Adherence to medication during pregnancy in systemic autoimmune diseases: results from a prospective study

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Abstract

Objective

To evaluate adherence to medication in patients with systemic autoimmune diseases (SAD), comparing pregnant and non-pregnant women.

Methods

200 patients with SAD were consecutively enrolled, 100 pregnant and 100 non-pregnant women. Each patient completed the 8-item Morisky Medication Adherence Scale (MMAS-8), one copy for hydroxychloroquine (HCQ) and one for other treatments for rheumatic disease, and Hospital Anxiety and Depression Scale (HADS).

Results

No significant differences were found in ongoing therapies between pregnant and non-pregnant women. 148 patients (74.0%) were taking HCQ and 160 (80.0%) other therapies for rheumatic disease. The mean MMAS-8 score was >6 in all groups indicating a good adherence, on average. The rate of patients with good medication adherence was higher in pregnant patients (73.9% vs. 63.3% and 76.5% vs. 64.5%, for HCQ and other therapies, respectively) although this difference was not statistically significant. Eight patients had very poor medical adherence, and all were non-pregnant women. Anxiety (15% of patients) was associated to low medication adherence for drugs other than HCQ (p=0.02), while depression (4% of patients) did not seem to have an impact on adherence.

Conclusion

In our cohort we recorded a good adherence to prescribed medication, although adequate adherence was not achieved in about 30% of patients, confirming that non-adherence is an important issue in SAD. It is difficult to define a profile of patients at risk of poor adherence, but it appears important to implement communication and adherence monitoring strategies since strict monitoring also during pregnancy could improve medical adherence.

Key words

medical adherence, pregnancy, systemic autoimmune diseases

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Introduction

Systemic autoimmune diseases (SAD) predominantly affect women of childbearing age; thus, pregnancy can be a complex phase in the life of patients living with these diseases (1). Pregnancy outcome in patients with SAD has greatly improved during the last decades and pregnancy planning during remission state and proper treatments are the major contributors to this improvement (2). Thus, good adherence to prescribed medications is of pivotal importance, especially during pregnancy.

The World Health Organisation (WHO) defines adherence as "the extent to which a person's behaviour-taking medication, following a diet, and/or executing lifestyle changes-corresponds with agreed recommendations from a healthcare provider" (3). Medical adherence can be evaluated with subjective and objective methods, and questionnaires are frequently used in clinical settings due to their simplicity and low cost, even though they can be susceptible to misrepresentation by the patients (4). One of the most frequently used is the 8-item Morisky Medication Adherence Scale (MMAS-8) (5).

Previous studies have shown that approximately 50–60% of patients do not have an adequate adherence to therapy (6, 7), and low medication adherence is a well-known issue in the management of SAD being responsible for treatment failure, misunderstandings between doctor and patient and increased costs (8, 9).

To date, adherence to medications during pregnancy is poorly studied, especially in patients with SAD. As in non-pregnant patients, the problem of poor adherence is complex with many contributing factors; in addition, during pregnancy, concern regarding potential adverse foetal effects seems to have a role in poor medical adherence (10).

Previous research on pregnant women with a large spectrum of chronic diseases showed that around 55.6% of women affected by a rheumatic disease (rheumatoid arthritis and psoriatic arthritis) had poor medical adherence, mostly due to a quiescent disease (11). Women with rheumatic diseases had the highest rates of low adherence with respect to those with epilepsy (40.0%), bowel disorders (36.1%), cardiovascular disorders (32.9%) and diabetes (17.1%).

The research hypothesis is that being pregnant would have an impact on treatment adherence in patients with SAD; the study of potential contributors to treatment adherence could help in creating strategies to make effective and improve this aspect in our patients during pregnancy.

Thus, the aim of our study was to analyse medical adherence in pregnant women with SAD and compare it with a control group of non-pregnant women with similar characteristics. Anxiety and depression as potential contributors to poor treatment adherence were also investigated.

Methods

Consecutive patients with an established diagnosis of SAD and under treatment for the underlying rheumatic condition were consecutively enrolled at Rheumatology Unit of University of Pisa between December 2017 and January 2022.

Diagnosis of each single SAD was based on the current classification criteria for each disease included in the analysis.

Pregnant patients were enrolled from the Pregnancy Clinic of the Unit: a joint gynaecology-rheumatology outpatient clinic where a tight monitoring protocol for high-risk pregnancies was applied. The monitoring protocol included monthly visits during which disease activity and ongoing treatments were assessed. Non-pregnant patients were recruited from the outpatient clinic of the Unit on the same day as regular follow-up visits.

Diagnoses were grouped into:

- Connective tissue diseases (CTD), which included: systemic lupus erythematosus, undifferentiated connective tissue diseases, mixed connective tissue diseases, Sjögren syndrome, systemic sclerosis and antiphospholipid syndrome;
- Arthritis, which included: rheumatoid arthritis and spondylarthritis.
- Systemic vasculitis, which included: Behçet's disease and granulomatosis with polyangiitis.

Table I. Characteristics of the cohort at enrolment.

	All n=200	Pregnant patients n=100	Non-pregnant patients n=100	*p*-value
Diagnosis				0.06
Arthritis (%)	30 (15.0)	20 (20.0)	10 (10.0)	
Connective tissue diseases (%)	161 (88.5)	74 (74.0)	87 (87.0)	
Vasculitis (%)	9 (4.5)	6 (6.0)	3 (3.0)	
Age at study entry, years, mean ±SD	35.6±5.3	35.5±4.4	35.7±6.2	0.80
Disease duration, years, mean ±SD	8.6±5.9	9.1±6.5	8.1±6.2	0.18
Disease duration <5 years (%)	121 (60.5)	65 (65)	56 (56)	0.19
Comorbidities (%)	80 (40.0)	42 (42)	38 (38)	0.56
Total number of of tablets/day, mean ±SD	3.5±1.4	4.11±2.0	4.09±2.3	0.94
Hydroxychloroquine (%)	148 (74.0)	69 (69.0)	79 (79.0)	0.10
Other treatments (%)	160 (80.0)	81 (81.0)	79 (79.0)	0.72

SD: standard deviation

Table II. Results of the questionnaires.

	All n=200	Pregnant patients n=100	Non-pregnant patients n=100	*p*-value
Score MMAS for HCQ, mean ±SD	6.7±1.47	6.7±1.46	6.7±1.49	0.85
MMAS ≥6 for HCQ (%)	101/148 (68.2)	51/69 (73.9)	50/79 (63.3)	0.07
MMAS <3 for HCQ (%)	5/148 (3.4)	0/69 (0)	5/79 (6.3)	0.06
Score MMAS for other treatment, mean ±SD	6.7±1.5	6.7±1.52	6.7±1.50	0.98
MMAS ≥6 for other treatment (%)	113/160 (70.6)	62/81 (76.5)	51/79 (64.5)	0.09
MMAS <3 for other treatment (%)	4/160 (2.5)	0/81 (0)	4/79 (5.1)	0.05
MMAS <3 for all therapies (both HCQ and/or other treatments)	8 (4.0)	0 (0)	8 (8.0)	**<0.01**
Score HADS for anxiety, mean ±SD	6.5±3.5	6.3±3.38	6.7±3.68	0.39
Score HADS for depression, mean ±SD	4.3±3.1	4.3±2.93	4.2±3.44	0.71
Anxiety (%)	30 (15.0)	11 (11.0)	19 (19.0)	0.10
Depression (%)	8 (4.0)	1 (1.0)	7 (6.0)	**0.03**

HADS: Hospital Anxiety and Depression Scale; HCQ: hydroxychloroquine; MMAS: Morisky Medication Adherence Scale; SD: standard deviation.

The following data were collected at enrolment: epidemiological and demographic characteristics, disease duration, comorbidities and type of medications including number of tablets/day. Comorbidities considered were the following: fibromyalgia, Hashimoto's thyroiditis, coeliac disease, diabetes mellitus, hypertension, obesity and osteoporosis.

Each patient completed the following anonymous questionnaires at enrolment: the MMAS-8 to assess the adherence to medications and the Hospital Anxiety and Depression Scale (HADS) to assess the presence of anxiety and depression. With regard to MMAS-8, we assessed adherence to hydroxychloroquine (HCQ) and to other drugs prescribed for the rheumatic disease separately, including oral and subcutaneous therapies. We considered a score ≥6 as an indicator of good adherence, and a score <3 as an indicator of very poor adherence. Vitamins and dietary supplements were not considered. With regard to HADS, we considered a score ≥11 as an indicator of anxiety or depression.

In cases of pregnant women, we also collected data on disease flare during pregnancy and pregnancy outcome. We considered as obstetric complications the occurrence of at least one of the following conditions: proteinuric preeclampsia, preterm delivery before 37 weeks of gestation, small for gestational age infant, low birthweight (less than 2500 grams), intra uterine growth restriction and intrauterine fetal death after 10 weeks of gestation of a morphologically normal foetus.

Cross-tabulated data were analysed using the chi-square test or Fisher's test when the cell count was less than 5, and *p*-values <0.05 were considered to be statistically significant.

This study was approved by the ethics committee "Comitato Etico Area Vasta Nord Ovest" and MMAS-8© license was regularly obtained for clinical use.

Results

A total of 200 patients were enrolled for this study, 100 pregnant and 100 non-pregnant women. The characteristics of the cohort at enrolment are detailed in Table I.

CTD was the most frequent diagnosis in our cohort, both in the pregnant and non-pregnant group (74.0% and 87.0%, respectively).

No significant differences were found with regard to age, disease duration, comorbidities and number of assumption/day between pregnant and non-pregnant women.

Overall, at enrolment, 148 patients (74.0%) were taking HCQ and 160 (80.0%) other therapies for rheumatic disease; the type of ongoing therapies were not statistically different in the two groups (69.0% *vs*. 79.0% p=0.10 and 81.0% *vs*. 79.0% p=0.72, in pregnant *vs*. non-pregnant, respectively). In the whole cohort, the mean MMAS-8 score for both HCQ and other therapies resulted greater than 6 in all groups indicating a good adherence, on average. However, 31.8% and 29.4% of patients had MMAS-8 <6 for HCQ and other therapies, respectively. The results of the questionnaires are detailed in Table II.

By groups, the mean MMAS was 6.7±1.46 for HCQ and 6.7±1.52 for other therapies in pregnant and 6.7±1.49 and 6.7±1.50 in non-pregnant women; the rate of patients with good medication adherence was higher in pregnant patients (73.9% *vs*. 63.3% and 76.5% *vs*. 64.5%, for HCQ and other therapies respectively) although this difference did not reach statistical significance.

Only 8 patients (4.0%) had very poor medical adherence: 4 for HCQ, 3 for other treatments and 1 patient for both kind of medications. Interestingly, all patients with very poor adherence were non pregnant women (p<0.01).

Considering the HADS score, overall, 30 patients (15.0%) had a positive score for anxiety and 8 (4.0%) for de-

Table III. Correlation between anxiety and depression and medical adherence.

All patients			
	MMAS ≥6 for HCQ (n=101)	MMAS <6 for HCQ(n=46)	*p*-value
Anxiety (%)	14 (13.9)	10 (21.7)	0.23
Depression (%)	2 (2.0)	4 (8.7)	0.07
	MMAS ≥6 for other therapies (n=113)	**MMAS <6 for other therapies (n=47)**	*p*-value
Anxiety (%)	12 (10.6)	12 (25.3)	**0.02**
Depression (%)	3 (2.7)	2 (4.3)	0.63
Pregnant patients			
	MMAS ≥6 for other therapies (n=62)	MMAS <6 for other therapies (n=19)	*p*-value
Anxiety (%)	4 (6.45)	5 (26.32)	**0.02**
Depression (%)	0	0	NA
	MMAS ≥6 for HCQ (n=51)	MMAS <6 for HCQ(n=18)	*p*-value
Anxiety (%)	4 (7.8)	4 (22.2)	0.08
Depression (%)	0 (0)	1 (5.5)	0.23
Non-pregnant patients			
	MMAS ≥6 for HCQ (n=50)	MMAS <6 for HCQ (n=29)	*p*-value
Anxiety (%)	10 (20.0)	6 (20.7)	1.0
Depression (%)	2 (4.0)	3 (10.3)	0.35
	MMAS ≥6 for other therapies (n=51)	MMAS <6 for other therapies (n=28)	*p*-value
Anxiety (%)	8 (15.7)	7 (25.0)	0.31
Depression (%)	3 (5.9)	2 (7.1)	1.0

HCQ: hydroxychloroquine; MMAS: Morisky Medication Adherence Scale.

pression; prevalence in the pregnant and non-pregnant group was 11.0% and 19.0% for anxiety and 1.0% and 6.0% for depression (p=0.10 and p=0.03, respectively).

Anxiety was found to be significantly associated to low medication adherence for drugs except HCQ in all patients and in pregnant women (p=0.02). Conversely, depression did not seem to have an impact on adherence on either group. The results of these analyses are reported in Table III.

In the pregnant women we recorded 18 cases of flare during pregnancy (18.0%) and 19 cases of obstetric complications (19.0%). No differences were found in terms of treatment adherence in patients with flares or obstetric complications.

Discussion

The literature data show that poor treatment adherence is an important issue in chronic diseases, especially during pregnancy when worry about possible harmful effects to the foetus are added to other concerns (10, 12).

The aims of our study were to analyse medical adherence in pregnant women with SAD, to compare it with a control group of non-pregnant women with similar characteristics and to explore the impact of anxiety and depression on medical adherence.

Overall, in our cohort, patients with SAD had a good adherence to prescribed medication, on the other hand, adequate adherence was not achieved in about 30% of patients, confirming that non-adherence is an important issue in SAD. In a review on adherence in patients with SAD, rates varied between 9.3% and 94%, and persistence rates between 23% and 80%, and the data were heterogeneous in terms of diseases and methods used to evaluate adherence (8). In a homogenous cohort of patients with flaring SLE, questionnaires classified 39.9% of patients as non-adherent (13). With regards to pregnant patients with rheumatic diseases, the available data reported 55.6% of patients with poor medical adherence (11).

With respect to the literature data, an interesting finding of our study is that overall pregnant patients had a good adherence to prescribed medications, even better than the non-pregnant patients. This is in contrast with previous studies reporting poor treatment adherence during pregnancy due to concerns regarding potential adverse foetal effects and risks of drug use during pregnancy (10, 12).

A possible explanation of our results could lie in the fact that all the pregnant patients included in this study received dedicated pre-conception counselling focused on the importance of disease activity control before and during pregnancy. Moreover, all the pregnant patients were included in a tight control programme receiving regular assessments of disease activity and ongoing therapies. This strategy may have had an impact on treatment adherence during pregnancy.

Most of the variables considered in our study do not have an impact on medical adherence. Only anxiety was associated with low adherence for therapies different from HCQ in all patients and in pregnant patients. Conversely, depression did not have an impact on adherence in either group. Several studies have reported mental health as a predictive factor of poor adherence, especially in cases of depression, although the cohorts were not homogeneous (9, 14, 15). Our study period included the SARS-CoV2 pandemic phase, but we did not record a high prevalence of

anxiety and depression in our cohort, and similar findings were previously reported by a study that disproved the assumption that the pandemic may have induced more anxiety and depression in SAD patients, making it improbable that these factors played an important role in therapeutic decisions (16).

Based on these data, it is difficult to define a profile of patients at risk of poor adherence in SAD, but it appears important to implement communication and adherence monitoring strategies. Similarly, in a cohort of patients with Behçet's disease, almost 73% believed that being educated about the treatment would help them to better manage their therapy and it may have had an impact on medical adherence (17)

Indeed, increasing patient knowledge about the disease and the benefits and mechanisms of action of prescribed therapies also during pregnancy could improve medical adherence, and previous studies have emphasised the importance of good communication between patients and physicians (12, 18).

Also in patients with SAD, good communication seems to be necessary to improve the care of CTD patients during pregnancy (19), and therefore formalised protocols for pre-pregnancy planning might lead to better pregnancy and foetal outcomes (20).

Moreover, the results of a recent Delphi consensus survey among Italian rheumatologists on adherence to therapy in people with rheumatic and musculoskeletal diseases suggested that digital health can provide valuable support in improving adherence (21).

Our study has some limitations. Firstly, the heterogeneity of the diseases included; however, to the best of our knowledge, this it is the first study that compares a large number of pregnant and non-pregnant patients with SAD with similar characteristics, followed by a single centre. Secondly, the use of only one method for assessing adherence, even though it is the most widely used and validated in the literature, may overestimate adherence with respect to objective assessment methods such as the measurement of drug levels.

The strength of our study is that all the patients were followed at a single centre, ensuring homogeneity in prescribed treatment regimens and communication strategies, which are well known factors that could influence medical adherence.

In conclusion, medical adherence remains a challenge in the management of SAD, and many factors may play a role, but proper counselling and strictly monitoring also during pregnancy may improve medical adherence.

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