ISSN 2689-8268 | Volume 4

American Journal of Surgery and Clinical Case Reports

Research Article Open Access

Adverse Pregnancy Outcomes in Patients with Systemic Lupus Erythematosus: The Role of Medication. Experience from A Single Tertiary Referral Center

Irene Dalpiaz[1], Valentina Canti[2*], Rebecca De Lorenzo[2], Maria Bernadette Cilona[2], Chiara Asperti[2], Girardelli Serena[1], Susanna Rosa[1], Maria Teresa Castiglioni[1] and Patrizia Rovere- Querini[2]

[1]Gynecology and Obstetrics Department, I.R.C.C.S. San Raffaele Hospital, University Vita-Salute, Milan, Italy

[2]Unit of Internal Medicine & Division of Immunology, Transplantation and Infectious diseases, I.R.C.C.S. San Raffaele Hospital, University Vita-Salute, Milan, Italy

[*]Corresponding author:

Valentina Canti,
Unit of Internal Medicine, IRCCS San Raffaele Hospital and University Via Olgettina, 60, 20132. Milano, Italy, Tel: +39 0226436768;
E-mail: canti.valentina@hsr.it

Received: 02 May 2022
Accepted: 23 May 2022
Published: 27 May 2022
J Short Name: AJSCCR

Citation:

Valentina Canti, Adverse Pregnancy Outcomes in Patients with Systemic Lupus Erythematosus: The Role of Medication. Experience from A Single Tertiary Referral Center. Ame J Surg Clin Case Rep. 2022; 4(16): 1-8

Keywords:

SLE; Pregnancy; Adverse pregnancy outcomes; Glucocorticoids; Azathioprine

1. Abstract

1.1. Objectives

To investigate whether treatment in SLE patients during pregnancy may influence the occurrence of adverse pregnancy outcomes (APO).

1.2. Methods

We performed a monocentric observational study in SLE pregnant patients prospectively followed at the 'high risk obstetrics' multidisciplinary outpatient clinic at San Raffaele Hospital, Milan, Italy from January 2003 to June 2021. We collected data from 58 SLE patients and 79 pregnancies. We also compared maternal and neonatal outcomes between pregnancies occurring before and after 2010.

1.3. Results

Thirteen out of 79 (16%) pregnancies had spontaneous abortions; in the other 66/79 (84%) APOs occurred in 29/66 (44%) pregnancies. Seventeen of them were SGA infants. Glucocorticoid treatment at medium-high-dosage was associated with an increased risk for APO (OR 4.431, p-value 0.018) and for SGA infants (OR 4.401, p-value 0.019). Preterm delivery (7/43, 16% versus 7/23, 30%), hypertension and/or preeclampsia (4/43, 9% versus 5/23, 22%) were observed with a lower incidence in those pregnancies occurring after 2010.

1.4. Conclusion

Our study supports the fact that treatment with glucocorticoids at medium-high-dosage during pregnancy adversely affects pregnancy outcomes with an increased risk of both APO and birth of SGA infants. These data can be related to both a direct action of the drug in determining maternal- fetal outcome and to an incomplete control over disease activity. The comparison between pregnancies occurring before and after 2010 shows that the introduction of drugs such as hydroxychloroquine and azathioprine from the beginning of the pregnancy can reduce the frequency of APO and allow a better control of autoimmune diseases.

2. Introduction

Systemic Lupus Erythematosus (SLE) is a multisystemic autoimmune disease with a female predilection, affecting mainly young women during childbearing age. It is important to consider not only the rheumatological aspects of the disease but even its impact on reproduction, pregnancy and lactation. For many years pregnancies in women with SLE were contraindicated; today, pregnancies in SLE patients are common, even though they are still considered high-risk due to the higher incidence of adverse pregnancy outcomes (APO) when compared to pregnancies in women without autoimmune diseases1. Thanks to the improvement of SLE disease activity prior to conception and during pregnancy we have achieved a significant reduction in miscarriages and complications during pregnancy, reaching 80-90% of successful pregnancies2 with a significant decrease in the rate of pregnancy losses, from 43% in the period between 1960-1965 to 17% in 2000-20033. Even with the optimization of pregnancy management in SLE patients, there is still a high incidence of APO including spontaneous abortion and stillbirth, prematurity, intrauterine growth restriction

(IUGR) and small for gestational age (SGA) babies, gestational hypertension and/or preeclampsia and neonatal lupus. SLE patients need proper counseling before conception in order to evaluate the disease activity and to choose the best medication to use during pregnancy, both for the mother and the fetus. A multidisciplinary approach involving a rheumatologist and a gynecologist with experience in high- risk pregnancies is the best strategy to approach and manage these patients. There are two crucial points that need to be addressed in SLE treatment during pre-conceptional counselling and during pregnancy: [1]. The lowest disease activity prior and during pregnancy, in order to minimize the risk of flares; [2]. The choice of adequate medication with the least possible risk of adverse maternal/fetal effects. Over the years, trends in the management of SLE in pregnancy have changed, leading to an increased use of drugs such as hydroxychloroquine (HCQ) and azathioprine (AZA) from 2010, currently among the first choices for medication in these gestations compared to the more traditional glucocorticoid-based treatments. Many studies have reported a role of high-dose glucocorticoids in the development of APO, in particular with regards to neonatal prematurity4–8 and SGA neonates9. Many publications agree on the relevant role of aggressive high-dose glucocorticoid- based treatment in contributing to increasing APO, however it remains to be clarified whether there is a parallel role of poor disease control as several studies also report an increased risk of APO in pregnancies with SLE flares 10–13.

3. Materials and Methods

3.1. Study Design and Population

We performed a monocentric observational study of SLE pregnant patients followed prospectively in the 'high risk obstetrics' multidisciplinary outpatient clinic at San Raffaele Hospital, Milan, Italy from January 2003 to June 2021. We collected data from 79 pregnancies in 58 patients with a diagnosis of SLE accordingly to the 1997 ACR criteria14. All patients also satisfied the 2019 EULAR/American College of Rheumatology criteria15. We compared 23 pregnancies in SLE patients before 2010 to 43 pregnancies occurring from 2010 to June 2021.

Approval was obtained from the Comitato Etico Ospedale San Raffaele, Milan, Italy (protocol "MED-Mol" PI Patrizia Rovere-Querini N. 62/INT/2021). This study was conducted in accordance with the Declaration of Helsinki.

3.2. Pregnancy Management

The patients were followed with monthly multidisciplinary appointments at the 'High Risk Obstetrics' outpatient clinic all through pregnancy and the routine post partum follow-up (forty days after delivery). In 50 pregnancies (63%) the patients underwent pre-conceptional counselling and an accurate medical history was collected in order to assess disease activity and drug history. When necessary, medication modifications were approved in order to obtain a safer and more effective disease control. Teratogenic drugs were discontinued in the pre-conceptional period in order to ensure wash out when necessary. Patients were also tested for several autoantibodies, in particular for anti- phospholipids (aPL) (anticardiolipin antibodies (aCL IgG and IgM), anti–beta2-glycoprotein I antibodies (aβ2GPI IgG and IgM) assessed by ELISA (QUANTA Lite), and lupus anticoagulant (LAC)) and anti-Ro/SSA and anti-La/SSB; however, anti-double strand DNA (aDNA) and anti- nucleus (ANA) where not regularly tested for. During pregnancy, patients were monitored monthly with physical examination, laboratory tests including complete blood count, C reactive protein (CRP) and urine analysis. During each trimester of pregnancy we evaluated SLE disease activity by using the systemic lupus erythematosus disease activity index, SLEDAI-2K16. Serial obstetric ultrasounds to monitor fetal growth and uterine artery pulsatility indices were also performed and recorded routinely.

4. Definitions

SLE flares were defined by increase in SLEDAI-2K value, new SLE symptoms or requirement to change treatment16. Spontaneous abortions were defined as spontaneous interruptions of pregnancy prior to the 22nd17 week of gestation, with a distinction between early and late miscarriage using a cut-off of 10 weeks of gestation.

We included the following in the definition of adverse pregnancy outcomes (APO):

- Gestational hypertension: hypertension developing during pregnancy starting from the 20th week of gestation, characterized by systolic pressure higher than 140 mmHg and/or diastolic pressure higher than 90 mmHg18.

- Preeclampsia: hypertension developing during pregnancy starting from the 20th week of gestation, characterized not only by systolic pressure higher than 140 mmHg and/or diastolic pressure higher than 90 mmHg but typically also by proteinuria >0.3 g/24 h18. Recent guidelines also suggest the following as complications that should be considered when diagnosing pre-eclampsia even in the absence of significant proteinuria: renal, haematological, hepatic or neurologic involvement, pulmonary oedema, fetal growth restriction or placental abruption.

- Small for gestational age babies: newborn with weight lower than the 10th percentile at birth using INeS anthropometric tables19.

- Late preterm: delivery between 34 and 36+6 wg; moderate preterm: delivery between 32 and 33+6 wg; early preterm: delivery between 28 and 31+6 wg; very early preterm: delivery before 28 wg17.

- Stillbirth or intrauterine fetal death (IFD): fetal death after 24 gestational weeks17.

5. Statistical Analysis

Statistical analysis was performed with IBM SPSS 21.0. Data were analyzed by calculating mean and standard deviation (SD)

for quantitative variables with normal distribution and by calculating frequency and percentage for dichotomous qualitative variables. Analysis of qualitative variables was conducted by chi-square test ($\chi 2$) or Fisher's exact test when appropriate, analysis of quantitative variables by t-test. We considered differences to be statistically significant at $p < 0.05$. Multivariate logistic regression was used in the analysis to identify risk factors for adverse events in pregnancy. The Odds Ratio (OR) and 95% confidence interval (CI) were calculated.

6. Results

Our study included 79 pregnancies in 58 patients recruited between 2003 and June 2021. Thirteen out of 79 (16%) pregnancies underwent spontaneous abortion while 66/78 (84%) evolved to more than 22 weeks' gestation. The study focused on the 66 pregnancies from the 22nd gestational week onwards: in this group we observed 29/66 (44%) adverse pregnancy outcomes (APO). By analyzing the proportion of each complication included in the definition of APO we found: 9/66 (14%) patients with gestational hypertension and preeclampsia, 17 (26%) patients with small for gestational age (SGA) fetuses and 14/66 (21%) preterm deliveries. Of the latter, 10/14 were late or moderate preterm, and 4/14 low or very low preterm. In several pregnancies, more than one type of complication was observed.

7. Baseline Characteristics

We divided the 66 pregnancies in two groups: 29/66 (44%) pregnancies with development of APO (APO+) and 37/66 (65%) pregnancies without APO (APO-). The baseline characteristics between the two groups were similar in terms of mean age and years of autoimmune disease. Pre-conceptional counselling in a similar proportion in the two groups (p-value 0.994) preceded the pregnancy. The mean SLEDAI during pregnancy was higher in the APO+ group (2.9 ± 3.3) than in the APO- group (1.7 ± 2.0), although this was not a statistically significant difference (p-value 0.056). There were also no significant differences between the two groups in term of autoantibody positivity, except for anti-phospholipid antibodies (aPL) (7/37 (19%) in the APO- group and 12/29 (41%) in the APO+ group, p-value 0.045), Table 1. The evaluation of the single aPL specificity, including anti-cardiolipin antibodies (aCL) IgG and/or IgM, anti-β2 glycoprotein (a2-GPI) IgG and/or IgM and lupus anticoagulant (LAC), did not show any significant difference between the two groups. Only one patient (3%) in the APO- group had a "triple positivity", defined as the positivity to both aCL, a2- GPI and LAC, while there were 4 cases (14%) of triple positivity in the APO+ group. Of note, this difference was not statistically significant. We also analyzed the differences in the two groups of patients considering the SLE complications prior to pregnancy: in the APO+ group there was a significantly higher rate of anti-phospholipid antibodies syndrome (APS) (p-value 0.018), SLE nephropathy (p-value 0.001) and chronic hypertension (p-value 0.038), as depicted in Table 1. Three out of 8 (40%) APS experienced a thrombotic event and 5/8 (60%) had a diagnosis of obstetric APS.

Table 1. Baseline characteristics of APO- and APO+ groups.

	Total n = 66	APO[a]- n = 37 (56%)	APO+n = 29 (44 %)	p
Baseline characteristics:				
Maternal age	32.6 ± 4.4	32.8 ± 4.1	31.1 ± 4.3	0.990
Years of disease	8.8 ± 6.1	9.8 ± 6.1	8.0 ± 5.8	0.376
Pre-conceptional counselling	41 (62%)	23 (62%)	18 (62%)	0.994
Mean SLEDAI during pregnancy	2.2 ± 2.7	1.7 ± 2.0	2.9 ± 3.3	0.056
Autoantibodies:				
ANA[b]	60 (91%)	34 (92%)	26 (89%)	0.754
aDNA[c]	17 (26%)	9 (24%)	8 (28%)	0.764
Ro/SSA; La/SSB	15 (23%)	8 (22%)	7 (24%)	0.809
aPL[d]	19 (29%)	7 (19%)	12 (41%)	**0.045**
aCL[e]	15 (23%)	7 (19%)	8 (28%)	0.404
a2-GPI[f]	9 (14%)	5 (13%)	4 (14%)	1.000
LAC[g]	8 (12%)	3 (8%)	5 (17%)	0.258
Triple positivity	5 (8%)	1 (3%)	4 (14%)	0.160
SLE complications				
APS[h]	8 (12%)	1 (3%)	7 (24%)	**0.018**
Nephropathy	8 (12%)	0 (0.0%)	8 (28%)	**0.001**
Chronic hypertension	7 (11%)	1 (3%)	6 (21%)	**0.038**

(α) APO: adverse pregnancy outcome; (b) ANA: antinuclear antibodies; (c) aDNA: (d) anti-dsDNA antibodies; (d) aPL: anti-phospholipid antibodies; (e) aCL: anti-cardiolipin antibodies; (f) aβ2-GPI: anti-β2-glycoprotein I antibodies; (g) LAC: lupus anticoagulant; (h) APS: anti-phospholipid syndrome.

7.1. SLE Treatment and Adverse Pregnancy Outcomes

We compared APO- and APO+ groups to assess whether there was any significant difference in treatment during pregnancy. In the APO+ group we observed a higher use of both low-dosage aspirin (LDA) and low molecular weight heparin (LMWH) (16% vs 41%, p-value 0.023), due to the higher rate of aPL positivity in this group of patients. Moreover, a medium-high dosage of glucocorticoids (≥ 5 mg) (19% vs 48%, p-value 0.011) was found in APO+ group due to a higher number of flares during these pregnancies (8/29, 28%) versus only in 1/37 (3%) in APO-, Table 2.

We conducted a multivariate analysis looking for a role of high-dose glucocorticoid in pregnancy outcomes, considering several drugs used during pregnancy in SLE patients. In patients treated with high-dose glucocorticoids, we observed both an increased incidence of APO (OR 4.431, p-value 0.018) and SGA infants (OR 4.401, p-value 0.019), Tables 3a and 3b. Moreover, we studied the association between APO and SLE complications during and prior to pregnancy, considering SLE flares, anti-phospholipid syndrome (APS) and chronic hypertension. The multivariate analysis showed a correlation between APO and both SLE flares (OR 8.669, p-value 0.029) and APS (OR 8.152, p-value 0.038), Table 4.

Table 2. Treatment and flares in APO- and APO+ groups.

	APO- n = 37 (56%)	APO+ n = 29 (44 %)	**p**
Treatment:			
HCQ[a]	26 (70%)	18 (62%)	0.483
AZA[b]	10 (27%)	14 (48%)	0.075
LDA[c]	24 (65%)	22 (76%)	0.335
LDA + LMWH[d]	6 (16.2%)	12 (41%)	**0.023**
Glucocorticoids < 5 mg	8 (22%)	4 (14%)	0.413
≥ 5 mg	7 (19%)	14 (48%)	**0.011**
Flares	1 (3%)	8 (28%)	**0.008**

(α) HCQ: hydroxychloroquine; (b) AZA: azathioprine; (c) LDA: low-dosage aspirin; (d) LMWH: low molecularweight heparin.

Table 3a. APO risk and treatment during pregnancy.

	OR (CI 95%)	**p**
AZA[a]	1.527 (0.439-5.312)	0.508
LDA[b] + LMWH[c]	3.605 (0.865-15.025)	0.071
Glucocorticoids ≥ 5 mg	4.431 (1.231-15.951)	**0.018**

(α) AZA: azathioprine; (b) LDA: low-dosage aspirin; (c) LMWH: low molecular weight heparin.

Table 3b. SGA risk and treatment during pregnancy.

	OR (CI 95%)	**p**
AZA[a]	1.265 (0.317-5.048)	0.714
LDA[b] + LMWH[c]	2.682 (0.655-10.985)	0.171
Glucocorticoids ≥ 5 mg	4.401 (0.317-5.048)	**0.019**

(α) AZA: azathioprine; (b) LDA: low-dosage aspirin; (c) LMWH: low molecular weight heparin.

Table 4. APO and SLE complications during and prior to pregnancy.

	OR (CI 95%)	**p**
Flares	8.669 (0.916-82.042)	**0.029**
APS[a]	8.152 (0.846-78.518)	**0.038**
Chronic hypertension	5.765 (0.555-59.919)	0.592

(a) APS: anti-phospholipid syndrome.

7.2. Pregnancies Before and after 2010

Between 2003 and June 2021, we observed 66 successful pregnancies: 23/66 (35%) were reported before 2010 and 43/66 (65%) after 2010. We also analyzed SLE disease characteristics and pregnancy outcomes between these two groups of patients. The two groups were homogeneous in terms of baseline characteristics and SLE complications (Table 5). The different therapeutic approach between the two groups of patients is depicted in table 6. Treatment at the beginning of pregnancy was different in the two groups: in the pregnancies occurring in the last decade we used more hydroxychloroquine (HCQ) and azathioprine (AZA), while reducing the use of medium-high dosage (≥ 5 mg) glucocorticoids, $p < 0.005$. No significant differences were observed in the use of low-dosage (<5 mg) glucocorticoids. Thirty-four out of 43 (79%) patients between 2010 and 2021 and 8/23 (35%) pregnancies occurring before 2010 were treated with HCQ (p-value <0.001). During the first trimester of pregnancy, 2/23 (9%) and 14/43 (33%) pregnancies before and after 2010 respectively were treated with AZA (p-value 0.037). The use of high-dose glucocorticoid decreased from 48% before 2010 to 23% after 2010, p-value < 0.05. We did not observe significant differences between the two groups in terms of use of LDA and LDA + LMWH. We also evaluated if there were any differences in SLE flares between the two groups of pregnancies: SLE flares complicated 5/23 (22%) pregnancies before 2010 and 4/43 (9%) pregnancies after 2010. This difference is not statistically significant. Pregnancy outcomes were different in patients before and after 2010 (Table 7); the gestational week at delivery was 36.4 ± 4.0 in the first group and 37.7 ± 2.1 in the second, p-value 0.006. Birth weight was lower for infants in pregnancies occurring before 2010, 2617 ± 802 g compared with 2825 ± 526 g for infants born from 2010 to 2021 (p-value 0.049). This is likely to be due to the higher number of premature deliveries. The placental weight was similar in the two groups. The difference between the two groups was not significant in terms of preterm delivery, even if the proportion of cases was higher before 2010 (30% vs 16%, p-value 0.180) particularly for early or very early preterm deliveries (13% vs 2%, p-value 0.080). Even without statistical significance, in the last decade the rate of chronic hypertension and/or preeclampsia was found to be lower (4/43, 9% versus 5/35, 28%) and similar to the one of a non-SLE pregnancy. In fact, hypertensive disorders affect as many as 10% of all pregnancies worldwide20. Furthermore, a similar rate of SGA was observed (6/23 (26%) and 11/43 (26%), respectively), while the rate of vaginal deliveries increased in the last decade from 26% to 51% (p-value 0.050).

Table 5. Baseline characteristics in pregnancies before 2010 and since 2010.

	Before 2010 n = 23 (35%)	From 2010 to 2021 n = 43 (65%)	p
Baseline characteristics			
Maternal age	30.5 ± 3.6	34.0 ± 4.3	0.229
Years of disease	8.5 ± 5	9.3 ± 6.1	0.706
Pre-conceptional counselling	14 (61%)	27 (63%)	0.878
SLE complications			
Active disease at conception	10 (44%)	22 (51%)	0.522
Nephropathy	5 (22%)	3 (7%)	0.115
Chronic hypertension	4 (17%)	3 (7%)	0.277

Table 6. SLE flares and Treatment in the first trimester of pregnancy before and from 2010.

	Before 2010 n = 23 (35%)	From 2010 to 2021 n = 43 (65%)	**p**
First trimester of gestation			
HCQ[a]	8 (35%)	34 (79%)	**<0.001**
AZA[b]	2 (9%)	14 (33%)	**0.037**
LDA[c]	17 (74%)	29 (67%)	0.586
LDA + LMWH[d]	7 (30%)	11 (26%)	0.673
Glucocorticoids			
< 5 mg	5 (22%)	7 (16%)	0.739
≥ 5 mg	11 (48%)	10 (23%)	**0.041**
Flares	5 (22%)	4 (9%)	0.258

(a) HCQ: hydroxychloroquine; (b) AZA: azathioprine; (c) LDA: low-dosage aspirin; (d) LMWH: low molecularweight heparin.

Table 7. Pregnancy outcome in pregnancies before and since 2010.

	Before 2010 n = 23 (35%)	From 2010 to 2021 n = 43 (65%)	**p**
Week at delivery	36.4 ± 4.0	37.7 ± 2.1	**0.006**
Preterm	7 (30%)	7 (16%)	0.180
Late or moderate preterm	4 (17%)	6 (14%)	0.730
Low or very low preterm	3 (13%)*	1 (2%)	0.080
SGA infants	6 (26%)	11 (26%)	0.964
Gestational hypertension and/or preeclampsia	5 (22%)	4 (9%)	0.258
Type of delivery:			
Vaginal delivery	6 (26%)	22 (51%)	**0.050**
ELCS[a]	13 (56%)	12 (28%)	**0.022**
EMCS[b]	4 (17%)	9 (21%)	1.000
Birth weight	2617 ± 802	2825 ± 526	**0.049**
Placental weight	468 ± 126	445 ± 137	0.652

*Infant with severe prematurity, born alive at 25 weeks of gestation and dead after 48 hours

(a) ELCS: Elective lower segment caesarean section; (b): EMCS: emergency caesarean segment.

8. Discussion

Our study investigated how different treatments could influence the pregnancy outcome in SLE patients. In the 79 pregnancies in our Outpatient Clinic we observed a low frequency in spontaneous abortions (16%), similar to that of the general population (15-20%)21 and in any case lower than that reported by other studies in SLE patients (23.3-29.2%)22–24. In literature, one or more adverse pregnancy outcomes (APO) complicates from 19.0% to 83.5% of SLE pregnancies that reach the 22nd week of gestation25,26; in our study APO were observed in 44% of successful pregnancies, which is lower than that reported by Barnado27 (51.7%) and Andrade28 (63.7%). The use of high-dose glucocorticoids was most adopted in pregnancies complicated by APO. Forty-four percent of pregnancies included in this group received glucocorticoid-based treatment. This confirms the association between high-dose glucocorticoids and APO, considering both the variety of events included in the definition of APO (OR 4.4, p-value 0.018) and the birth of small for gestational age (SGA) infants (OR 4.401, p-value 0.019) (Tables 3a and 3b). Our result agrees with many other studies that describe a role of high-dose glucocorticoids in the development of APO, in particular in prematurity and intrauterine growth restriction (IUGR). Chen29 described an association between glucocorticoids and prematurity, preeclampsia and stillbirth, although the dosage defined as high- dose was higher (>20 mg) than the one in our study. Chakravarty30 reported a correlation between prednisone used at the beginning of pregnancy and prematurity, with a relative risk (RR) of 1.8. In 2009, De Man31 suggested the use of high-dose glucocorticoids as not being directly correlated with the birth of SGA infants but with the birth of premature infants. Although most authors agree on the role of high-dose glucocorticoid treatment in the development of APO, it is necessary to consider that the choice of this therapeutic approach often derives from an SLE flare during pregnancy, which represents a risk factor for APO regardless of ongoing treatment32–34. An autoimmune disease flare was observed in 17% of pregnancies included in our study that reached the 22 weeks' gestation. In agreement with previous literature, flares were more frequent in pregnancies complicated by APO: 8/9 SLE flares were in the group of pregnancies with APO, suggesting a role of flares in the worsening of maternal-fetal outcome. The long period of almost 20 years between 2003 and 2021 within which the management of high- risk SLE pregnancies has developed has led us to question whether there has been an improvement in the management of autoimmune disease in pregnancy and in maternal-fetal outcomes. At the beginning, the therapeutic tools were limited, with little use of hydroxychloroquine (HCQ) and contraindication to the administration of azathioprine (AZA) in the first trimester of pregnancy. Only since 2010, the number of patients treated with HCQ and AZA from the beginning of pregnancy, as well as in the pre-conceptional period, was consistent: we therefore compared pregnancies between 2003 and 2010 and those after 2010. We observed a reduction both in SLE-associated complications, particularly in flares, and in APO such as gestational hypertension, preeclampsia and prematurity, even though the frequency of SGA infants remained high. In a study conducted on a large sample of SLE patients collected between 1988 and 2015, Mehta35 aimed, as in our study, to evaluate the changes made to the management of SLE in pregnancy and respective outcomes. Reductions in maternal mortality and APO events, particularly preeclampsia, were observed, although pregnancies complicated by SLE continue to be associated with a worse maternal-fetal outcome than pregnancies in women not affected by the autoimmune disease. In our study, a therapeutic strategy based on the use of HCQ and AZA with possible associations of low-dose glucocorticoids, was asso-

ciated with a good disease activity control and with a reduction of preeclampsia and/or gestational hypertension to one similar to that of low risk pregnancies20. Moreover, 84% of patients who delivered after 2010 had at term delivery (i.e. ≥ 37 wg) with a mean gestational week of 37.7 versus 36.4 mean gestational weeks' of patients who delivered before 2010 (p.0.006, table 7). In the last decade, 51% of deliveries were vaginal, a significantly different proportion compared to that before 2010 (26%). Consequently, the neonatal weight at delivery were seen to be higher (2825g before 2010 versus 2617g after 2010, p = 0.049) On the contrary, the rate of SGA and the placental weight were not different in the two groups under examination. The persistence of a high frequency in SGA deliveries could partly be explained by alterations in placentation. In 2015, Kim et al.36 described chronic inflammatory lesions of the placenta and reported how the presence of chronic villitis, defined as an inflammatory lesion, are associated with both the birth of SGA infants and premature deliveries. In addition to chronic inflammatory lesions, in the context of vasculopathic autoimmune diseases such as SLE, it is necessary to consider vascular alterations of the placenta that may have a role in the pathogenesis of IUGR, SGA, and prematurity, at described by Marder et al37 in SLE placentas even with uncomplicated pregnancies. Placental tissue in SLE patients shows vascular inflammatory lesions that are indistinguishable from those in preeclamptic placentas playing a potential role in the development of APO. Alterations in placentation may represent the key in understanding why we are able to control pregnancies in SLE patients relatively well but continue to have a high frequency of births of SGA infants. The publications that have investigated placental alterations in SLE pregnancies are few and related to small numbers of patients. For this reason further studies will be necessary both for the identification of the optimal therapeutic strategy to reduce the births of SGA infants and for a better understanding of the mechanisms underlying IUGR and SGA development in pregnancies complicated by SLE.

9. Limits of the Study

Our study has limitations that must be considered when interpreting the results. The small number of patients included and the retrospective nature of the study constitute the two main limitations of the study. The limited number of cases related to some variables considered made it difficult to highlight statistically significant differences and associations.

10. Conclusions

Our study revealed the role of high-dose glucocorticoid treatment in the development of adverse events in the pregnancies of patients affected by SLE, with an association probably due to the coexistence of three factors. (1) the direct role of the drug in determining maternal-fetal outcome, (2) the difficulty in obtaining optimal control of disease activity, (3) a development of maternal-fetal complications of SLE in pregnancy independent of treatment and consisting of alterations in placentation and placental function itself implicated in APO, especially in the birth of SGA infants.

Reviewing the clinical activity in managing pregnancies in SLE patients from 2003 to 2021, it is evident that changes were adopted in the approach to the disease, with increasing use of hydroxychloroquine administration and immunosuppressive treatment with azathioprine from the first trimester of pregnancy. The SLE-flares during pregnancy, the onset of gestational hypertension and/or preeclampsia as well as prematurity proved to be less frequent maternal-fetal complications in the second decade of management of SLE patients' pregnancies. The percentage of delivery at term (e.i ≥ 37 gw) and the rate of vaginal delivery were higher in the last decade. In spite of the evident improvements in the treatment of SLE in pregnancy, there continue to be numerous births of SGA infants: the emerging literature related to anatomic and pathological alterations of the placentas of SLE pregnancies support a pathogenesis of the phenomena of IUGR and SGA independent of a good control of autoimmune disease and of drug use. Future studies are therefore required in order to answer the following two questions: (1) what is the best therapeutic strategy for lupus pregnancies, suitable for optimal SLE control but without harmful effects on fetal outcomes? (2) Is the birth of SGA infants at least partly independent of the control of the autoimmune disease? If so, the mechanism underlying SGA/growth restriction is yet to be fully clarified.

References

1. Moroni G, Ponticelli C. Pregnancy in women with systemic lupus erythematosus (SLE). Eur. J. Intern. Med. 2016; 32: 7-12.
2. Lateef A, Petri M. Managing lupus patients during pregnancy. Best Pract. Res. Clin. Rheumatol. 2013; 27: 435–447.
3. Clark C A, Spitzer K A, Laskin CA. Decrease in pregnancy loss rates in patients with systemic lupus erythematosus over a 40-year period. J. Rheumatol. 2005l 32: 1709-1712.
4. Wei S, Lai K, Yang Z, Zeng K. Systemic lupus erythematosus and risk of preterm birth: A systematic review and meta-analysis of observational studies. Lupus .2017; 26: 563-571.
5. Al Arfaj, A S, Khalil N. Pregnancy outcome in 396 pregnancies in patients with SLE in Saudi Arabia. Lupus. 2010; 19: 1665-1673.
6. Christine A Clark, Karen A Spitzer, Jamie N Nadler, Carl A Laskin. Preterm deliveries in women with systemic lupus erythematosus. J. Rheumatol. 2003; 30: 2127-2132.
7. Kristin Palmsten, Julia F Simard, Christina D Chambers. Medication use among pregnant women with systemic lupus erythematosus and general population comparators. Rheumatol. (United Kingdom). 2017; 56: 561-569.
8. Kobashi N. Hypocomplementemia Correlates with Intrauterine Growth Retardation in Systemic Lupus Erythematosus. Am. J. Reprod Immunol. 1999; 42: 153-159.
9. Leroux M. Impact of hydroxychloroquine on preterm delivery and intrauterine growth restriction in pregnant women with systemic lupus erythematosus: A descriptive cohort study. Lupus. 2015; 24:

1384-1391.

10. Cortes-Hernandez J. Clinical predictors of fetal and maternal outcome in systemic lupus erythematosus: A prospective study of 103 pregnancies. Rheumatology 41, 643–650 (2002). Chinese Med. Assoc. 2015; 78: 235-240.
11. Whitelaw DA, Hall D, Kotze T. Pregnancy in systemic lupus erythematosus: A retrospective study from a developing community. Clin Rheumatol. 2008; 27: 577-580.
12. Petri, M. Prospective study of systemic lupus erythematosus pregnancies. Lupus. 2004; 13: 688-689.
13. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1997; 40: 1725.
14. Aringer M. European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. Arthritis Rheumatol. 2019; 71: 1400-1412.
15. Gladman DD, Ibanez D, Urowitz MB. Systemic Lupus Erythematosus Disease Activity Index 2000. J Rheumatol. 2002; 29: 288-291.
16. Pignotti MS, Moratti S. Regulation of treatment of infants at the edge of viability in Italy: The role of the medical profession? J. Med. Ethics. 2010; 36: 795-797.
17. Hutcheon JA, Lisonkova S, Joseph KS. Epidemiology of pre-eclampsia and the other hypertensive disorders of pregnancy. Best Pract. Res Clin Obstet Gynaecol. 2011; 25: 391-403.
18. Medicin AC. of obstetricians and G. C. on P. B. and T. S. for M.-F. ACOG Practice Bulletin No. 204 Summary: Fetal Growth Restriction. Obstet. Gynecol. 2019; 133: 390-392.
19. American College of Obstetricians and Gynecologists. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet. Gynecol. 2013; 122: 1122-31.
20. Robinson GE. Pregnancy loss. Best Pract. Res. Clin. Obstet. Gynaecol. 2014; 28: 169-178.
21. Jakobsen IM, Helmig RB, Stengaard-Pedersen K. Maternal and foetal outcomes in pregnant systemic lupus erythematosus patients: an incident cohort from a stable referral population followed during 1990-2010. Scand. J Rheumatol. 2015; 44: 377-384.
22. Teh CL, Wan SA, Cheong YK, Ling GR. Systemic lupus erythematosus pregnancies: Ten-year data from a single centre in Malaysia. Lupus. 2017; 26: 218-223.
23. Essouma M. Outcomes of systemic lupus erythematosus pregnancies and associated factors in sub-saharan Africa: a systematic scoping review. Lupus Sci. Med. 2020.
24. Chen J. Risk factors associated with adverse pregnancy outcomes in patients with new- onset systemic lupus erythematosus during pregnancy. Lupus. 2021; 30: 393-402.
25. Buyon JP. Predictors of pregnancy outcomes in patients with lupus: A cohort study. Ann Intern Med. 2015; 163: 153-163.
26. Barnado A, Wheless L, Meyer AK, Gilkeson GS, Kamen DL. Pregnancy outcomes among African-American patients with systemic lupus erythematosus compared with controls. Lupus Sci Med. 2014; 1: 1-8.
27. Andrade R. Adverse pregnancy outcomes in women with systemic lupus erythematosus from a multiethnic US cohort: LUMINA (LUI). Clin. Exp. Rheumatol. 2008; 26: 268-274.
28. Chen YJ. Maternal and perinatal outcomes of pregnancies in systemic lupus erythematosus: A nationwide population-based study. Semin. Arthritis Rheum. 2020; 50: 451-457.
29. Chakravarty EF. Factors that predict prematurity and preeclampsia in pregnancies that are complicated by systemic lupus erythematosus. Am. J. Obstet. Gynecol. 2005; 192: 1897-1904.
30. De Man YA. Association of higher rheumatoid arthritis disease activity during pregnancy with lower birth weight: Results of a national prospective study. Arthritis Rheum. 2009; 60: 3196-3206.
31. Clowse MEB, Magder LS, Witter F, Petri M. The impact of increased lupus activity on obstetric outcomes. Arthritis Rheum. 2005; 52: 514-521.
32. Palma dos Reis, CR. Prediction of Adverse Pregnancy Outcomes in Women with Systemic Lupus Erythematosus. Clin. Rev. Allergy Immunol. 2020; 59: 287-294.
33. Ko HS. Pregnancy outcomes and appropriate timing of pregnancy in 183 pregnancies in Korean patients with SLE. Int. J. Med. Sci. 2011; 8: 577-583.
34. Mehta B. Trends in maternal and fetal outcomes among pregnant women with systemic lupus erythematosus in the United States. Ann. Intern. Med. 2019; 171: 164-171.
35. Kim C, Romero R, Chaemsaithong P, Kim J. Chronic Inflammation of the Placenta: Definition, Classification, Pathogenesis, and Clinical Significance. Am. J. Obstet. Gynecol. 2015; 213: 53-59.
36. Marder W. Placental histology and neutrophil extracellular traps in lupus and pre- eclampsia pregnancies. Lupus Sci. Med. 2016; 3: 1-9.