

MANUSCRIPT TEXT FILE

INTRODUCTION

Asthma is one of the most common chronic medical condition 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 prepregnancy 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 beta2-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.

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.

Statement of 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.

RESULTS

Characteristics of Patients

In 2014-2019 period, a total of 82 pregnant women with asthma were identified. The mean age was 31.3 ± 6.5 years (range 18-49 years) and the mean age of asthma onset was 16.8 ± 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 D).

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 beta2-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 effect 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 R²) of the variance in the medication adherence and correctly classified 71% of cases. Mild asthma and marital status of single, separated or divorced was 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 = 7) 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 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 influenced significantly 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 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.

CONCLUSION

Almost 30% of the included females 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 Interest: None

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