Rwanda Medical Journal RMJ

ORIGINAL RESEARCH Open Access

# Complications in pregnant women with autoimmune diseases

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**ABSTRACT**

**BACKGROUND:** Autoimmune diseases complicate pregnancy in several manners. This study aimed at describing the most common complications in pregnant women with autoimmune diseases.

**METHODS:** This was a descriptive and retrospective study. Two groups of pregnant women with autoimmune diseases were included: 1) Those who since the beginning of gestation received obstetrical care at a tertiary-level hospital and 2) Women who were treated first in a medical unit not specialized in rheumatological diseases. Odds ratio, logistic regression and multinomial logistic regression were used to determine risk of complicated pregnancy.

**RESULTS:** The distribution of autoimmune diseases in our sample is as follows: systemic lupus erythematosus (SLE): 6, rheumatoid arthritis (RA): 4, primary anti-phospholipid syndrome (APS): 4, systemic sclerosis (SS): 2, mixed connective tissue disease (MCTD): 1. Eight patients were seen throughout their gestation at a tertiary-level hospital and nine were referred from other non-specialized hospitals. Patients in the first group had four complications, and those of the second group, 28. The Odds Ratio (OR) of having a complication in the hospitals of reference compared to the "Mónica Pretelini Sáenz" Maternal-Perinatal Hospital (HMPMPS) was of 29.8 (95% CI: 1.29-692.46; Z statistic 2.11, p = 0.03). In relation to the logistic regression, this test was not significant neither for the group nor the treatment scheme for the presence of at least one complication. The multinomial logistic regression did not show significant predictive probabilities of the different possible outcomes for the group and drug treatment scheme.

**CONCLUSION:** Pregnant women with autoimmune diseases can have an OR up to 29.8 to develop complications when they are not cared for by specialized personnel.

**Keywords (MeSH):** Autoimmune diseases; Complications; Arthritis; Rheumatoid; Lupus Erythematosus; Systemic.

## INTRODUCTION

Autoimmune diseases are common in pregnancy [1,2]. Disorders of autoimmunity are classified as follows: a) systemic multiorganic, in which the antibodies attack antigens that are not specific to a particular organ — a clear example of which is Systemic Lupus Erythematosus (SLE) and b) non-systemic, in which specific organs are affected. To date, > 80 types of autoimmune diseases have been identified that could affect the population, with a notable prevalence of 7.6-9.4%, and therefore women with autoimmune disease may suffer spontaneous abortions and even infertility [3]. An autoimmune crisis can commonly affect blood vessels, red blood cells, skin, muscles, and joints, among others [4,5]. All of these complications are enhanced during pregnancy [5–7].

When women of reproductive age are affected by autoimmune

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**Review**: This manuscript was peer-reviewed by three reviewers in a double-blind review process; **Type-editor:** Dennis Hopkinson (USA)

**Received:** 12th April 2019; **Initial decision given:** 30th April 2019; **Revised manuscript received:** 15th September 2019**; Accepted:** 23th September 2019

 **Publisher:** Rwanda Biomedical Centre (RBC)/Rwanda Health Communication Center, P.O.Box 4586, Kigali.

**ISSN:** 2079-097X (print); 2410-8626 (online)

**Citation for this article**: J. Meneses-Calderón; J. Meneses Figueroa; M. I. Ospina-Arzate et al. Complications in pregnant women with autoimmune diseases. Rwanda Medical Journal, Vol 77, no 1, pp 1-6, 2020

diseases, they suffer more severe consequences; therefore, this implies a risk in case of pregnancy due to the possibility of clinical deterioration. One of the diseases of this group that generates most concern is SLE, as population studies have detected complication rates between 2 and 8% in pregnant women, who may be more prone to preeclampsia or hypertension, leading to maternal-fetal morbidity and mortality. Another example is the antiphospholipid syndrome (APS), which can cause such maternal-fetal complications as preeclampsia, eclampsia, and placental abruption; additionally, thrombotic manifestations added to other obstetric complications can coexist in 2.5–5% of cases [8]. Rheumatoid arthritis (RA) affects between 0.5 and 1.0% of adults, with a frequency 2–4-times higher in women of reproductive age. It has been shown that the increase of progesterone in pregnancy decreases the immune response and consequently the level of proinflammatory cytokines, generating remission of the disease in a small amount of pregnant women [9].

Hence, patients with autoimmune diseases require extra care during pregnancy to avoid the development of complications associated with these conditions. Therefore, we share a glimpse into the major complications of pregnant women with autoimmune diseases when they are not treated at specialized hospitals.

## METHODS

This was a descriptive and retrospective study. Pregnant women seeking care at the "Mónica Pretelini Sáenz" Maternal-Perinatal Hospital (HMPMPS), Health Institute of the State of Mexico (ISEM), Toluca, Mexico, were included during the period January-December 2012. Two groups of pregnant women with autoimmune diseases were established: the first group was seen from the beginning of gestation at this tertiary-level hospital, and a second group consisted of patients referred from a secondary-level hospital. We excluded patients with a history of intellectual disability. Those without complete medical files were removed from the final analysis.

**Sample**: The next formula was used to determine the sample to be evaluated.

$$n_0 = \frac{\left(Z_\alpha\sqrt{2p(1-p)} + Z_\beta\sqrt{p_1(1-p_1)+p_2(1-p_2)}\right)^2}{(p_1-p_2)^2};$$

no = required subjects in each of the samples
Zα = Z alpha corresponding to the 1.645
Zβ = Z beta value corresponding to 1.282
p1 = Value of the proportion of pregnancies without complications in patients with autoimmune disease receiving a high-level medical attention = 90%.
p2 = Value of the proportion of pregnancies without complications in patients with delay in attention by a third level hospital = 25%.
p = Mean of the two proportions p1 and p2.

After substituting the values, no = 7.89 patients per group.

**Clinical follow-up**: The patient's demographic data and family history were obtained from the clinical history in the medical chart, and all the information was recorded in an Excel spreadsheet designed for this purpose. Because this was a retrospective and descriptive study, the latter was considered without risk and without the need to employ an informed consent form. The protocol was approved by the research ethics committee of the HMPMPS and it was adhered to the Declaration of Helsinki (Fortaleza, Brazil).

**Statistical Analysis:** Variables were represented in frequencies. Odds ratio (OR) with 95% confidence interval (CI) was calculated for the risk of a patient of any group to have a complicated pregnancy. For the categorical variable "Presence/Absence" of complication, a logistic regression was done for the nominal variables "Group" and "Treatment scheme". The multinomial logistic regression was performed with 12 possible combinations of complications, and five registered combinations of antirheumatic treatments. A p-value ≤ 0.05 was considered statistically significant. All tests were performed with SPSS version 20 (SPPS, Inc., Chicago, IL, USA).

## RESULTS

Seventeen cases of pregnant patients with autoimmune diseases were treated, including six with SLE, four with RA, four with primary APS, two with systemic sclerosis (SS), and one with mixed connective tissue disease (MCTD). Average ages for these were 26.8, 28.5, 23.5, 26.5, and 22 years, respectively. Of all of the patients, eight were cared for throughout their gestation at HMPMPS, and nine were referred from other non-specialized hospitals. The former reached 37.8 weeks of gestation (WG) and the second, 34.1 WG. The medical management of each patient is shown in Table 1.

Data such as the socioeconomic status of the population group-in-question were also measured and we found that the study patients belonged in 76.4% to the low-income categorization in Mexico (less than 461 US$ per month) and 23.5% were referred as medium-income (> 461 and < 2051 US$ per month). According to the gynecological and obstetrical analyses performed on these patients, five patients with SLE were found to be primigravidae and only one was multigesta; one patient with RA was primigravida, another patient was in her second pregnancy, and only one was multigesta. Among patients with APS, one was primigravida, three secundigravidae, and one was multigesta. The two patients with SS were primigravidae, and finally, the patient with MCTD was secundigravida.

Of note, 42 family members of the patients seen had one of the autoimmune diseases (SLE, RA, SS, or MCTD) and 17 (40.5%) of the patients had at least one family member who had the same disease (Table 2).

Regarding location of care during pregnancy and its relation to outcomes, there were greater number of complications, which also were more severe, in those treated in other non-specialized hospitals, thus increasing risk at time-of-delivery (Table 3). In addition, there were two perinatal deaths — these patients were receiving treatment in non-specialized hospitals at the beginning of their gestations. Of the deliveries seen in other hospitals, seven of nine infants had a birthweight of < 2,500 g compared to deliveries

**Table 1. Medical Management of Patients**

| Patient | Diagnosis | Therapy | Annotations |
|---|---|---|---|
| 1 | Rheumatoid arthritis | CFT + DCF+ PTTH + PDN | |
| 2 | Rheumatoid arthritis | PDN | |
| 3 | Rheumatoid arthritis | PDN | |
| 4 | Rheumatoid arthritis | AMP + OMP + PDN | |
| 5 | SLE | CFT + DOPA + ENX + FM + HZN + MPS (pulses) + NFP + PD +PDN + TLM | |
| 6 | SLE | CFT + DMP + DXM + ENX + HZN + PDN + TLM | |
| 7 | SLE | AML + CFT + CTC + DOPA + DXM + ENX + FM + HZN + PD + TLM | MV (76 h) |
| 8 | SLE | AML + CFT + DOPA + DXM + FM + HZN + PD + PDN + sHEP | MV (42 h) |
| 9 | SLE | CFT + DXM + ENX + HXC | |
| 10 | SLE | CFT + PDN + sHEP | |
| 11 | SLE | CFT + NFD + PTP + SCR | |
| 12 | PSS | FT/SLM + RNT + SCR | |
| 13 | MCTD | AZT + CFT + DXM + ENX + HZN + PDN + TLM | Exacerbation in the immediate puerperium |
| 14 | AFS | Prior to admission to the HMPMPS: DXM + MD + EC (3 U) + PLT for HPTX. In the HMPMPS: PA (10 U), AHT (CVD/LST/NFD/PZN/) + ATB (CLM/LFX / MRP) + ENX + FM + HPD + NTP + SD (MDZ/PPF-DMT) + TFS + TT + CPR (29 U) + EC (14 U) + FFP (9 U) + rFVII (2 flasks) + PD (103) + EN | MV (312 h) in the HMPMPS |
| 15 | AFS | ASA + CFT + ENX + HZN + PDN + TLM | |
| 16 | AFS | AMP + PDN + TLM | |
| 17 | AFS | AMP + ASA + PDN | |

*AFS: antiphospholipid syndrome, AHT: antihypertensives, AML: amlodipine, AMP: ampicillin, ASA: acetylsalicylic acid, ATB: antibiotics, AZT: azathioprine, CFT: ceftriaxone, CLM: clindamycin, CPR: cryoprecipitates, CTC: citicoline, CVD: carvedilol, DCF: diclofenac, DMT: dexmedetomidine, DOPA: dopamine, DPM: desmopressin, DXM: dexamethasone (Magann doses), EC: erythrocyte concentrates, EN: enteral nutrition, ENX: enoxaparin, FFP: fresh frozen plasma, FM: furosemide, FT/SLM: fluticasone/salmeterol, HMPMPS: "Mónica Pretelini Sáenz" Maternal-Perinatal Hospital, HPTX: hemopneumothorax, HPR: haloperidol, HXC: hydroxychloroquine, HZN: hydralazine IV, LFX: levofloxacin, LST: losartan, MCTD: mixed connective tissue disease, MD: methyldopa, MDZ: midazolam, MPS: methylprednisolone, MRP: meropenem, MTC: metoclopramide, MV: mechanical ventilation, NFD: nifedipine, NTP: nitroprusside, OMP: omeprazol, PA: platelet apheresis, PD: peritoneal dialysis, PDN: prednisone, PLT: pleurotomy, PPF: propofol, PSS: progressive systemic sclerosis, PTP: pantoprazol, PTTH: phototherapy, PZN: prazosin, rFVII: Recombinant factor VII, RNT: ranitidine, SC: subclavian catheter, SCR: sucralfate, SD: sedation, sHEP: subcutaneous heparin, SLE: systemic lupus erythematosus, TLM: telmisartan, TFS: transfusions, TT: tracheostomy, U: units*

**Table 2. Hereditary family history in the clinical history in women with autoimmune diseases**

| | Autoimmune disease present in pregnancy | | | |
|---|---|---|---|---|
| Hereditary family history | APS (N = 4) | RA (N = 4) | SLE (N = 6) | SS (N = 2) |
| Cancer in family members | | | 1 | |
| Familiar thromboembolic disease | 1 | | | |
| Family Preeclampsia | 3 | | 2 | |
| Hypertension | | 1 | 1 | |
| IURG in the family | | | 4 | |
| Other autoimmune diseases in the family | | | | 5 |
| Same illness in the family | 1 | 8 | 4 | 4 |
| T2DM in the family | 6 | | 1 | |
| Total | 11 | 9 | 13 | 9 |

*APS: primary antiphospholipid syndrome, IUGR: intrauterine growth restriction, RA: rheumatoid arthritis, SLE: systemic lupus erythematosus, SS: systemic sclerosis, T2DM: Type 2 Diabetes mellitus*

**Table 3. Acute complications**

| Complication | Institution | |
|---|---|---|
| | HMP-MPS (N = 8) | Referred from other hospital (N = 9) |
| Acute renal failure | | 4 |
| Anemia | | 5 |
| Associated hepatopathy during pregnancy | | 2 |
| Bacterial pneumonia | | 2 |
| Cerebral hemorrhage | | 2 |
| Diabetes insipidus | | 1 |
| Exacerbation of autoimmune disease in the puerperium | 1 | 0 |
| Oligohydramnios | 1 | 0 |
| Peptic ulcer disease | | 1 |
| Polyhydramnios | 1 | 0 |
| Premature membrane rupture | 1 | 0 |
| Proteinuria | | 4 |
| MATHI | | 2 |
| MODS | | 1 |
| Thrombocytopenia | | 4 |
| Total | 4 | 28 |

*HMPMPS: "Mónica Pretelini Sáenz" Maternal-Perinatal Hospital, MATHI: thrombotic microangiopathy with intravascular hemolysis, MODS: multiple organ dysfunction syndrome*

at HMPMPS, in which one of eight infants had a birthweight of < 2,500 g.

Of the six SLE patients, two (33.3%) had recurrent infections (two or more infections during pregnancy), four (66.7%) had constitutional manifestations, two (33.3%) had oral ulcers, and one (16.66%) had hyperemesis gravidarum (HG). Of the patients with RA, four (100%) had repetitive infections, one (25%) had thromboembolic phenomena, and one (25%) had constitutional manifestations. Of the patients with primary APS, one (25%) had recurrent infections, two (50%) had thromboembolic phenomena, and one (25%) had hemorrhagic phenomena. Of the patients with SS, one (50%) presented with constitutional manifestations, one (50%) was malnourished, and one (50%) had Raynaud's phenomenon. Finally, the patient with MCTD had repetitive infections.

According to the established rheumatologic treatment, once the women became pregnant, eight patients were treated with prednisone alone, two patients were receiving prednisone and acetylsalicylic acid, one patient was managed with prednisone and diclofenac, and one patient received hydroxyquinoline. By their own decision, four patients suspended treatment for their autoimmune disease, one woman that was asymptomatic, another that suffered from bronchospasms, a third one operated of hemopneumothorax and the last case in chronic dialysis. The OR of having a complication in the hospitals of reference compared to the HMPMPS was 29.8 (95% CI: 1.287-692.46, Z statistic 2.11, p = 0.0342). In relation to the logistic regression, this test was not significant for the type of hospital the patient was in or for the treatment scheme for the presence of at least one complication. The multinomial logistic regression did not show again significant predictive probabilities neither for the type of hospital the patient was in nor for the drug treatment scheme. Actual status of the patients is summarized in Appendix 1.

## DISCUSSION

These results demonstrate that there are more complications in pregnancies of mothers with autoimmune diseases when they are cared for in non-specialized hospitals, with an OR almost reaching 30, increasing the risks for both mother and baby.

A study by Ngian et al. [10] showed that pregnant women with RA usually take a longer time to conceive, are more likely to have a Cesarean delivery, and are more likely to have complications such as preeclampsia, and in many cases can deliver prematurely or have miscarriages, low-birthweight infants and postpartum complications. However, patients with a well-controlled RA during their pregnancy had favorable outcomes. In this regard, our study results were similar in that the majority were primigravidae, all had repetitive infections and some had infants with low birthweight. In contrast, another case-control study by Postfai et al. [9] found that mothers with RA had low socioeconomic status and the most frequent complication was iron deficiency anemia; furthermore, there was a higher incidence of acute diseases (Influenza-common cold and affection of the respiratory, digestive and urinary tract systems and in genital organs) compared to healthy mothers. Finally, Postfai et al. found that a small percentage of infants from mothers with RA were low birthweight, which is in agreement with our study as we documented that these patients presented more acute complications than usual for a normal pregnancy.

A study by Schreiber et al. in women with SLE corroborated that if good disease control is maintained in pregnancy, complications can be reduced [11]. A more recent study suggests that alteration in T-helper cell 17 leads to SLE activation, decreasing regulatory T cell levels, leading to increased cytokine and autoantibody proliferation rates, increasing the disease severity [12]. Obviously, conducting this type of molecular study, although desirable, lies outside of routine practice; thus, clinical evaluation remains the principal tool to determine the course of a rheumatic disease in pregnancy.

Available pharmacological alternatives have increased over the last decade [13]. This has reduced the risk of teratogenic effects because, for example, tumor necrosis factor alpha (TNF-α) inhibitors are promising for maintaining remission in rheumatologic patients and these may be continued for at least the first half of the pregnancy [14]. One limitation for implementing this least harmful option is cost; therefore, more economical drugs are expected to be developed. In this respect, preliminary studies have demonstrated that phototherapy reduces the expression of TNF-α [15,16], posi-

tioning it as an alternative in women with autoimmune diseases, yet to our knowledge no guidelines have been established for this potential treatment.

Given the results of the logistic and multinomial regressions, it appears that the better outcome in the patients who were managed in a specialized hospital was not due to a better pharmacological scheme, on the contrary, it is likely that the availability of a multitude of resources, including multispecialty attention and laboratories, result in better outcomes.

A limitation of this study is the low number of cases, but the findings of this study are still valuable as publications on rheumatological diseases in pregnancy are not as numerous as expected. For example, Galapatthy et al. [17], described that from a full population cohort of 72 women with SLE three became pregnant and underwent successful pregnancies. In a screening performed by Spinillo et al. [18] in 2,458 pregnant women in their first trimester, the authors identified 62 (2.5%) women with previously undiagnosed undifferentiated connective tissue disease and 24 (0.98%) women with previously undiagnosed definite systemic rheumatic disease.

In summary, we found that pregnant women with autoimmune diseases can have up to seven times more complications when they are not seen by skilled personnel. As a result of this observation, it is important for pregnant women with an autoimmune disease to attend specialized hospitals and be cared for by highly trained personnel. This can reduce risks and increase the chances of a good outcome both in the gestation period and at time-of-delivery. Another more realistic solution could be training physicians employed at non-tertiary hospitals to start the most appropriate treatment schemes. Along these lines, a possible tool to evaluate skill in the treatment of autoimmune diseases during pregnancies could be reduction in relative risk (RR) for complications when pregnant women are seen by non-specialized institutions. How much should be an acceptable RR? This evaluation method could be not restricted to rheumatologic disease only but could be used for any disease.
The narrower the margin of difference between a specialized hospital or one of the second level of care, the more qualified the health system as a whole will be to treat this type of pathology.

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**Appendix 1. Actual status of the patients**

| Patient | Diagnosis | Evolution |
|---|---|---|
| 1 | Rheumatoid arthritis | After delivery (cesarea) she was treated with PDN, MTX and PTTH, the RAQoL test decreased from 56 in immediate puerperium to 17 after four years. Last medical visit was on September 2017 when she moved to the north of Mexico. |
| 2 | Rheumatoid arthritis | Her baby was born by vaginal delivery. She missed several medical appointments. She was treated with DMARDs. She was programmed for puncture-aspiration and steroid application for hemarthrosis in the left knee but she no longer returned after June 2015. |
| 3 | Rheumatoid arthritis | After delivery (cesarea) she received MTX, SSZ and PDN for seven months and she did not return. Last medical visit on May 2012. |
| 4 | Rheumatoid arthritis | After pregnancy interruption through vaginal delivery she had a 41 joints with pain and a RAQoL of 30. She was prescribed a treatment with HXC, MTX, PDN and PTTH. The symptomatology had a remission after seven weeks and she is actually on treatment with only MTX. Las medical visit on June 2019. |
| 5 | SLE | Pregnancy attended by caesarean section and after two months she was referred to her medical service. Last medical consultation on 2011. |
| 6 | SLE | Pregnancy attended by caesarean section and was treated with PDN and dipyridamole. Last medical visit on 2010. |
| 7 | SLE | She have had repeated upper respiratory infections and depression. Las medical visit on May 2019. |
| 8 | SLE | She was programmed for renal biopsy but she did not return. Last medical visit on 2010. |
| 9 | SLE | She was kept on treatment based on PDN until March 2010 when she moved to USA. |
| 10 | SLE | The maintenance treatment was based on PDN, statins and fibrates but PDN was suspended when she was diagnosed with depression and was changed to HXC. |
| 11 | SLE | Pregnancy attended by caesarean section and almost immediately she changed of medical health insurance system. |
| 12 | PSS | First pregnancy attended by cesarean on July 2011. She only came back for two medical consultations and did not return until the year 2016 with a second pregnancy attended again by cesarean section on August 2016 and did not come back until a third pregnancy on 2018 leading to a third cesarea. Last medical visit on January 2019. |
| 13 | MCTD | Pregnancy attended by caesarean section. She experienced clinical deterioration despite treatment with AZT, MTX and high doses of PDN, so was referred to a National Institute of Health on December 2011. |
| 14 | AFS | She required cesarean surgery plus hysterectomy. Maintenance treatment was with ASA and dipyridamole and was referred to her local General Hospital in the year 2010. |
| 15 | AFS | She was submitted to cesarean surgery and chronic treatment was established with warfarin and after two months of follow-up she moved to another Mexican State (year 2009). |
| 16 | AFS | She was submitted to vaginal delivery but the baby died in utero. She was receiving multidisciplinary treatment to be in good health condition for another pregnancy but she moved to another Mexican State (year 2010). |
| 17 | AFS | Pregnancy attended by caesarean section. After the third medical consultation she did not return to the Hospital (year 2010). |