

C. SANTA<sup>1</sup>, E. MILHEIRO TINOCO<sup>2</sup>, P. BARREIRA<sup>1</sup>, R. LIMA<sup>2</sup>

# Predictive factors of non-adherence to asthma medication in pregnancy

<sup>1</sup>Department of Allergy, Centro Hospitalar Vila Nova de Gaia/Espinho, EPE, Vila Nova de Gaia, Portugal

<sup>2</sup>Department of Pulmonology, Centro Hospitalar Vila Nova de Gaia/Espinho, EPE, Vila Nova de Gaia, Portugal

## KEY WORDS

*Asthma; pregnancy; medication adherence; non-adherence; risk factors.*

## Corresponding author

Cátia Santa  
Immunoallergology Service  
Centro Hospitalar Vila Nova de Gaia/Espinho  
Rua Conceição Fernandes S/N  
4434-502 Vila Nova de Gaia, Portugal  
ORCID ID: 0000-0002-7260-4896  
E-mail: catia\_santa@hotmail.com

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## IMPACT STATEMENT

*Mild asthma and marital status of single, separated or divorced were independent predictors of poor adherence to asthma medications in pregnant females.*

## Summary

**Background.** Adherence to asthma medications is a significant problem among pregnant women. **Objective.** To evaluate asthma medication adherence in pregnant women and to determine the factors that may predict non-adherence in a real-life setting. **Methods.** A cross-sectional study was performed with pregnant women with asthma followed in a specialized asthma consultation at the Pulmonology Department, between 2014 and 2019. Sociodemographic and clinical variables were collected. Structured telephone interviews were conducted to determine regular medication use during pregnancy. Multiple logistic regression was used to identify predictive factors of asthma medication non-adherence (cessation or dose reduction). **Results.** A total of 82 pregnant women were included: mean age of  $31.3 \pm 6.5$  years, non-adherence was detected in 29% ( $n = 24$ ). Multivariable logistic regression analysis revealed that mild asthma during pregnancy (OR 4.8; 95% CI 1.4-17.1;  $p = 0.015$ ) and single, separated or divorced mothers (OR 4.0; 95% CI 1.3-11.8;  $p = 0.014$ ) were independent predictors of poor adherence to asthma medications. **Conclusions.** Asthma severity and marital status can strongly predict the asthma medication non-adherence in pregnant females. These findings may help improve asthma education strategies to promote medication adherence.

## Introduction

Asthma is one of the most common chronic medical conditions complicating pregnancy, affecting up to 13% of pregnant women worldwide (1-4). Maternal asthma, particularly poorly controlled asthma, has been associated with increased risk of perinatal complications, including pre-eclampsia, gestational diabetes, placental abruption, placenta praevia, low birthweight, small for gestational age, preterm delivery and increased risk of maternal and perinatal mortality (5-10). To maintain asthma control, guidelines recommend the continued use of pre-pregnancy medication throughout pregnancy and adjusted according to the current treatment steps if required. The maternal and

fetal risks associated with uncontrolled asthma are greater than the risks from using asthma medications (10, 11). However, there are some concerns about complications of pregnancy resulting from asthma treatment. These concerns usually lead to a behavioral change in pregnant women with asthma against the medications that they had previously used. Some studies have demonstrated that women tend to decrease or cease their asthma medication during pregnancy. One study demonstrated that 40% of females with asthma reported non-adherence to inhaled corticosteroids (ICS) during pregnancy (12). Similarly, in another study, the authors reported a decrease of asthma medication use in early pregnancy (from 5 to 13 weeks). During the first trimester, there was a 23% decline in ICS prescriptions,

a 13% decline in short-acting  $\beta_2$ -agonist (SABA) prescriptions, and a 54% decline in rescue corticosteroid prescriptions (13). However, factors that may influence this adherence change have not been well addressed.

The identification of these factors can help prevent this behaviour, increasing treatment compliance, and consequently improving asthma control, which might contribute to decrease maternal and perinatal complications.

Therefore, the aim of this study was to evaluate asthma medication adherence in pregnant women and to determine the factors that may predict non-adherence in a real-life setting in our population.

## Methods

### *Study design*

Cross-sectional, descriptive and inferential study conducted in a specialized asthma consultation at the Pulmonology Department from a tertiary hospital in Northern Portugal. Patients followed up in the department at any time between January 2014 and December 2019 (6 years) were considered for inclusion.

### *Ethics*

This study was approved by the Ethics Committee of the Centro Hospitalar Vila Nova de Gaia/Espinho (Registration No. 132/2020) and was conducted according to ethical standards established in the Declaration of Helsinki. Verbal informed consent was obtained from all participants before enrolment in the study.

### *Patient selection*

Female patients referenced from the Gynecology and Obstetrics medical appointment or emergency department were included. Patient files were reviewed, and the criteria for inclusion in the study were pregnant women with a diagnosis of asthma. A total of 94 cases were identified, nine of which were excluded after clinical file review for not fulfilling asthma criteria, and three were excluded for not being pregnant.

### *Data collection and study variables*

Data collection was performed in 2020 and reported to the time of pregnancy. All patients were included after delivery.

The following variables were evaluated: age, age of asthma onset, asthma treatment, control and severity, asthma medication adherence, asthma status during pregnancy, admission to emergency department or hospitalization due to asthma symptoms during pregnancy, worsened asthma in a previous pregnancy, smoking habits, presence of atopy and rhinitis, number of pregnancies and children, place of residence, economic status, educational status, employment, and marital status.

Structured telephone interviews were conducted by the lead author (allergist resident with 4 years of clinical experience) to

determine asthma medication adherence, asthma status, educational status, employment and marital status during pregnancy. The remaining data were collected from hospital chart records. Medication adherence during the 3 trimesters of pregnancy was assessed in a non-judgemental and nonthreatening manner by asking: "It can be difficult to remember all of your medicines when things get busy. How many times in a week have you missed a dose of your control medication in the first trimester?", "And in the second and third trimester?". The assessment of the therapeutic plan and adherence during pregnancy followed a review of the medication prescriptions and patient's medical records on medication adherence. All asthma medication classes were evaluated. Although there is no consensus regarding what an acceptable adherence rate is, most researchers consider an adherence rate greater than 80% to be adequate (14). Participants were considered to be adherent if they missed  $\leq 20\%$  of their prescribed medication doses. Following this evaluation, the patients were allocated into two groups; group I consisted of pregnant women with good adherence (if they took 80% of their prescribed doses) and group II was comprised of poor adherent pregnant (if they reduce or cease medication).

We also asked the patients to classify their asthma status during pregnancy into worse, improved or stable.

Educational status, employment and marital status were classified into the groups described below. Educational status was divided in 3 groups: basic education (less than 9 years of education), upper secondary education (between 10 and 12 years) and tertiary education (more than 12 years of education). Employment was divided in 2 groups: employed and unemployed. Marital status included 2 groups: single, separated or divorced group and married or in a cohabitating relationship group.

Economic status included 2 groups: the presence or absence of economic insufficiency that is defined by the Portuguese Tax and Customs Authority, according to the average monthly income.

The assessment of control and severity of asthma was performed according to GINA-guidelines (11).

### *Statistical analysis*

All analyses were performed using Statistical Package for the Social Sciences, version 24.0 (SPSS Inc., Chicago, IL, USA). Nominal values are described as frequencies and percentages. Quantitative variables are expressed as mean  $\pm$  standard deviation (SD). Two independent sample paired t-test or Mann-Whitney U test was used for comparison of the continuous variables. Differences in distributions for categorical variables were tested using chi-square test or Fisher's exact test. Univariate and multiple logistic regression models were developed using independent variables as risk factors for non-adherence to asthma medication; results were presented as odds ratio (OR) with 95% confidence interval (CI). Variables used in the model included age, age of asthma onset, asthma control and severity, asthma status during

pregnancy, worsened asthma in a previous pregnancy, smoking during pregnancy, atopy, rhinitis, number of pregnancies, number of children, place of residence, economic status, educational status, employment and marital status. The variables that had  $P$ -value  $< 0.25$  in the univariate analysis were included in the multivariable model and a forward stepwise method was used to reach the final model. The goodness of fit of the logistic regression model was confirmed by the Hosmer-Lemeshow test. A  $P$ -value  $< 0.05$  was considered statistically significant.

## Results

### *Characteristics of patients*

In 2014-2019 period, a total of 82 pregnant women with asthma were identified. The mean age was  $31.3 \pm 6.5$  years (range 18-49 years), and the mean age of asthma onset was  $16.8 \pm 9.1$  years (range 1-37 years). In our population, the minority of patients (17%) had mild asthma, 52% had moderate asthma and the remaining 31% had severe asthma, according to GINA guidelines. According to the patients' own evaluations, asthma status improved in 9% of pregnant patients, remained unchanged in 38%, and worsened in 50% of the subjects during pregnancy. Three patients (4%) only initiated their symptoms during pregnancy. Twenty-seven patients (33%) were classified as having well-controlled asthma, whereas 39 patients (48%) and 16 patients (20%), respectively, had partly controlled and uncontrolled asthma. Atopy was present in 61% and rhinitis in 77%. Most patients did not smoke during pregnancy (71%). Seventy patients (73%) were single, separated or divorced while pregnant and 22 females (27%) were married or cohabiting couples. Sixteen patients (20%) went to an emergency department for asthma acute exacerbation, and 3 (4%) had been hospitalized during pregnancy.

In general, self-reported adherence was consistent throughout the pregnancy period. Fifty-eight patients (71%) had good asthma medication adherence, and 24 patients (29%) had poor adherence. **Table I** shows the characteristics for subjects with good and poor adherence. The two groups were statistically different in terms of asthma severity, asthma status during pregnancy and marital status. Females with mild asthma used their asthma medication significantly less during pregnancy compared with pregnant women with moderate and severe asthma ( $p = 0.024$ ). Pregnant patients with stable asthma had significant lower adherence to asthma medication than those with improved or worsened asthma ( $p = 0.014$ ). In single, separated or divorced females, the rate of medication non-adherence was 71%, which was significantly higher compared with married or cohabiting couples (29%;  $p = 0.012$ ) (**table I**).

No differences were found between the 2 groups regarding asthma control. Among pregnant women with asthma with poor adherence, 50% ( $n = 12$ ) used ICS, 50% ( $n = 12$ ) used SABA, and 42%

( $n = 10$ ) used long-acting  $\beta_2$ -agonist (LABA) during pregnancy. The usage rates of asthma medications according to the medication class were not significantly different between the 2 groups. In this study the ICS and LABA medications used by patients were fluticasone or budesonide and formoterol or salmeterol, respectively. There were no significant differences between the groups in terms of age, onset age of asthma, worsened asthma in a previous pregnancy, acute exacerbation of asthma requiring emergency service or hospitalization during pregnancy, smoking habits during pregnancy, atopy, rhinitis, number of pregnancies or children, place of residence, economic status, educational status, or employment (**table I**).

### *Multiple Logistic Regression*

The effects of asthma severity, asthma status during pregnancy, worsened asthma in a previous pregnancy and marital status were tested in the multivariable logistic regression. Asthma severity and marital status remained in the final model; it had a good fit ( $P$ -value for Hosmer-Lemeshow test: 0.592). The model explained 34% (Nagelkerke  $R^2$ ) of the variance in the medication adherence and correctly classified 71% of cases. Mild asthma and marital status of single, separated or divorced were associated with medication poor adherence; asthma status during pregnancy and worsened asthma in a previous pregnancy were not associated with medication compliance. The subjects with mild asthma were 4.8 times more likely to exhibit poor adherence of asthma medication than the subjects with moderate or severe asthma (95% CI 1.4-17.1;  $p = 0.015$ ). Single, separated or divorced mothers were 4.0 times more likely to exhibit poor adherence of asthma medication than the married or cohabiting couple (95% CI 1.3-11.8;  $p = 0.014$ ) (**table II**).

## Discussion

Our results revealed that almost 30% of the pregnant women with asthma did not use their controller medications regularly during pregnancy. Similarly, a survey of 501 females with asthma reported that 39% of women were reported to discontinue or reduce asthma medication use while pregnant, mostly without consultation with their physician, mainly because of concerns related to the safety of these medications on the foetus (15). Despite that, Yilmaz *et al.* in a study with 32 pregnant women with asthma, demonstrated that the regular use of asthma medications increased 12% during pregnancy when compared to the pre-pregnant period, but without statistical significance. The rate of irregular asthma medication use was 68% ( $n = 17$ ) before pregnancy and 56% ( $n = 14$ ) during pregnancy ( $p = 0.561$ ) (16). In non-pregnant asthma population, adherence to inhaled corticosteroids might be as low as 20% (17).

Most pregnant women had moderate or severe asthma (83%), according to GINA guidelines. These data can be explained by the fact that the study was carried out with patients followed in

**Table I** - Comparison of pregnant women with asthma according to asthma medication adherence (n = 82).

Variable	Good adherence (n = 58)	Poor adherence (n = 24)	P-value
Age, years, mean ± SD (min-max)	31.3 ± 6.5 (19-49)	30.6 ± 7.0 (18-42)	0.407
Age of asthma onset, years, mean ± SD (min-max)	16.0 ± 9.0 (1-37)	18.0 ± 9.1 (6-37)	0.812
Asthma control			
Well-controlled	17 (29.3)	10 (41.7)	0.435
Partly controlled	28 (48.3)	11 (45.8)	
Uncontrolled	13 (22.4)	3 (12.5)	
Asthma severity			
Mild	6 (10.3)	8 (33.3)	0.024
Moderate or severe	52 (89.6)	16 (66.7)	
Asthma status during pregnancy			
Stayed stable	17 (29.3)	14 (58.3)	0.014
Improved	7 (12.1)	0 (0)	
Worsen	33 (56.9)	8 (33.3)	
Initiated during pregnancy	1 (1.7)	2 (8.3)	
Worsened asthma in a previous pregnancy	12 of 28 (42.9)	1 of 9 (11.1)	0.119
Smoked during pregnancy	15 (25.9)	7 (29.2)	0.725
Atopy	35 (60.3)	15 (62.5)	0.487
Rhinitis	44 (75.9)	19 (79.2)	0.423
Number of pregnancies, mean ± SD (min-max)	2.1 ± 1.1 (1-5)	2.1 ± 1.4 (1-6)	0.277
Number of children, mean ± SD (min-max)	1.7 ± 0.8 (0-5)	1.8 ± 1.0 (1-5)	0.262
Place of residence (Urban area)	22 (37.9)	9 (37.5)	0.971
Economic status (insufficiency)	21 (36.2)	9 (37.5)	0.912
Educational status			
Basic education	14 (24.1)	3 (12.5)	0.278
Upper secondary education	15 (25.9)	10 (41.7)	
Tertiary education	29 (50.0)	11 (45.8)	
Employment	35 (60.3)	13 (54.2)	0.899
Marital status			
Single, separated or divorced	5 (8.6)	17 (70.8)	0.012
Married or cohabiting couple	53 (91.4)	7 (29.2)	

Data are presented as n (%), except when indicated otherwise.

a specialized asthma consultation at the Pulmonology Department. The remaining with mild asthma (17%) had significantly worse asthma treatment compliance. Some studies corroborate this finding, Murphy *et al.* demonstrated that females with mild asthma used significantly less ICS in all trimesters and had inadequate inhaler technique compared with females with moderate and severe asthma (12).

Another finding of our study was that marital status significantly influenced the asthma medication adherence, with single, separated or divorced mothers being less adherent. To our knowledge, there is no published information regarding the relationship between asthma medication adherence during pregnancy and marital status. The authors hypothesize that family support

and emotional stability is greater in married or cohabiting couples, and can contribute to therapy compliance during pregnancy. In fact, this finding is similar to studies on other health conditions. One study reported that married pregnant participants with HIV-infection have a better chance of anti-retroviral medication adherence than separated, single and widowed patients (18). In another study, single marital status was a factor for inadequate preconception use of folic acid, when compared to married or living together participants (19).

The clinical effect of pregnancy on asthma is variable, as demonstrated by Schatz *et al.* (20), in this prospective study 366 pregnancies were followed in women with asthma, of which 35% suffered worsening asthma, 28% improved and in 33% no changes were

**Table II** - Multiple logistic regression using the forward stepwise method of the factors associated with non-compliance with asthma medication in pregnant women with asthma ( $n = 82$ ).

Factor	Initial model			Final model		
	OR	95% CI	P-value	OR	95% CI	P-value
<b>Asthma severity</b>						
Mild	5.1	1.0-26.5	0.051	4.8	1.4-17.1	0.015
Moderate or severe	1.0					
<b>Asthma status during pregnancy</b>						
Improved	1.0					
Stayed stable	0.5	0.1-2.0	0.357	---	---	
Worsened	1.5	0.1-21.1	0.576	---	---	
Initiated during pregnancy	2.8	0.2-41.8	0.458	---	---	
<b>Worsened asthma in a previous pregnancy</b>	0.3	0.03-3.2	0.336	---	---	
<b>Marital status</b>						
Single, separated or divorced	3.3	1.0-10.9	0.052	4	1.3-11.8	0.014
Married or cohabiting couple	1.0					

OR: odds ratio; CI: confidence interval.

detected; in about 4%, it was not possible to classify the course of asthma during pregnancy. In contrast, in our study population we found that half of pregnant women reported worsened asthma symptoms during pregnancy, 38% remained unchanged, and the minority (9%) improved their asthma status. Only 3 patients (4%) initiated their symptoms during pregnancy. The group with stable asthma symptoms had significant lower adherence to asthma medication. Another Portuguese study, that included 26 pregnant women, found that only 4% improved, 54% remained stable and 42% worsened their asthma symptoms.

Asthma control seems to be poor in most pregnant women with asthma (48% partly controlled and 20% uncontrolled asthma), and with only 33% having well-controlled asthma. Consequently, they needed to use medications regularly to keep their asthma in a more stable state. Considering these evaluations, we can infer that poor asthma control during pregnancy may positively influence pregnant women to use their asthma medications.

Some clinical parameters, such as hospital and emergency room admissions, showed that asthma was not controlled well enough in some women with asthma during pregnancy, with percentages of 20% and 4%, respectively. Other studies reported that between 20 and 36% of females with asthma had exacerbations during pregnancy (20-22), especially in the second trimester (23). The suggested reason for this unequal distribution has been the possibility that several women may decrease or even discontinue preventive therapy shortly after pregnancy identification, especially with regard to ICS (23).

Using multivariable logistic regression analysis, we can demonstrate that marital status of single, separated or divorced mothers and mild asthma during pregnancy are independent predictors of poor adherence of asthma medications in pregnant women. Asthma medication non-adherence is a particular problem in pregnancy, due to the potential for maternal and fetal complications. Females with asthma may benefit from closer monitoring of their asthma during pregnancy, in order to ensure optimum treatment and control during this period. Asthma self-management education programmes are an important component of asthma management and should include education, self-monitoring, regular review with optimisation of pharmacotherapy, inhaler technique training and a written plan for the management of unstable asthma. Our findings may help improve asthma education strategies, particularly in those who are single, separated or divorced mothers or have a mild asthma, in order to promote medication adherence. This may lead to improved outcomes for both mother and child.

There are many limitations of this study. Firstly, this is a cross sectional, single-centered, questionnaire-based study; some data used in this study (like regular medication usage, status of asthma during pregnancy compared to a previous period) depend on the patients' statements and recall capacity. Level of medication adherence may depend on the adherence cut-off used. An important factor for recording or recall bias is the time that elapsed between delivery and the study interview, especially those women who were pregnant in 2014, as the elapsed time is long this bias is expected to increase. To decrease the impact of this limitation, these data



were compared with clinical records and the medications prescriptions during pregnancy where evaluated. Another limitation of this study is the small number of cases. Finally, it was not possible to evaluate the different trimesters in a specific week of pregnancy; instead, the assessment was made globally over the trimesters. Despite these limitations, this study can provide important information about factors that may predict the non-adherence to asthma medication in pregnant women.

### Conclusions

Almost 30% of the included female had low asthma medication adherence during pregnancy. Single, separated or divorced females and mild asthma were independent factors that influence poor-adherence. These findings may help improve asthma education strategies, namely reinforcing the recommendations for continuing the appropriate use of medication, in order to allow good control of the disease and minimize complications inherent to exacerbations, in particular in women with these risk factors.

### Conflict of interests

The authors declare that they have no conflict of interests.

### References

- Huang K, Yang T, Xu J, *et al.* Prevalence, risk factors, and management of asthma in China: a national cross-sectional study. *Lancet* 2019;6736(19):1–12.
- Sawicki E, Stewart K, Wong S, Leung L, Paul E, George J. Medication use for chronic health conditions by pregnant women attending an Australian maternity hospital. *Aust New Zeal J Obstet Gynaecol* 2011;51:333–8.
- Kwon HL, Belanger K, Bracken MB. Asthma Prevalence among Pregnant and Childbearing-aged Women in the United States: Estimates from National Health Surveys. *Ann Epidemiol* 2003;13(5):317–24.
- Charlton RA, Hutchison A, Davis KJ, Vries CS De. Asthma Management in Pregnancy. *PLoS One* 2013;8(4):e60247.
- Ali Z, Hansen AV, Ulrik CS. Exacerbations of asthma during pregnancy: Impact on pregnancy complications and outcome. *J Obstet Gynaecol* 2016;36(4):455–61.
- Enriquez R, Griffin MR, Carroll KN, *et al.* Effect of maternal asthma and asthma control on pregnancy and perinatal outcomes. *J Allergy Clin Immunol* 2007;120(3):625–30.
- Murphy VE, Namazy JA, Powell H, *et al.* A meta-analysis of adverse perinatal outcomes in women with asthma. *BJOG* 2011;118(11):1314–23.
- 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(5):1082–90.
- Murphy VE, Clifton VL, Gibson PG. Asthma exacerbations during pregnancy: incidence and association with adverse pregnancy outcomes. *Thorax* 2006;61(2):169–76.
- Robijn AL, Murphy VE, Gibson PG. Recent developments in asthma in pregnancy. *Curr Opin Pulm Med* 2019;25(1):11–7.
- Initiative G. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2020. Available at: <http://www.ginasthma.org>. Last access date: 02/25/2021.
- Murphy VE, Gibson PG, Talbot PI, Kessell CG, Clifton VL. Asthma self-management skills and the use of asthma education during pregnancy. *Eur Respir J* 2005;26(3):435–41.
- Enriquez R, Wu P, Griffin MR, *et al.* Cessation of asthma medication in early pregnancy. *Am J Obstet Gynecol* 2006;195(1):149–53.
- Osterberg L, Blaschke T. Adherence to Medication. *N Engl J Med* 2005;353(5):487–97.
- Chambers K. Asthma education and outcomes for women of childbearing age. *Case Manager* 2003;14(6):58–61.
- Yilmaz I, Erkekol FO, Celen S, *et al.* Does drug compliance change in asthmatic patients during pregnancy? *Multidiscip Respir Med* 2013;8(1):38.
- Williams LK, Pladevall M, Xi H, *et al.* Relationship between adherence to inhaled corticosteroids and poor outcomes among adults with asthma. *J Allergy Clin Immunol* 2004;114(6):1288–93.
- Mukosha M, Chiyesu G, Vwalika B. Adherence to antiretroviral therapy among HIV infected pregnant women in public health sectors: a pilot of Chilenje level one Hospital Lusaka, Zambia. *Pan Afr Med J* 2020;35(49):1–9.
- Timmermans S, Jaddoe VW, Mackenbach JP, Hofman A, Steegers-theunissen RPM, Steegers EAP. Determinants of folic acid use in early pregnancy in a multi-ethnic urban population in The Netherlands: The Generation R study. *Prev Med (Baltim)* 2008;47(4):427–32.
- Schatz M, Harden K, Forsythe A, *et al.* The course of asthma during pregnancy, post partum, and with successive pregnancies: A prospective analysis. *J Allergy Clin Immunol* 1988;81(3):509–17.
- Gluck JC. The Change of Asthma Course During Pregnancy. *Clin Rev Allergy Immunol* 2004;26(3):171–80.
- Murphy VE, Gibson P, Talbot PI, Clifton VL. Severe Asthma Exacerbations During Pregnancy. *Obstet Gynecol* 2005;106(5):1046–54.
- Stenius-Aarniala BS, Hedman J, Teramo KA. Acute asthma during pregnancy. *Thorax* 1996;51(4):411–4.