Clinical Rheumatology (2019) 38:3211–3215
https://doi.org/10.1007/s10067-019-04682-3

ORIGINAL ARTICLE

The effect of lupus disease on the pregnant women and embryos: a retrospective study from 2010 to 2014

Elham Rajaei[1] · Nahid Shahbazian[2] · Hadi Rezaeeyan[3] · Amal Kia Mohammadi[1] · Saeed Hesam[4] · Zeinab Deris Zayeri[1]

Received: 14 March 2019 / Revised: 29 June 2019 / Accepted: 5 July 2019 / Published online: 27 July 2019

Abstract

Background and aims Pregnancy in women with systemic lupus erythematosus (SLE) is one of the challenges of recent studies. Women should prevent the onset of relapses with medications before and after pregnancy, and on the other hand, the effect of these medicines considers the health and development of the fetus. In this retrospective study, the effects of anti-phospholipid syndrome and the use of common drugs such as methotrexate, cyclosporine, and azathioprine and their side effects on maternal health and ultimately the development of the fetus have been investigated.

Material and methods This study is a descriptive and retrospective epidemiologic study that was conducted in 2016 to investigate maternal and fetal complications in SLE patients. We prepared forms of data recording, including age, occupation, and other important information and then analyzed them in SPSS version 22.

Result The results showed that the presence of anti-phospholipid syndrome in pregnant women can lead to abnormalities such as preterm, IUGR, abortion, and fetal death (*P* value 0.0001). It also leads to complications such as nephritis, arthritis, and preeclampsia in the mother (*P* value 0.003). This study suggests that methotrexate and cyclosporine medications could cause fetal developmental disorders. The *P* value of cyclosporine was 0.0001 and the *P* value of methotrexate was 0.001.

Conclusion Anti-phospholipid syndrome in women with SLE who intend to become pregnant can disrupt the development of the embryo. The consumption of methotrexate and cyclosporine medications before and during the pregnancy can have irreparable effects on fetal growth.

Key Points
- *Anti-phospholipid syndrome can disrupt the development of the embryo in women with SLE who intend to become pregnant.*
- *Methotrexate and cyclosporine consumption before and during pregnancy can affect fetal growth.*
- *7 to 33% of patients whose disease had been suppressed and controlled 6 months before pregnancy seams to relapse during the pregnancy.*
- *Taking medications to control the disease during pregnancy plays an important role in the progression of pregnancy and fetus health.*

Keywords Anti-phospholipid syndrome · Cyclosporine · Fetus complications · Methotrexate · Pregnancy · Systemic lupus erythematous

✉ Zeinab Deris Zayeri
zeynabderisgenetice@gmail.com

[1] Golestan Hospital Clinical Research Development Unit, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

[2] Department of Obstetrics and Gynecology, Fertility, Infertility and Perinatology Research Center, Faculty of Medicine, Ahvaz Jundishapour University of Medical Sciences, Ahvaz, Iran

[3] Thalassemia and Hemoglobinopathy Research Center, Research Institute of Health, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

[4] Department of Statistics and Epidemiology School of Public Health, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

Introduction

Systemic lupus erythematosus (SLE) is a multi-system inflammatory disease with unknown etiology that produces autoantibodies against the antigens found in various organs of the body such as the kidneys, blood cells, and the central nervous system. The disease is more common in women and, moreover, the symptoms of the disease become more severe in women who are pregnant and have adverse effects on the health of the mother and the fetus, which sometimes even results in maternal and fetal mortality or impairment of fetal development [1, 2]. In past decades, the main concern about SLE was the pregnancy in SLE patients which affects the health of the mother and the fetus [3, 4]. However,

recent progresses in technology and a better understanding of the SLE pathophysiology made the pregnancy more successful in SLE patients and decreased the prevalence of mortality among pregnant women significantly [4]. However, the most important principle in successful pregnancy is the control of SLE before pregnancy [5]. So the disease should be controlled and inactivated for about 6 months before pregnancy. Hence, the results of the recent studies have shown that the progression of the disease and the exacerbation of its symptoms before or during pregnancy can lead to an increased risk of abortion, early delivery, preeclampsia, and fetus complications [6]. On the other hand, taking medications to control the disease during pregnancy plays an important role in the progression of pregnancy and fetus health [7]. Medicines such as methotrexate and cyclophosphamide have been shown to interfere with the development of the fetus due to the passage of the placenta and their teratogenic properties, and sometimes cause infertility in pregnant women [8]. Consequently, immune system inhibitors such as cyclosporins and tacrolimus are used in SLE pregnancy to control the disease. However, overdosing of these drugs will also result in abortion or early birth of the fetus and will have adverse effects on the development of the fetus. Hence, protecting the mother and the fetus, as well as identifying safe drugs for the fetus and identifying factors that can exacerbate SLE disease during pregnancy, can be a good strategy to improve maternal and fetal health, as well as reducing the mortality in them [9, 10].

In this study, we run a retrospective study for the first time in southwest of Iran to examine the clinical status of pregnant women with SLE as well as the drugs they used and the factors that exacerbated or controlled the disease during pregnancy.

Materials and methods

This is a descriptive and retrospective epidemiologic study that was conducted in 2016 to investigate maternal and fetal complications in SLE patients in Golestan Hospital, Jundishapur University of Medical Sciences in Ahwaz, Iran. The statistical population of this study consisted of pregnant women with SLE who visited the rheumatology clinic of Ahvaz Golestan Hospital, the main center of southwestern rheumatology in 2010 to 2014. Patient selection criteria were based on the fact that all patients had diagnostic criteria for SLE based on the American Rheumatologic Institute, which was established in 1997, and patients whose records were incomplete or unsatisfied to participate in the study were excluded. We studied all pregnant cases with SLE with and without diabetes or other complications. In this study, we prepared forms of data recording, including age, occupation, initiate time of disease onset, disease duration, the onset of pregnancy, number of pregnancies, abortion history, type and dose of current medications, and previous pregnancy outcomes (abortion, fetal death in the womb, intrauterine growth restriction, premature rupture of membranes, eclampsia, and preeclampsia), severity, and disease activity systemic lupus erythematosus in pregnancy activity index (SLEPDAI) which takes into account the physiological changes of pregnancy. In order to standardize the assessment of SLE activity during pregnancy, this score was used. In 1999, SLEPDAI and other scoring systems were defined; for complete definition, read the review conducted by Marzena Olesińska et al. [11]

Statistical analysis

To describe the data, the mean and standard deviation as well as quantitative data were presented as percentage and frequency, and the data were presented as (median and mid-range quartile). Chi-square was used to analyze the qualitative variables. We used an independent sample *t* test to analyze binary variables and also to analyze quantitative variables from one-way Anova. All analyses were performed using SPSS version 22 software. A P value of < 0.05 was considered statistically significant.

Results

The mean age of pregnant women with SLE was 28.83 ± 4.26 years. Also, the mean duration of the disease period was 3.46 ± 2.12 years and the mean of silence duration before pregnancy was 1.60 ± 1.32 years. The mean dose of prednisolone for patient treatment was 2.84 ± 5. 87.5% of patients (210 patients) had no symptoms associated with SLE, 2.1% (5 patients) had deep vein thrombosis (DVT), 0.4% (1 patient) had pulmonary embolism, 1.3% (3 patients) with pancytopenia/thrombocytopenia, 3.3% (8 cases) had arthritis, and 1.7% (4 patients) had nephritis. 68.8% (165) of pregnant women did not have fetal echocardiography, and the rest were 28.3% (68 patients) normal, while 2.9% (7 cases) were abnormal. 30.4% (73 patients) had RO antibodies and 69.6% (167 patients) had no antibodies. Also, 22.9% (55 patients) had anti-phospholipid antibodies and 77.1% (185 patients) were anti-phospholipid antibodies negative. Data analysis showed that 185 patients had no anti-phospholipid antibodies, while 55 had anti-phospholipid antibodies. 88.6% of non-antibody-free women compared with 83.6% of women with this antibody had no complications. 7.3% of women who had anti-phospholipid antibodies had DVT and 3.6% of patients had preeclampsia and pancytopenia/thrombocytopenia.

Data analysis showed that 185 patients had no anti-phospholipid antibodies, while 55 had anti-phospholipid antibodies. 88.6% of non-antibody-free women compared with 83.6% of women with this antibody had no complications. 7.3% of women who had anti-phospholipid antibodies had

DVT and 3.6% of patients had preeclampsia and pancytopenia/thrombocytopenia. 1.8% of women had pulmonary embolism. Interestingly, none of the women who had anti-phospholipids did not have nephritis and arthritis but the women who had no antibodies had nephritis and arthritis 4% and 8% respectively. These results indicated that there is a significant association between anti-phospholipid antibodies and complications of the health of pregnant women (*P* value 0.003) (Fig. 1). However, the studies on the effect of anti-phospholipid antibodies on fetus development showed that 40% of the women with anti-phospholipid antibodies faced abortion in comparison to 11.4% of the women without anti-phospholipid antibodies. Also, 10.9% of women with anti-phospholipid antibodies had IUFD, while only 1.12% of women who had no anti-phospholipid antibodies had IUFD. However, none of the women with anti-phospholipid antibodies had congenital heart disease, preterm, IUGR, and fetus death, while 2.7%, 5.9%, 1.6%, and 1.1% of women with no anti-phospholipid antibodies faced these complications respectively. Therefore, the results of the analyses showed that there is a significant association between anti-phospholipid antibodies and development complications of the fetus (*P* value 0.0001) (Table 1).

During the pregnancy, and before that, patients took medicines in order to control and prevent the deterioration of the disease. The results showed that there was no significant association between the fetus development and the use of azathioprine (*P* value 0.79), hydroxychloroquine (*P* value 0.59), enoxaparin (*P* value 0.27), ASA (*P* value 0.17), and folic acid and vitamin D (*P* value = 0.05). But there was a significant association between fetus development and methotrexate and cyclosporine (*P* value = 0.0001 for cyclosporine and *P* value = 0.001 for methotrexate). These results showed that taking methotrexate in compared to cyclosporine had a deteriorated effect on fetus development (Table 2).

Discussion

SLE is an autoimmune disease that is characterized by autoantibodies against many organs [12]. Autoimmune antibodies lead to inflammatory responses in the skin, joints, kidneys, and the nervous system. Clinical symptoms of the disease are very various, and after complete recovery, the disease may relapse and lead to worsening of the clinical symptoms and progression of the disease [13]. In the past, usually SLE women who were at the age of pregnancy were advised to prevent pregnancy because it was possible that pregnancy not only led to a relapse and progression but also caused irreparable harm to fetus development [14]. Nowadays women with SLE who are pregnant usually give birth to their baby successfully as a result of the advancement of treatment and diagnostic methods. The results showed that 7 to 33% of patients whose disease had been suppressed and controlled 6 months before pregnancy reoccurred and progressed during the pregnancy [15, 16]. However, compared with women who are not pregnant and have SLE, this is far lower. Recent studies were conducted to identify the factors that may cause relapse of the disease and endangered fetus development during pregnancy. Yang et al. showed that there was a significant association between the disease and the incidence of pre-

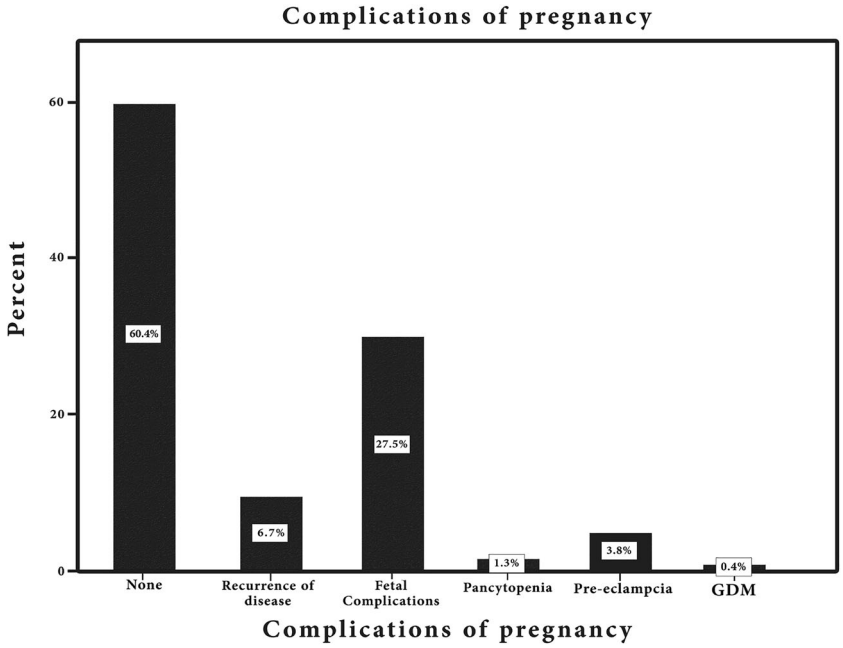

Fig. 1 Complications of pregnancy

Table 1 The evaluation of anti-phospholipid antibody and silence period on maternal health

Complication	Anti-phospholipid antibody		Inactivation period (month or year)
	Positive (%)	Negative (%)	Mean ± SD
No	83.6	88.6	1.68 ± 1.34
Preeclampsia	3.6	3.8	1.12 ± 0.89
DVT	7.3	0.5	1.00 ± 0.50
Pulmonary embolism	1.8	0	1.00 ± 0.50
Pancytopenia/thrombocytopenia	3.6	1	0.16 ± 0.28
Arthritis	0	8	1.43 ± 1.49
Nephritis	0	4	0.62 ± 1.31
P value	0.003		0.009

and post-pregnancy complications such as preterm birth (*P* value 0.03), chronic hypertension (*P* value 0.04), renal failure (P value 004), and intrauterine fetal growth restriction (*P* value 0.01). This study suggested that longer silence period of the disease before pregnancy causes the occurrence of preterm labor to be reduced and this study was in agreement with our study [17]. Phansenee et al. showed that pregnant patients with anti-phospholipid syndrome, thrombocytopenia, proteinuria, and chronic hypertension are more likely to face abortion, low birth weight, preterm birth, and preeclampsia and the association was statistically significant (*P* value 0.01 for chronic hypertension, *P* value < 0.001 for anti-phospholipid syndrome, thrombocytopenia, proteinuria) [18]. The results of our study showed that there was a significant relationship between the presence of anti-phospholipid syndrome during pregnancy and maternal and fetal complications (*P* value 0.0001 for fetal complications and *P* value 0.003 for maternal complications) (Tables 1 and 2). On the other hand, it has been shown that the use of certain drugs before and during pregnancy in SLE patients can disrupt the fetus development. Leroux et al. showed that patients with SLE who consumed hydroxychloroquine (HCQ) during pregnancy had less side effects on their fetuses in comparison to those who did not consume HCQ, which was statistically significant (*P* value 0006). HCQ use prevents intrauterine growth restriction (IUGR) and preterm delivery [19]. Reggia et al. suggested that SLE patients taking cyclosporine during pregnancy had no complications or fetus development disruption. This study showed cyclosporine is not transmitted to the baby through the milk and has no toxicity for the baby. This study is in contrast with our study [20]. A meta-analysis conducted by Ponticelli C. et al. in rheumatic patients suggested no significant difference in birth defects between pregnancies with prenatal exposure to cyclosporine and controls. Thus, cyclosporine does not appear to be a major human teratogen. However, it may favor the development of hypertension and preeclampsia in pregnant women [21]. On the other hand, Weber-Schoendorfer et al. showed that pregnant women with rheumatoid arthritis who used methotrexate before and during pregnancy experienced abnormal spontaneous abortions as well as fetus development disruption which is in agreement with our study [22]. Our study showed that there was no relationship between the use of azathioprine (*P* value 0.79), hydroxychloroquine (*P* value 0.59), enoxaparin (*P* value 0.27), ASA (*P* value 0.17), and other drugs such as folic acid and vitamin D (*P* value = 0.05) and fetus development complications. On the other hand, it was found that the use of cyclosporine and methotrexate could prevent the development of the fetus and increase the risk of the pregnancy complications (Table 2).

Table 2 The effect of the medicines used on the fetus development

Complication	Methotrexate (%)	Cyclosporine (%)	Prednisolone Mean ± SD
No	36.8	50	3.50 ± 2.23
Recurrence of disease	18.4	0	5.00 ± 1.82
Fetal complication	39.5	0	3.71 ± 2.06
Pancytopenia	0	25	15.00 ± 13.22
Preeclampsia	5.3	25	4.45 ± 3.01
GDM	0	0	10.00 ± 0.00
P value	0.001	0.0001	0.0001

Conclusion

This study showed that the use of cyclosporine and methotrexate before and during pregnancy can be harmful to the development of the fetus and other medicines which do not have a teratogenic effect on the fetus. Also, the presence of anti-phospholipid syndrome in pregnant women can increase the risk of both maternal and fetal complications and appropriate therapeutic strategies should be used to control them. The present study had a good estimation of the condition in pregnant mothers with systemic lupus erythematosus and conditions of the disease and complications. The first limitation was sample size which was determined based on randomization in the input and output factors. Due to the fact that patients were not filtered and a general survey, regardless of ethical groups and other biological factors, demographic factors had more heterogeneous dispersion which might affect the statistical correlation. Another limitation was considering the conditions of the patients and the lack of the information about their disease status and symptoms over the previous years. We suggest prospective studies in the field of clinical trials in a pharmacological comparative study on the incidence of complications and long-term studies on the health of the babies to estimate the effect of SLE and the therapeutic approach on latent terms.

Authors' contributions All authors contributed equally to this work.

Funding information This study was supported by the Student Research Committee of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

Compliance with ethical standards

Disclosures None.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

References

1. Mowla K, Rajaei E, Jalali MT, Zayeri ZD (2018) Threatening biomarkers in lupus pregnancy: biochemistry and genetic challenges. Front Biol:1–8
2. Petri M (1994) Systemic lupus erythematosus and pregnancy. Rheum Dis Clin N Am 20(1):87–118
3. Tincani A, Bompane D, Danieli E, Doria A (2006) Pregnancy, lupus and antiphospholipid syndrome (Hughes syndrome). Lupus 15(3):156–160
4. Dhar JP, Sokol RJ (2006) Lupus and pregnancy: complex yet manageable. Clin Med Res 4(4):310–321
5. Witter FR (2007) Management of the high-risk lupus pregnant patient. Rheum Dis Clin N Am 33(2):253–265
6. Ruiz-Irastorza G, Khamashta MA (2011) Lupus and pregnancy: integrating clues from the bench and bedside. Eur J Clin Investig 41(6):672–678
7. Boumpas DT, Fessler BJ, Austin HA III, Balow JE, Klippel JH, Lockshin MD (1995) Systemic lupus erythematosus: emerging concepts: part 2: dermatologic and joint disease, the antiphospholipid antibody syndrome, pregnancy and hormonal therapy, morbidity and mortality, and pathogenesis. Ann Intern Med 123(1):42–53
8. Alijotas-Reig J, Esteve-Valverde E, Ferrer-Oliveras R (2016) Treatment with immunosuppressive and biologic drugs of pregnant women with systemic rheumatic or autoimmune disease. Medicina Clínica (English Edition) 147(8):352–360
9. Jabs DA, Rosenbaum JT, Foster CS, Holland GN, Jaffe GJ, Louie JS, Nussenblatt RB, Stiehm ER, Tessler H, Van Gelder RN (2000) Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: recommendations of an expert panel. Am J Ophthalmol 130(4):492–513
10. Levy RA, de Jesus GR, de Jesus NR, Klumb EM (2016) Critical review of the current recommendations for the treatment of systemic inflammatory rheumatic diseases during pregnancy and lactation. Autoimmun Rev 15(10):955–963
11. Olesińska M, Wiesik-Szewczyk E, Chwalińska-Sadowska H (2007) Evaluation of systemic lupus erythematosus activity during pregnancy. Pol Arch Med Wewn 117(7):312–316
12. Clowse ME, Magder LS, Witter F, Petri M (2005) The impact of increased lupus activity on obstetric outcomes. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology 52(2):514–521
13. Nalli C, Iodice A, Andreoli L, Lojacono A, Motta M, Fazzi E, Tincani A (2014) The effects of lupus and antiphospholipid antibody syndrome on foetal outcomes. Lupus 23(6):507–517
14. Doria A, Tincani A, Lockshin M (2008) Challenges of lupus pregnancies. Rheumatology 47(suppl_3):iii9–iii12
15. Clowse ME, Magder LS, Witter F, Petri M (2006) Early risk factors for pregnancy loss in lupus. Obstet Gynecol 107(2):293–299
16. Clowse ME, Magder LS, Petri M (2011) The clinical utility of measuring complement and anti-dsDNA antibodies during pregnancy in patients with systemic lupus erythematosus. The Journal of rheumatology:jrheum 100746
17. Yang M-J, Chen C-Y, Chang W-H, Tseng J-Y, Yeh C-C (2015) Pregnancy outcome of systemic lupus erythematosus in relation to lupus activity before and during pregnancy. Journal of the Chinese Medical Association 78(4):235–240
18. Phansenee S, Sekararithi R, Jatavan P, Tongsong T (2018) Pregnancy outcomes among women with systemic lupus erythematosus: a retrospective cohort study from Thailand. Lupus 27(1):158–164
19. Leroux M, Desveaux C, Parcevaux M, Julliac B, Gouyon J-B, Dallay D, Pellegrin J, Boukerrou M, Blanco P, Lazaro E (2015) Impact of hydroxychloroquine on preterm delivery and intrauterine growth restriction in pregnant women with systemic lupus erythematosus: a descriptive cohort study. Lupus 24(13):1384–1391
20. Reggia R, Bazzani C, Andreoli L, Motta M, Lojacono A, Zatti S, Ramazzotto F, Nuzzo M, Tincani A (2016) The efficacy and safety of cyclosporin A in pregnant patients with systemic autoimmune diseases. Am J Reprod Immunol 75(6):654–660
21. Ponticelli C, Moroni G (2015) Immunosuppression in pregnant women with systemic lupus erythematosus. Taylor & Francis, Immunosuppression in pregnant women with systemic lupus erythematosus,
22. Weber-Schoendorfer C, Chambers C, Wacker E, Beghin D, Bernard N, Centers NFP, Shechtman S, Johnson D, Cuppers-Maarschalkerweerd B, Pistelli A (2014) Pregnancy outcome after methotrexate treatment for rheumatic disease prior to or during early pregnancy: a prospective multicenter cohort study. Arthritis Rheum 66(5):1101–1110