

Pregnancy in Patients with SLE

Sayumi Baba^{1,*}, Hiroshi Okamoto² and Hisashi Yamanaka¹

¹Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

²Minami-Otsuka Institute of Technology, Minami-Otsuka Clinic, Tokyo, Japan

Abstract

Systemic Lupus Erythematosus (SLE) is a systemic autoimmune disease predominantly affecting women of childbearing age. Pregnancy in women with SLE is associated with higher fetal and maternal risk compared with the general population. SLE flares, higher rates of pregnancy complications and the risk of Neonatal Lupus Syndromes (NLS), especially congenital Complete Heart Block (CHB) are major concerns. Pregnancy complications include fetal loss, preeclampsia, preterm delivery and Intra-Uterine Growth Restriction (IUGR). High disease activity, renal involvement and the presence of antiphospholipid (aPL) antibodies, anti-SSA/Ro and SSB/La specific antibodies are particularly at risk. As normal physiological changes during pregnancy could show symptoms and signs resembling those with active SLE, it is sometimes difficult to distinguish between these conditions. One of the candidate clinical markers would be high titer of anti-double-stranded DNA antibodies to distinguish between flare of SLE and normal physiological changes during pregnancy. Medications during pregnancy are also an important issue. Some immune-suppressants such as cyclophosphamide or Mycophenolate Mofetil (MMF) should not be taken during pregnancy. Non-fluorinated steroids, calcineurin inhibitors and azathioprine can be used and continuous use of hydroxy chloroquine during pregnancy is considered beneficial. Administration of low-dose aspirin prior to 16 weeks of gestation should be considered in all

pregnant women with SLE at elevated risk of preeclampsia. In conclusion, it is important that disease progression and development of auto antibodies be monitored in pregnant women at risk of SLE in order to ensure good outcomes.

Keywords: Fetal Loss; Intra-Uterine Growth Restriction (IUGR); Neonatal Lupus; Pregnancy; Preeclampsia; Systemic Lupus Erythematosus

***Corresponding Author:** Sayumi Baba, Institute of Rheumatology, Tokyo Women's Medical University, 10-22 Kawada-cho, Shinjuku, Tokyo 162-0054, Japan; Tel: +81-3-5269-1725; Fax: +81-3-5269-1726; E-mail: sbaba@ior.twmu.ac.jp

Introduction

Systemic Lupus Erythematosus (SLE) is a chronic inflammatory systemic autoimmune disease predominantly affecting women of childbearing age. Although survival rate and success rates of pregnancy in women with SLE have considerably improved in the past few decades [1], women with SLE are associated with a higher rate of complications during pregnancy compared with general population and often these women have fewer children than they desired [2].

Mutual interactions between SLE and pregnancy can occur. Whether pregnancy influences the disease activity of SLE has been a matter of debate in previous reports [3]. Major organ involvements including renal/cardiac/pulmonary disease, high disease activity, antiphospholipid syndrome, presence of anti-

SSA/Ro and /or anti-SSB/La antibodies, and history of severe obstetric complications are often associated with poor fetal/maternal outcomes [3]. And under these conditions, indication to pregnancy should be considered cautiously. Pre-pregnancy counseling is important to estimate the fetal/maternal risk. The main issues with pregnancies in patients with SLE are SLE flares, the increased risk of pregnancy complications and Neonatal Lupus Syndromes (NLS) including congenital Complete Heart Block (CHB). In all pregnant women with SLE, maternal and fetal health should be monitored frequently as a high risk pregnancy. In this mini-review, we focus on the issue associated with pregnancy in patients with SLE and propose the requirement of careful management for these patients.

Normal physiologic changes during Pregnancy

Many physiological changes of pregnancy may make assessment of SLE activity difficult.

Intravascular volume increases 30%-50% during normal pregnancy, and sometimes this increase might be intolerable for patients with severe renal or cardiac disease. Mild anemia, proteinuria up to 300mg/day can occur during normal pregnancy. Although platelet production normally increases during pregnancy, thrombocytopenia commonly appears in uncomplicated pregnancies. Plasma level of fibrinogen, prothrombin and many other procoagulant proteins increase. Free and total Protein S decreases. As a result, the risk of venous thromboembolism is increased. Complement levels rise by 10-50% during normal pregnancy and may appear to remain in the normal range, despite disease activity. Some reports indicate low and declining levels of complement during pregnancy, and this in turn has been associated with poor pregnancy outcomes [4]. Anti-double-stranded DNA antibodies may be helpful in the evaluation of disease activity.

SLE flares

Reported rates of SLE flares during pregnancy vary between 25-65%, as the frequency may depend on the differences in the genetic background of patients, definition of a flare and improvement of treatment [3, 5-7]. Renal and hematological

flares are reported commonly. Disease may flare during all three trimesters of pregnancy and postpartum period [6]. Although it is generally agreed that pregnancy may lead to higher rates of disease flares [5, 7], some investigators found no differences between the rate of flares in pregnant patients vs healthy individuals [8]. Active disease at the time of conception is a strong predictor of continued disease activity and flares during pregnancy, increasing fetal/maternal risk by threefold to four fold [9, 10]. Presence of lupus nephritis, preexisting hypertension, proteinuria and azotemia have been reported to increase the risk of renal exacerbations [11]. Discontinuation of hydroxy chloroquine also increase the risk of flares, treatment should be continued throughout the pregnancy [12, 13].

Although several pregnancy-specific disease activity scales including, the SLE pregnancy Disease Activity Index (SLEPDAI), LAI in pregnancy (LAI-P), and BILAG2004-Pregnancy Index, have been developed, these scales have been used primarily as a research tools [14-16].

Complications of Pregnancy

Fetal loss

The rate of fetal loss in women with SLE has decreased from 43% to 17% in recent decades, a level that is approximately equivalent to that of the general population [1]. Antiphospholipid Syndrome (APS) and the presence of antiphospholipid antibodies (aPLs) are strongly associated with fetal loss. Among aPLs, lupus anticoagulant is the best predictor of adverse pregnancy outcomes [17, 18]. Even asymptomatic women with positive aPLs, who are not exhibiting the antiphospholipid syndrome, have higher rate of fetal loss, preeclampsia, IUGR and preterm delivery. Despite limited evidence, low-dose aspirin alone is a choice of treatment for those women [17, 19]. Other risk factors of fetal loss are lupus nephritis, hypertension [20], high disease activity [21], hypocomplementemia, elevated levels of anti-DNA antibodies, and thrombocytopenia [20].

Management of recurrent pregnancy loss still remains a great challenge. A meta-analysis showed the superiority of a heparin

and aspirin combination compared to aspirin alone in patients with recurrent pregnancy loss and positive aPLs [22]. There is no evidence showing the effect of the administration of the heparin and aspirin combination in refractory cases.

Preeclampsia

The preeclampsia is defined by high blood pressure (greater than 140/90 mmHg) and proteinuria (greater than 300mg per day) in the latter half of pregnancy. Sometimes it associated with deteriorating renal function, edema, thrombocytopenia and hyper uricemia. If seizures occur, the syndrome is defined as eclampsia. Preeclampsia is still associated with an increased rate of maternal and fetal mortality and is an important cause for preterm birth. Although the pathology remains poorly understood, involvement of inflammation, endothelial dysfunction, and an unbalanced thromboxane A₂/prostacyclin ratio have been suggested. For women with SLE, the risk of developing preeclampsia is much higher, and ranges from 9% to 35% [23, 24], compared to 5-7% in pregnancies among healthy individuals. The predisposing factors for preeclampsia include advanced maternal age, previous personal or family history of preeclampsia, preexisting hypertension, diabetes mellitus and obesity. In women with SLE, additional risk factors include active or a history of nephritis, presence of APS, aPLs, thrombocytopenia and declining levels of complement [25]. Treatment with aspirin during pregnancy has shown to have beneficial effects among women at high risk for preeclampsia. Recent studies indicates that a low-dose of aspirin started before the 16th week of gestation decreased the risk for severe preeclampsia, perinatal death and fetal growth restriction, while

low-dose aspirin initiation after 16 weeks of gestation did not provide these protective effects [26, 27]. Thus, for SLE patients at elevated risk of preeclampsia, especially with aPLs, and a history of preeclampsia, hypertension and/or renal disease, low-dose aspirin administration prior to 16 weeks of gestation and continuing throughout the pregnancy is recommended. Some specialists recommend the use of low-dose aspirin administration for all SLE patients starting prior to the 16th week of gestation [28]. The HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets) is a systemic thrombotic microangiopathy that complicates pregnancy. It is associated with a high maternal death rate and is considered to be a severe variant of preeclampsia. There is growing evidence showing that APS is a possible risk factor of HELLP syndrome; suggesting that APS is not only a thrombotic disease, but also associated with micro angiopathy [29].

Sometimes it may be difficult to distinguish preeclampsia and a SLE flare, and in fact they may co-exist (Table 1). A lupus flare is often associated with proteinuria and/or active urine sediment, increased titers of anti-DNA antibodies and evidence of disease activity in other organs. When the urinary abnormalities occur before the third trimester, a flare of lupus nephritis is highly suspected. Elevated serum levels of liver enzymes, hyperuricemia and decreased urinary excretion of calcium are more prominent in preeclampsia. Preeclampsia does not respond to steroid therapy. The treatment of preeclampsia is to deliver the placenta and the fetus. In some cases, termination of pregnancy may be the only definite answer..

Table : 1

	Normal changes during pregnancy	Preeclampsia	Flare of Lupus
Proteinuria	May be present <0.3 g/day	++ >0.3g/day or PCR>30	++ (in lupus nephritis)
Casts in MSU	Absent	Absent	Present (in lupus nephritis)
RBC in MSU	Absent	Absent	Present (in lupus nephritis)
Hypertension	May be present	Present	May be present
Involvement of skin and joints	No	No	Malar rash, photosensitive rash or arthritis

Seisures	No	Present in eclampsia	Present if there is neurological involvement
Urate	Not elevated	elevated	Not elevated unless CKD
Albumin	Unchanged	Low	Low if nephritic syndrome
Liver function test	Unchanged	May be reraged	Rarely daranged
C3 and C4	Slightly elevated	Unchanged	Low
Anti-ds DNA	Unchanged	Unchanged	elevated

PCR: Protein Creatinin Ratio; MSU: Mid Stream Urine; RBC: Red Blood Cells; CKD: Chronic Kidney Disease

Thrombocytopenia during SLE pregnancy occurs in several patterns. Thrombocytopenia in association with aPL usually occurs before 15 weeks and with counts greater than $50 \times 10^9/L$. Thrombocytopenia in association with preeclampsia usually occurs after 25 weeks of pregnancy and worsens progressively. Severe idiopathic thrombocytopenia purpura, a type of severe thrombocytopenia may occur also, with counts often less than $10 \times 10^9/L$.

Preterm delivery

Preterm delivery, defined as <37 weeks' gestation, is common in SLE pregnancies. It occurs 30-40% of the pregnancies in women with SLE compared about 10% in the general population [3, 21]. Presence of nephritis, high disease activity during pregnancy are the risk factors of early delivery [21, 30]. Thyroid disease, hypertension, proteinuria and aPL positivity were also associated with a higher risk of preterm deliveries in women with SLE [30-32]. Recently, Clowse et al found that serum levels of ferritin, oestradiol and uric acid might predict preterm birth [33].

Intra-Uterine Growth Restriction (IUGR)

Intra-Uterine Growth Restriction (IUGR) is a common complication, reported in approximately 10-30% of pregnancies in women with SLE. The rate of lower birth weight at every gestational age is higher among women with SLE compared with general the population. Risk factors are lupus nephritis, presence of aPL and high disease activity during pregnancy [3, 10].

Neonatal Lupus Syndromes (NLS)

Anti- Ro/SSA and/or anti-La/SSB antibodies are found in approximately a third of women with SLE. Trans-placental passage of maternal antibodies is presumed to cause neonatal lupus syndromes. Manifestations of rash, hematologic abnormalities (thrombocytopenia and neutropenia) and hepatic abnormalities (asymptomatic increase in liver enzymes) are transient and mostly resolved within 6-8 month, as maternal antibodies disappear from the child. By contrast, cardiac manifestations including conduction disease, structural abnormalities, cardiomyopathy and congestive heart failure are permanent [34]. The most serious complication of cardiac manifestations is congenital Complete Heart Block (CHB). CHB is irreversible and is associated with significant mortality and morbidity. Mortality rates vary depending on the time of presentation. One study showed that fetal/neonatal mortality may be as high as 40% [35]. The usual presentation is fetal bradycardia and/or congestive cardiac failure. Prospective studies of anti-SSA/Ro positive women without previously affected pregnancies have shown an approximately 2% risk of CHB [36]. The recurrence rates in subsequent pregnancies are 10-20 fold higher [37]. High titers of anti-SSA antibodies increased the risk of CHB [38, 39]. Other suggested risk factors include maternal hypothyroidism and fetal genetic polymorphisms, involving the Fc-gamma receptors and transforming growth factor- β [40, 41]. In most cases, CHB develops between 18-24 weeks of gestation. All at-risk fetuses should be monitored by fetal echocardiography weekly between 16-26 weeks. Once CHB is developed, it is not reversible. New methods, such as fetal kinetocardiography have been developed

to detect first-degree heart block, the precursor of CHB [42]. Currently, there is no consensus regarding trans-placental treatment with corticosteroids, Intra Venous Immunoglobulin (IVIg) or plasma exchange to reduce the risk of CHB in asymptomatic fetus. Although, for mothers of fetuses with incomplete heart block, transprenatal treatment with fluorinated glucocorticoid/immunoglobulin as soon as possible after detection has been reported to prevent progression to CHB [43-46]. Hydroxychloroquine use during pregnancy may reduce rates of cardiac neonatal lupus syndrome in mothers at high risk [47, 48].

Treatment during pregnancy

Prednisone, prednisolone, and methylprednisolone are relatively safe for fetus because they are metabolized by the placenta and cross the placenta at low concentration [49]. Fluorinated steroids, dexamethasone and betamethasone reach the fetus at higher concentrations because they are metabolized less efficiently, and should not be used unless there is intent to treat the fetus. The influence of glucocorticoid exposure during pregnancy on the cleft lip/palate clefts in infants and has been controversial [50-54]. Some studies reported that corticosteroid does increase the risk of oral cleft 3-5-fold, whereas others found no statistical increase in the rate of oral clefts [52, 53]. Since oral clefts occur at about 1:1,000 births in the general population, the possible increase of 3 or 4 individuals for every 1,000 births after embryonic exposure to corticosteroids is marginal [51]. The association between glucocorticoid exposure during pregnancy and hypertension and IUGR remains unclear [51]. One report suggests cognitive impairment in premature infants given corticosteroids [55]. Thus, it is advisable to use the lowest possible doses of prednisone to control the disease.

Intravenous methylprednisolone at 1000mg daily for three days can help to achieve quick control of a SLE flare, avoiding the need for a high daily maintenance dose. If glucocorticoids have been used for a prolonged period during pregnancy, suppression of hypothalamic-pituitary-adrenal

function should be considered and stress-dose glucocorticoids should be administered during labor and delivery.

Hydroxychloroquine should be continued in all pregnant women with SLE. Several studies showed the beneficial effects of hydroxychloroquine in SLE during pregnancy [12, 13]. The risk of CHB was also reduced in at-risk women with SLE using hydroxychloroquine during pregnancy [47, 48].

Azathioprine is considered generally safe in pregnancy. The dose should be limited to a maximum of 2mg/kg/day, to avoid the risk of fetal cytopenia and immune suppression. A recent study reported a possible association between maternal azathioprine therapy during pregnancy and fetal development delays. Even though more studies are required to further evaluate this possibility, it is prudent to advise women about this possible association [56].

Calcineurin inhibitors, cyclosporine and tacrolimus, are considered relatively safe with no reported fetal risk [51]. Cyclophosphamide, methotrexate and mycophenolate mofetil are contra-indicated during pregnancy, and should be discontinued before conception [51]. Several women given cyclophosphamide during late pregnancy had normal infants, but a larger sample size is needed. Mycophenolate Mofetil (MMF) has been associated with fetal malformations [57]. A recent study reported that patients with quiescent lupus nephritis who switched from MMF to azathioprine during pregnancy had mostly good pregnancy outcomes [58]. Although Intra Venous Immunoglobulin (IVIg) and plasmapheresis remain alternative options, higher risk of thrombosis and fluid overload have to be considered in these cases.

Prognosis of children born to women with SLE

A study showed that children born to women with SLE had a high positive rate of Anti Nuclear Antibodies (ANA) and might be predisposed to SLE [59]. Some literature suggests that learning disabilities were more frequent in children born to women with SLE, especially in male children, since maternal auto antibodies can cross the placenta and affect the fetal brain.

Disease activity and the presence of anti-Ro/La antibodies in mothers with SLE were reported to be associated with learning disabilities in their children [60].

Conclusions

As presented above, pregnancy in women with SLE is a highly risky condition. For mothers, pregnancy increases the risk for the exacerbation of their SLE and for preeclampsia. For babies, his/her mother's disease and the medicine she uses are important determinants for his/her birth and future life. These babies are at a high risk to experience preterm birth, Growth Restriction (IUGR), neonatal lupus syndrome and learning disabilities. Evaluation of the risk before conception, and close monitoring and judicious use of medications are important for the management of SLE patients during pregnancy. Although much information has been obtained to assist in the management of pregnancy in patients with SLE, a therapeutic strategy for the management of these patients has not been established thus far. To this end, further clinical studies with large cohorts are required to determine an adequate management strategy for better pregnancy outcomes in patients with SLE.

References

1. Clark, C.; Spitzer, K.; Laskin, C., Decrease in pregnancy loss rates in patients with systemic lupus erythematosus over a 40-year period. *Journal of rheumatology* 2005, 32 (9), 1709-1712.
2. Clowse, M. E.; Chakravarty, E.; Costenbader, K. H.; Chambers, C.; Michaud, K., Effects of infertility, pregnancy loss, and patient concerns on family size of women with rheumatoid arthritis and systemic lupus erythematosus. *Arthritis Care Res (Hoboken)* 2012, 64 (5), 668-74.
3. Smyth, A.; Oliveira, G. H. M.; Lahr, B.; Bailey, K.; Norby, S.; Garovic, V., A systematic review and meta-analysis of pregnancy outcomes in patients with systemic lupus erythematosus and lupus nephritis. *Clinical journal of the American Society of Nephrology* 2010, 5 (11), 2060-2068.
4. Clowse, M. E. B.; Magder, L.; Petri, M., The clinical utility of measuring complement and anti-dsDNA antibodies during pregnancy in patients with systemic lupus erythematosus. *Journal of rheumatology* 2011, 38 (6), 1012-1016.
5. Ruiz Irastorza; Lima; Alves; Khamashta; Simpson; Hughes; Buchanan, Increased rate of lupus flare during pregnancy and the puerperium: a prospective study of 78 pregnancies. *British journal of rheumatology* 1996, 35 (2), 133-138.
6. Carvalheiras, G.; Vita, P.; Marta, S.; Trovão, R.; Farinha, F.; Braga, J.; Rocha, G.; Almeida, I.; Marinho, A.; Mendonça, T.; Barbosa, P.; Correia, J.; Vasconcelos, C., Pregnancy and systemic lupus erythematosus: review of clinical features and outcome of 51 pregnancies at a single institution. *Clinical reviews in allergy & immunology* 2010, 38 (2-3), 302-306.
7. Petri; Howard; Repke, Frequency of lupus flare in pregnancy. The Hopkins Lupus Pregnancy Center experience. *Arthritis & rheumatism* 1991, 34 (12), 1538-1545.
8. Lockshin; Reinitz; Druzin; Murrman; Estes, Lupus pregnancy. Case-control prospective study demonstrating absence of lupus exacerbation during or after pregnancy. *The American journal of medicine* 1984, 77 (5), 893-898.
9. Imbasciati, E.; Tincani, A.; Gregorini, G.; Doria, A.; Moroni, G.; Cabiddu, G.; Marcelli, D., Pregnancy in women with pre-existing lupus nephritis: predictors of fetal and maternal outcome. *Nephrology, Dialysis, Transplantation* 2009, 24 (2), 519-525.
10. Gladman, D.; Tandon, A.; Ibañez, D.; Urowitz, M., The effect of lupus nephritis on pregnancy outcome and fetal and maternal complications. *Journal of rheumatology* 2010, 37 (4), 754-758.

11. Saavedra, M. A.; Cruz-Reyes, C.; Vera-Lastra, O.; Romero, G. T.; Cruz-Cruz, P.; Arias-Flores, R.; Jara, L. J., Impact of previous lupus nephritis on maternal and fetal outcomes during pregnancy. *Clin Rheumatol* 2012, 31 (5), 813-9.
12. Levy, R. A.; Vilela, V. S.; Cataldo, M. J.; Ramos, R. C.; Duarte, J. L.; Tura, B. R.; Albuquerque, E. M.; Jesús, N. R., Hydroxychloroquine (HCQ) in lupus pregnancy: double-blind and placebo-controlled study. *Lupus* 2001, 10 (6), 401-4.
13. Clowse, M. E. B.; Magder, L.; Witter, F.; Petri, M., Hydroxychloroquine in lupus pregnancy. *Arthritis & rheumatism* 2006, 54 (11), 3640-3647.
14. Ruiz-Irastorza, G.; Khamashta, M. A.; Gordon, C.; Lockshin, M. D.; Johns, K. R.; Sammaritano, L.; Hughes, G. R., Measuring systemic lupus erythematosus activity during pregnancy: validation of the lupus activity index in pregnancy scale. *Arthritis Rheum* 2004, 51 (1), 78-82.
15. Buyon, J. P.; Kalunian, K. C.; Ramsey-Goldman, R.; Petri, M. A.; Lockshin, M. D.; Ruiz-Irastorza, G.; Khamashta, M., Assessing disease activity in SLE patients during pregnancy. *Lupus* 1999, 8 (8), 677-84.
16. Yee, C. S.; Akil, M.; Khamashta, M.; Bessant, R.; Kilding, R.; Giles, I.; Farewell, V. T.; Gordon, C., The BILAG2004-Pregnancy index is reliable for assessment of disease activity in pregnant SLE patients. *Rheumatology (Oxford)* 2012, 51 (10), 1877-80.
17. Lockshin, M.; Kim, M.; Laskin, C.; Guerra, M.; Branch, Merrill, J.; Petri, M.; Porter; Sammaritano, L.; Stephenson, M.; Buyon, J.; Salmon, J., Prediction of adverse pregnancy outcome by the presence of lupus anticoagulant, but not anticardiolipin antibody, in patients with antiphospholipid antibodies. *Arthritis & rheumatism* 2012, 64 (7), 2311-2318.
18. Opatrny, L.; David, M.; Kahn, S.; Shrier, I.; Rey, E., Association between antiphospholipid antibodies and recurrent fetal loss in women without autoimmune disease: a metaanalysis. *Journal of rheumatology* 2006, 33 (11), 2214-2221.
19. Petri, M.; Qazi, U., Management of antiphospholipid syndrome in pregnancy. *Rheum Dis Clin North Am* 2006, 32 (3), 591-607.
20. Clowse, M. E. B.; Magder, L.; Witter, F.; Petri, M., Early risk factors for pregnancy loss in lupus. *Obstetrics and gynecology* 2006, 107 (2 Pt 1), 293-299.
21. Clowse, M. E. B.; Magder, L.; Witter, F.; Petri, M., The impact of increased lupus activity on obstetric outcomes. *Arthritis & rheumatism* 2005, 52 (2), 514-521.
22. Mak, A.; Cheung, M. W.-L.; Cheak, A.; Ho, R., Combination of heparin and aspirin is superior to aspirin alone in enhancing live births in patients with recurrent pregnancy loss and positive anti-phospholipid antibodies: a meta-analysis of randomized controlled trials and meta-regression. *Rheumatology* 2010, 49 (2), 281-288.
23. Erkan, D.; Sammaritano, L., New insights into pregnancy-related complications in systemic lupus erythematosus. *Current rheumatology reports* 2003, 5 (5), 357-363.
24. Bramham, K.; Hunt, B.; Bewley, S.; Germain, S.; Calatayud, I.; Khamashta, M.; Nelson Piercy, C., Pregnancy outcomes in systemic lupus erythematosus with and without previous nephritis. *Journal of rheumatology* 2011, 38 (9), 1906-13.
25. Clowse, M. E., Lupus activity in pregnancy. *Rheum Dis Clin North Am* 2007, 33 (2), 237-52, v.
26. Roberge, S.; Giguère, Y.; Villa, P.; Nicolaides, K.; Vainio, M.; Forest, J.-C.; von Dadelzen, P.; Vaiman, D.; Tapp, S.; Bujold, E., Early administration of low-dose aspirin for the prevention of severe and mild preeclampsia: a systematic review and meta-analysis. *American journal of perinatology* 2012, 29 (7), 551-556.
27. Villa, P. M.; Kajantie, E.; Räikkönen, K.; Pesonen, A. K.; Hämläinen, E.; Vainio, M.; Taipale, P.; Laivuori,

- H.; group, P. S., Aspirin in the prevention of pre-eclampsia in high-risk women: a randomised placebo-controlled PREDO Trial and a meta-analysis of randomised trials. *BJOG* 2013, 120 (1), 64-74.
28. Schramm, A.; Clowse, M. E. B., Aspirin for prevention of preeclampsia in lupus pregnancy. *Autoimmune Diseases* 2014, 2014, 920467-920467.
 29. Appenzeller S1, Souza FH, Wagner Silva de Souza A, Shoenfeld Y, de Carvalho JF. HELLP syndrome and its relationship with antiphospholipid syndrome and antiphospholipid antibodies. *Semin Arthritis Rheum.* 2011, 41(3):517-23.
 30. Ko, H.; Ahn, H.; Jang, D.; Choi, S.-K.; Park, Y.-G.; Park, I.; Lee, G.; Park, S.-H.; Shin, J., Pregnancy outcomes and appropriate timing of pregnancy in 183 pregnancies in Korean patients with SLE. *International journal of medical sciences* 2011, 8 (7), 577-583.
 31. Stagnaro Green, A., Maternal thyroid disease and preterm delivery. *The Journal of clinical endocrinology and metabolism* 2009, 94 (1), 21-25.
 32. He, X.; Wang, P.; Wang, Z.; Xu, D.; Wang, B., Thyroid antibodies and risk of preterm delivery: a meta-analysis of prospective cohort studies. *European journal of endocrinology* 2012, 167 (4), 455-464.
 33. Clowse, M. E. B.; Wallace, D.; Weisman, M.; James, A.; Criscione Schreiber, L.; Pisetsky, D., Predictors of preterm birth in patients with mild systemic lupus erythematosus. *Annals of the rheumatic diseases* 2013, 72 (9), 1536-1539.
 34. Hornberger, L. K.; Al Rajaa, N., Spectrum of cardiac involvement in neonatal lupus. *Scand J Immunol* 2010, 72 (3), 189-97.
 35. Buyon, J. P.; Hiebert, R.; Copel, J.; Craft, J.; Friedman, D.; Katholi, M.; Lee, L. A.; Provost, T. T.; Reichlin, M.; Rider, L.; Rupel, A.; Saleeb, S.; Weston, W. L.; Skovron, M. L., Autoimmune-associated congenital heart block: demographics, mortality, morbidity and recurrence rates obtained from a national neonatal lupus registry. *J Am Coll Cardiol* 1998, 31 (7), 1658-66.
 36. Brucato, A.; Doria, A.; Frassi, M.; Castellino, G.; Franceschini, F.; Faden, D.; Pisoni, M. P.; Solerte, L.; Muscarà, M.; Lojacono, A.; Motta, M.; Cavazzana, I.; Ghirardello, A.; Vescovi, F.; Tombini, V.; Cimaz, R.; Gambari, P. F.; Meroni, P. L.; Canesi, B.; Tincani, A., Pregnancy outcome in 100 women with autoimmune diseases and anti-Ro/SSA antibodies: a prospective controlled study. *Lupus* 2002, 11 (11), 716-21.
 37. Llanos, C.; Izmirly, P. M.; Katholi, M.; Clancy, R. M.; Friedman, D. M.; Kim, M. Y.; Buyon, J. P., Recurrence rates of cardiac manifestations associated with neonatal lupus and maternal/fetal risk factors. *Arthritis Rheum* 2009, 60 (10), 3091-7.
 38. Jaeggi, E.; Laskin, C.; Hamilton, R.; Kingdom, J.; Silverman, E., The importance of the level of maternal anti-Ro/SSA antibodies as a prognostic marker of the development of cardiac neonatal lupus erythematosus a prospective study of 186 antibody-exposed fetuses and infants. *J Am Coll Cardiol* 2010, 55 (24), 2778-84.
 39. Anami; Fukushima, K.; Takasaki, Y.; Sumida, T.; Waguri, M.; Wake, N.; Murashima, A., The predictive value of anti-SS-A antibodies titration in pregnant women with fetal congenital heart block. *Modern rheumatology* 2013, 23 (4), 653-658.
 40. Spence, D.; Hornberger, L.; Hamilton, R.; Silverman, E. D., Increased risk of complete congenital heart block in infants born to women with hypothyroidism and anti-Ro and/or anti-La antibodies. *J Rheumatol* 2006, 33 (1), 167-70.
 41. Buyon, J. P.; Clancy, R. M.; Friedman, D. M., Cardiac manifestations of neonatal lupus erythematosus: guidelines to management, integrating clues from the bench and bedside. *Nat Clin Pract Rheumatol* 2009, 5 (3), 139-48.
 42. Mevorach, D.; Elchalal, U.; Rein, A. J. J. T., Prevention of complete heart block in children of mothers with anti-SSA/Ro and anti-SSB/La

- autoantibodies: detection and treatment of first-degree atrioventricular block. *Current opinion in rheumatology* 2009, 21 (5), 478-482.
43. Rein, A. J.; Mevorach, D.; Perles, Z.; Gavri, S.; Nadjari, M.; Nir, A.; Elchalal, U., Early diagnosis and treatment of atrioventricular block in the fetus exposed to maternal anti-SSA/Ro-SSB/La antibodies: a prospective, observational, fetal kinetocardiogram-based study. *Circulation* 2009, 119 (14), 1867-72;
 44. Routsias, J. G.; Kyriakidis, N. C.; Friedman, D. M.; Llanos, C.; Clancy, R.; Moutsopoulos, H. M.; Buyon, J.; Tzioufas, A. G., Association of the idiotype:antiidiotype antibody ratio with the efficacy of intravenous immunoglobulin treatment for the prevention of recurrent autoimmune-associated congenital heart block. *Arthritis Rheum* 2011, 63 (9), 2783-9.
 45. Saxena, A.; Izmirly, P. M.; Mendez, B.; Buyon, J. P.; Friedman, D. M., Prevention and Treatment in Utero of Autoimmune Associated Congenital Heart Block. *Cardiol Rev* 2014.
 46. Hutter, D.; Silverman, E. D.; Jaeggi, E. T., The benefits of transplacental treatment of isolated congenital complete heart block associated with maternal anti-Ro/SSA antibodies: a review. *Scand J Immunol* 2010, 72 (3), 235-41.
 47. Izmirly, P.; Kim, M.; Llanos, C.; Le, P.; Guerra, M.; Askanase, A.; Salmon, J.; Buyon, J., Evaluation of the risk of anti-SSA/Ro-SSB/La antibody-associated cardiac manifestations of neonatal lupus in fetuses of mothers with systemic lupus erythematosus exposed to hydroxychloroquine. *Annals of the rheumatic diseases* 2010, 69 (10), 1827-1830;
 48. Izmirly, P.; Costedoat Chalumeau, N.; Pisoni, C.; Khamashta, M.; Kim, M.; Saxena, A.; Friedman, D.; Llanos, C.; Piette, J.-C.; Buyon, J., Maternal use of hydroxychloroquine is associated with a reduced risk of recurrent anti-SSA/Ro-antibody-associated cardiac manifestations of neonatal lupus. *Circulation* 2012, 126 (1), 76-82.
 49. Benediktsson, R.; Calder, A. A.; Edwards, C. R.; Seckl, J. R., Placental 11 beta-hydroxysteroid dehydrogenase: a key regulator of fetal glucocorticoid exposure. *Clin Endocrinol (Oxf)* 1997, 46 (2), 161-6.
 50. Park-Wyllie, L.; Mazzotta, P.; Pastuszak, A.; Moretti, M. E.; Beique, L.; Hunnisett, L.; Friesen, M. H.; Jacobson, S.; Kasapinovic, S.; Chang, D.; Diav-Citrin, O.; Chitayat, D.; Nulman, I.; Einarson, T. R.; Koren, G., Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. *Teratology* 2000, 62 (6), 385-92.
 51. Østensen, M.; Khamashta, M.; Lockshin, M.; Parke, A.; Brucato, A.; Carp, H.; Doria, A.; Rai, R.; Meroni, P.; Cetin, I.; Derksen, R.; Branch, W.; Motta, M.; Gordon, C.; Ruiz-Irastorza, G.; Spinillo, A.; Friedman, D.; Cimaz, R.; Czeizel, A.; Piette, J. C.; Cervera, R.; Levy, R. A.; Clementi, M.; De Carolis, S.; Petri, M.; Shoenfeld, Y.; Faden, D.; Valesini, G.; Tincani, A., Anti-inflammatory and immunosuppressive drugs and reproduction. *Arthritis Res Ther* 2006, 8 (3), 209.
 52. Czeizel, A. E.; Rockenbauer, M., Population-based case-control study of teratogenic potential of corticosteroids. *Teratology* 1997, 56 (5), 335-40;
 53. Källén, B., Maternal drug use and infant cleft lip/palate with special reference to corticoids. *Cleft Palate Craniofac J* 2003, 40 (6), 624-8.
 54. Hviid, A.; Mølgaard-Nielsen, D., Corticosteroid use during pregnancy and risk of orofacial clefts. *CMAJ* 2011, 183 (7), 796-804.
 55. Yeh, T. F.; Lin, Y. J.; Lin, H. C.; Huang, C. C.; Hsieh, W. S.; Lin, C. H.; Tsai, C. H., Outcomes at school age after postnatal dexamethasone therapy for lung disease of prematurity. *N Engl J Med* 2004, 350 (13), 1304-13.
 56. Marder, W.; Ganser, M. A.; Romero, V.; Hyzy, M. A.; Gordon, C.; McCune, W. J.; Somers, E. C., In utero azathioprine exposure and increased utilization of

- special educational services in children born to mothers with systemic lupus erythematosus. *Arthritis Care Res (Hoboken)* 2013, 65 (5), 759-66.
57. Sifontis, N. M.; Coscia, L. A.; Constantinescu, S.; Lavelanet, A. F.; Moritz, M. J.; Armenti, V. T., Pregnancy outcomes in solid organ transplant recipients with exposure to mycophenolate mofetil or sirolimus. *Transplantation* 2006, 82 (12), 1698-702.
 58. Fischer Betz, R.; Specker, C.; Brinks, R.; Aringer, M.; Schneider, M., Low risk of renal flares and negative outcomes in women with lupus nephritis conceiving after switching from mycophenolate mofetil to azathioprine. *Rheumatology* 2013, 52 (6), 1070-1076.
 59. Murashima; Fukazawa; Hirashima; Takasaki; Oonishi; Niiijima; Yamashiro; Yamataka; Miyano; Hashimoto, Long term prognosis of children born to lupus patients. *Annals of the rheumatic diseases* 2004, 63 (1), 50-53.
 60. Ross, G.; Sammaritano, L.; Nass, R.; Lockshin, M., Effects of mothers' autoimmune disease during pregnancy on learning disabilities and hand preference in their children. *Archives of pediatrics & adolescent medicine* 2003, 157 (4), 397-402