successive pregnancies: a prospective analysis. *J Allergy Clin Immunol*. 1988;81:509-517.
- Namazy JA, Murphy VE, Powell H, Gibson PG, Chambers C, Schatz M. Effects of asthma severity, exacerbations and oral corticosteroids on perinatal outcomes. *Eur Respir J*. 2013;41:1082-1090.
- Murphy VE, Namazy JA, Powell H, Schatz M, Chambers C, Attia J, et al. A meta-analysis of adverse perinatal outcomes in women with asthma. *BJOG*. 2011;118:1314-1323.
- Murphy VE, Clifton VL, Gibson PG. Asthma exacerbations during pregnancy: incidence and association with adverse pregnancy outcomes. *Thorax*. 2006;61:169-176.
- NAEPP expert panel report. Managing asthma during pregnancy: recommendations for pharmacologic treatment-2004 update. *J Allergy Clin Immunol*. 2005;115:34-46.
- Powell H, Murphy VE, Taylor DR, Hensley MJ, McCaffery K, Giles W, et al. Management of asthma in pregnancy guided by measurement of fraction of exhaled nitric oxide: a double-blind, randomised controlled trial. *Lancet (London, England)*. 2011;378:983-990.
- Murphy VE, Jensen ME, Mattes J, Hensley MJ, Giles WB, Peek MJ, et al. The Breathing for Life Trial: a randomised controlled trial of fractional exhaled nitric oxide (FENO)-based management of asthma during pregnancy and its impact on perinatal outcomes and infant and childhood respiratory health. *BMC Pregnancy Childbirth*. 2016;16:111.
- Kircher S, Schatz M, Long L. Variables affecting asthma course during pregnancy. *Ann Allergy Asthma Immunol*. 2002;89:463-466.
- Ali Z, Nilas L, Ulrik CS. Low risk of adverse obstetrical and perinatal outcome in pregnancies complicated by asthma: a case control study. *Respir Med*. 2016;120:124-130.
- Barnes CB, Hansen AV, Ulrik CS. Enrolment in an Asthma Management Program during Pregnancy and Adherence with Inhaled Corticosteroids: the 'Management of Asthma during Pregnancy' Program. *Respiration*. 2016;92:9-15.
- Grarup PA, Janner JH, Ulrik CS. Passive smoking is associated with poor asthma control during pregnancy: a prospective study of 500 pregnancies. *PLoS ONE*. 2014;9:e112435.
- Ali Z, Nilas L, Ulrik CS. Excessive gestational weight gain in first trimester is a risk factor for exacerbation of asthma during pregnancy: a prospective study of 1283 pregnancies. *J Allergy Clin Immunol*. 2017. Epub ahead of print.
- Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26:319-338.
- Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. *Eur Respir J*. 2005;26:948-968.
- Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med*. 2009;180:59-99.
- Schatz M. Interrelationships between asthma and pregnancy: a literature review. *J Allergy Clin Immunol*. 1999;103:S330-S336.
- Zairina E, Abramson MJ, McDonald CF, Rochford P, Nolan G, Stewart K, et al. A prospective cohort study of pulmonary function during pregnancy in women with and without asthma. *J Asthma*. 2016;53:155-163.
- Maxim LD, Niebo R, Utell MJ. Screening tests: a review with examples. *Inhalation Toxicol*. 2014;26:811-828.
- Enriquez R, Wu P, Griffin MR, Gebretsadik T, Shintani A, Mitchel E, et al. Cessation of asthma medication in early pregnancy. *Am J Obstet Gynecol*. 2006;195:149-153.
- Chambers K. Asthma education and outcomes for women of child-bearing age. *Case Manager*. 2003;14:58-61.
- Schatz M, Leibman C. Inhaled corticosteroid use and outcomes in pregnancy. *Ann Allergy Asthma Immunol*. 2005;95:234-238.
- Matsui D. Adherence with drug therapy in pregnancy. *Obstet Gynecol Int*. 2012;2012:796590.
- Murphy VE, Gibson P, Talbot PI, Clifton VL. Severe asthma exacerbations during pregnancy. *Obstet Gynecol*. 2005;106:1046-1054.
- Stenius-Aarniala BS, Hedman J, Teramo KA. Acute asthma during pregnancy. *Thorax*. 1996;51:411-414.
- Blais L, Kettani FZ, Forget A, Beauchesne MF, Lemiere C. Asthma exacerbations during the first trimester of pregnancy and congenital malformations: revisiting the association in a large representative cohort. *Thorax*. 2015;70:647-652.
- Blais L, Forget A. Asthma exacerbations during the first trimester of pregnancy and the risk of congenital malformations among asthmatic women. *J Allergy Clin Immunol*. 2008;121:1379-1384, 84 e1.
- Jarvis D, Chinn S, Luczynska C, Burney P. The association of smoking with sensitization to common environmental allergens: results from the European Community Respiratory Health Survey. *J Allergy Clin Immunol*. 1999;104:934-940.
- Polosa R, Thomson NC. Smoking and asthma: dangerous liaisons. *Eur Respir J*. 2013;41:716-726.
- Siroux V, Pin I, Oryszczyn MP, Le Moual N, Kauffmann F. Relationships of active smoking to asthma and asthma severity in the EGEA study. Epidemiological study on the Genetics and Environment of Asthma. *Eur Respir J*. 2000;15:470-477.
- Stapleton M, Howard-Thompson A, George C, Hoover RM, Self TH. Smoking and asthma. *J Am Board Fam Med*. 2011;24:313-322.
- Murphy VE, Clifton VL, Gibson PG. The effect of cigarette smoking on asthma control during exacerbations in pregnant women. *Thorax*. 2010;65:739-744.
- Gilman SE, Breslau J, Subramanian SV, Hitsman B, Koenen KC. Social factors, psychopathology, and maternal smoking during pregnancy. *Am J Public Health*. 2008;98:448-453.
- Najman JM, Lanyon A, Andersen M, Williams G, Bor W, O'Callaghan M. Socioeconomic status and maternal cigarette smoking before, during and after a pregnancy. *Aust N Z J Public Health*. 1998;22:60-66.
- Yan BD, Meng SS, Ren J, Lv Z, Zhang QH, Yu JY, et al. Asthma control and severe exacerbations in patients with moderate or severe asthma in Jilin Province, China: a multicenter cross-sectional survey. *BMC Pulm med*. 2016;16:130.
- Hodyl NA, Stark MJ, Scheil W, Grzeskowiak LE, Clifton VL. Perinatal outcomes following maternal asthma and cigarette smoking during pregnancy. *Eur Respir J*. 2014;43:704-716.
- Gesche J, Renault K, Norgaard K, Nilas L. Representativeness of participants in a lifestyle intervention study in obese pregnant women - the difference between study participants and non-participants. *Obes Facts*. 2014;7:351-360.

How to cite this article: Ali Z, Nilas L, Ulrik CS. Determinants of low risk of asthma exacerbation during pregnancy. *Clin Exp Allergy*. 2017;00:1-7. <https://doi.org/10.1111/cea.13033>