Original Article
Food Science and Technology

ISSN 0101-2061 (Print)
ISSN 1678-457X (Online)

DOI: https://doi.org/10.1590/fst.56921

Maternal and neonatal outcomes of pregnancy complicated with Systemic Lupus Erythematosus

Jie LI[1], Zengyan LI[1]*, Limin YU[1], Jing SU[1]

Abstract

To study the maternal and neonatal outcomes of pregnancy complicated with Systemic Lupus Erythematosus (SLE). Clinical data of 84 pregnant women complicated with SLE were collected. All patients were divided into the different groups based on the pregestational status of SLE, SLE status during pregnancy and the type of medicine administration respectively. The incidence rates of pregnancy loss and preterm labor in the pregestational and gestational stable SLE groups were significantly lower and the incidence rate of full-term labor was considerably higher than those in the active SLE groups. In the pregestational stable SLE group, the incidence of PIH was significantly lower than that in the active SLE group. The incidence of PIH and FGR in the gestational active SLE group was dramatically higher than that in the gestational stable SLE group. Among 84 women, 56 (66.7%) received cesarean section, 18 (21.4%) vaginal delivery and 10 (11.9%) labor induction. The status of SLE is intimately correlated with maternal and neonatal outcomes. PIH is a major complication of active SLE and associated with adverse pregnancy outcomes. SLE can cause congenital fetal injury, especially congenital heart block.

Keywords: delivery; neonatal outcome; pregnancy; systemic lupus erythematosus.

Practical Application: Reducing the risk of adverse maternal and neonatal outcomes in pregnant women complicated with SLE.

1 Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease. In this disease, the body's immune system mistakenly attacks healthy tissue. It primarily affects the kidney, skin, joints, brain, and alternative vital organs. SLE is more common in women than men. It may occur at any age, whereas it most frequently appears most often in women between the ages of 20 and 40. SLE affects African Americans and Asians more often than people from other races (McCarty et al., 1995; Pons-Estel et al., 2010). More and more efforts have been attached to the understanding, diagnosis and treatment of pregnancy complicated with SLE. Relevant factors of pregnancy complicated with SLE have been extensively investigated by multiple researchers. Besides, different guidelines on the diagnosis and treatment of pregnancy complicated with SLE have been established, aiming to enhance the success rate of pregnancy in SLE patients. The relationship between pregnancy and SLE remains elusive and complicated (Stojan & Baer, 2012). Previous studies have demonstrated that SLE pregnant woman can obtain relatively favorable pregnancy outcomes (Carmona et al., 1999), whereas other scholars have found that the incidence of adverse pregnancy outcomes in SLE pregnant women is higher compared with that in healthy counterparts (Chen et al., 2015; Ku et al., 2016). The recurrence rate of SLE is up to 60% during the period of pregnancy (Petri et al., 1991), but others have reported a relatively low recurrence rate (Carmona et al., 1999; Stojan & Baer, 2012). In addition, SLE pregnant women have a higher risk of pregnancy-induced hypertension syndrome (PIH), fetal growth restriction (FGR), fetal distress, pregnancy loss, preterm labor and other adverse pregnancy outcomes compared with those of healthy counterparts.

A recent meta-analysis consisting of 1842 SLE pregnant women has reported that the incidence rate of SLE recurrence, PIH, nephritis, preeclampsia and eclampsia is 25.6%,16.3%,16.1%,7.6% and 0.8%, respectively. However, the risk of serious obstetrics complications, such as lupus encephalopathy and maternal death is merely 1% (Smyth et al., 2010). Another systemic review has reported that the incidence of induced abortion is 5.9%, 16.0% for natural abortion, 3.6% for dead birth, 2.5% for neonatal death, 12.7% for FGR, 23.4% for pregnancy failure and 39.4% for preterm labor, respectively.

SLE pregnant women have a higher risk of neonatal heart disease than their healthy counterparts.Neonatal lupus (NL) is caused by the migration of the anti-Sjogren syndrome A (SSA) antibody and SSB antibody from the maternal blood into the fetus through placental circulation. The incidence of heart abnormality complicated with NL is 1-2%, and 18% for women who have a history of delivery of neonatal heart defects. In addition, rash and heart block are the major clinical manifestations of NL. Previous research has revealed that the mean age of rash onset is 6 weeks after labor (Llanos et al., 2009). In general, rash can disappear spontaneously, whereas it may exist due to telangiectasis and excessive pigment deposition (Gladman et al., 2002). The mortality rate of neonatal NL complicated with heart abnormality is high

Received 09 July, 2021
Accepted 17 Aug., 2021
[1]*Obstetrical Department, Tianjin Medical University General Hospital, Tian Jin, China*
*Corresponding author: zengyan_li@aol.com

up to 16-17.5%, and approximately 10% of them have to receive pacemaker treatment before age of 10 (Eliasson et al., 2011).

In this study, the conception timing, pregnancy monitoring and postpartum management were explored to prevent the incidence and progression of SLE and reduce the risk of adverse maternal and neonatal outcomes in pregnant women complicated with SLE.

2 Materials and methods

2.1 Baseline data

Clinical data of 84 pregnant women complicated with SLE admitted to Tianjin Medical University General Hospital between January 2010 and December 2016 were retrospectively collected and analyzed. Six SLE patients were also complicated with APS. All patients received joint treatment from obstetrics and rheumatism immunity departments. Baseline data including name, age, time of pregnancy, time of labor and delivery mode were recorded. The course of SLE and pregestational SLE status were evaluated. Pregestational clinical manifestations, laboratory examination, medication status, obstetrics complications, pregnancy outcomes and neonatal status were observed and performed.

2.2 Diagnostic criteria for SLE

According to the American College of Rheumatology revised criteria for the classification of SLE (Wagner et al., 2009), 11 parameters were included for comprehensive assessment including malar rash, discoid rash, photosensitivity, oral ulcers, non-erosive arthritis, pleuritis or pericarditis, renal disorder, neurologic disorder, hematologic disorder, immunologic disorder (positive findings of anti-DNA, anti-Sm and anti-phospholipid antibodies) and positive anti-nuclear antibody. The diagnosis of SLE can be validated if 4 or above parameters are identified. An abnormal tier of anti-nuclear antibody and immunologic disorder are of diagnostic significance.

2.3 Patient grouping

According to the pregestational status of SLE, all patients were divided into the pregestational stable (group A, n=55) and active SLE groups (group B, n=29). Pregestational stable SLE group: usage of prednisone at a dose of <=15 mg/d; no usage of cytotoxin or discontinued for >= 6 months; stable laboratory parameters. Pregestational active SLE group: usage of prednisone at a dose of >15 mg/d; use of cytotoxin or discontinued within 6 months; laboratory parameters, such as reduction in hemoglobin, white blood cell, thrombocytopenia and complement, progressive increase in urinary protein and increase in the titer of anti-ds-DNA antibody. Active SLE was evaluated if systemic lupus erythematosus disease activity index (SLEDAI) >4 (Carvalheiras et al., 2012).

Based upon the status of SLE during pregnancy, all women were assigned into the gestational stable (group C, n=46) and active SLE groups (group D, n=38). The severity of SLE is aggravated if one of the follows occurs: presence of albuminuria and/or hematuria; mental or central nervous system manifestations; mental or central nervous system abnormality induced by alternative factors except preeclampsia, eclampsia and HELLP syndrome, etc. White blood cell decrease or thrombocytopenia, hemolytic anemia, positive Coombs test; new onset of skin rash, photosensitivity, joint tumor and oral ulcers; body temperature>38 °C; presence of PIH, HELLP syndrome, liver and kidney dysfunction, *etc*.

According to the type of medicine administration, all patients were assigned into the hormone (group E, n=62), hormone combined with oxychloroquine (group F, n=17) and hormone combined with aspirin groups (group G, n=5). Based upon the medical history of adverse pregnancy, 84 patients were divided into two groups.

2.4 Laboratory and immune parameters

Laboratory parameters included red blood cell, white blood cell, hemoglobin and platelet count; D-dimer; qualitative assessment of urinary protein, 24-h quantitative analysis of urinary protein, urine creatinine, glutamic-pyruvic transaminase, glutamic oxalacetictransaminase, albumin, serum creatinine; immune parameters consisted of antinuclear antibody (ANA), anti-double-stranded DNA, dsDNA antibody, anti-Sm antibody, complement C3, complement C4, anti-SSA antibody, anti-SSB antibody, anti-phospholipid antibody, anticardiolipin antibody (ACA) and anti-β2 glycoprotein I (β2GPI) antibody.

2.5 Clinical parameters

Clinical parameters included blood pressure, subjective symptom, such as headache, dizziness, blurry visual acuity, joint pain, photosensitivity, skin rash, recurrent oral ulcers, dry mouth, dry eye and fever. Obstetrics and obstetrics complications consisted of PIH, FGR and fetal distress.

2.6 Pregnancy outcomes

Pregnancy outcomes included pregnancy loss, such as abortion, still birth, death birth, neonatal death and pregnancy success consisting of preterm labor and full-term labor.

2.7 Statistical analysis

SPSS 19.0 statistical software was utilized for data analysis (SPSS Inc., Chicago, U.S.). Normally-distributed data were expressed as mean ± standard deviation ($x \pm s$). Group comparison was conducted by independent sample *t*-test. Qualitative data were expressed as number of cases (percentage). Group comparison was performed by chi-square test or Fisher exact test. A value of $P<0.05$ was considered as statistically significant.

3 Results

3.1 Baseline data

All 84 enrolled SLE women had singleton pregnancies conceived naturally. The average age was (29.89 ± 4.27) years (range: 21-41). The mean course of SLE was (4.89 ± 3.82) years (range: 0-16). The gestational age was (35.35 ± 6.14) weeks on

average (range: 16-40^{+6}), as demonstrated in Table 1. The initial onset of SLE was observed in 6 women (7.1%) during pregnancy, in 32 (38.1%) during the 1st pregnancy, in 29 (34.5%) during the 2nd pregnancy, in 23 (27.4%) during the 3rd pregnancy, SLE complicated with APS in 6 (7.1%), LN in 7 (8.3%) and thrombocytopenia in 8 patients, accounting for 9.5%.

3.2 Immune parameters

Among 84 SLE pregnant women, 82 (97.6%) were positive for ANA antibody, 72 (85.7%) positive for ds-DNA, 22 (26.2%) positive for anti-Sm antibody, 13 (15.5%) positive for anti-SSA antibody, 5 (6.0%) positive for anti-SSB antibody, reduction in complement C3 in 59 (70.2%), complement C4 reduction in 35 (41.7%) and positive ACA in 6 women (7.1%), as shown in Table 1.

3.3 Effect of SLE on pregnancy outcomes

Among 84 patients, 11 (13.1%) suffered from pregnancy loss and 73 (86.9%) obtained natural pregnancy including 23 (27.4%) preterm labor and 50 (59.5%) full-term labor. In group A, 2 (3.6%) women had pregnancy loss, 10 (18.2%) had preterm labor and 43 (78.2%) full-term labor. In group B, 9 (31.0%) women had pregnancy loss, 13 (44.8%) had preterm labor and 7 (24.2%) full-term labor. The incidence rate of pregnancy loss (χ^2=10.233, P=0.001), preterm labor (χ^2=6.780, P=0.009) and full-term labor (χ^2=23.019, P=0.000) significantly differed between groups A and B. No pregnancy loss, 8 (17.4%) preterm labor and 38 (82.6%) full-term labor were observed in group C. In group D, 11 (28.9%) women had pregnancy loss, 10 (18.2%) had preterm labor and 43 (78.2%) full-term labor. In group B, 9 (31.0%) women had pregnancy loss, 15 (39.5%) had preterm labor and 12 (31.6%) full-term labor. The incidence rate of pregnancy loss (P=0.000), preterm labor (χ^2=5.103, P=0.024) and full-term labor (χ^2=22.494, P=0.000) significantly differed between groups C and D.

Table 1. Baseline data of pregnant women complicated with SLE.

Parameter	Value
Age (year, x ± s, range)	29.89 ± 4.27 (21-41)
Course of SLE (year, x ± s, range)	4.89 ± 3.82 (0-16)
Gestational age (week, x ± s, range)	35.35 ± 6.14 (16-40^{+6})
Initial onset of SLE during pregnancy	6(7.1%)
The 1st pregnancy	32(38.1%)
The 2nd pregnancy	29(34.5%)
≥ the 3rd pregnancy	23(27.4%)
APS	6(7.1%)
LN	7 (8.3%)
Thrombocytopenia	8 (9.5%)
Immune parameters	
Positive ANA	82 (97.6%)
Positive ds-DNA	72 (85.7%)
Positive anti-Sm-antibody	22 (26.2%)
Positive anti-SSA/Ro antibody	13 (15.5%)
Positive anti-SSA/La antibody	5 (6.0%)
Decrease in complement C3	59 (70.2%)
Decrease in complement C4	35 (41.7%)
Positive ACA	6 (7.1%)

3.4 Effect of SLE on obstetric complications

The percentage of PIH significantly differed between groups A and B (χ^2=26.802, P=0.000), whereas no statistical significance was observed in terms of the incidence of FGR (χ^2=1.454, P=0.228) and fetal distress (χ^2=0.000, P=1.000). Pregestational active status of SLE could enhance the incidence of PIH. In group C, the mean age was (30.40 ± 3.34) years (range: 22-36), and (30.60 ± 5.14) years (range: 21-41) in group D with no statistical significance between two groups (both P>0.05). Among 55 women with pregestational stable SLE, 9 (16.4%) had active SLE during pregnancy. In group B, all 29 women had active SLE during pregnancy. The incidence rate of PIH (P=0.000) and FGR (P=0.038) significantly differed, whereas the incidence of fetal distress did not significantly differ between groups C and D (χ^2=0.102, P=0.750).

3.5 Effect of SLE on delivery method

Among 84 SLE pregnant women, 56 (66.7%) received cesarean section, 18 (21.4%) vaginal delivery and 10 (11.9%) labor induction. In the active SLE group, 1 woman received cesarean section at a gestational age of 26^{+2} weeks due to HELLP syndrome. Postoperatively, she was transferred to Intensive Care Unit for comprehensive treatment. In group A, 36 (65.5%) received cesarean section, 17 (30.9%) vaginal delivery and 2 (3.6%) labor induction. In group B, 20 (69.0%) received cesarean section, 1 (3.4%) vaginal delivery and 8 (27.6%) labor induction. The incidence rate of vaginal delivery (χ^2=6.952, P=0.008) and labor induction (χ^2=8.227, P=0.004) significantly differed, whereas the incidence of cesarean section (χ^2=0.105, P=0.746) did not significantly differ between groups A and B. In group C, 29 women (63.0%) received cesarean section, 17 (37.0%) vaginal delivery and no case received labor induction. In group D, 27 (71.1%) received cesarean section, 1 (2.6%) vaginal delivery and 10 (26.3%) labor induction. The incidence of vaginal delivery (χ^2=12.595, P=0.000) and labor induction (P=0.000) significantly differed, whereas percentage of cesarean section did not significantly differ between groups C and D (χ^2=0.601, P=0.438).

3.6 Cesarean section and surgical indications

Seventy-three women were successfully pregnant. Among them, 55 cases (75.3%) received cesarean section including 34 (61.8%) full-term labor and 21 (38.2%) preterm labor. In terms of surgical indications of cesarean section, SLE was documented in 18 women (32.7%), PIH/HELLP syndrome in 15 (27.3%), and complications induced by active SLE accounted for 43.7%. Preventing the progression of SLE during pregnancy could significantly reduce the percentage of cesarean section. Twenty-three patients had preterm labor, 21 terminated the pregnancy by cesarean section and 11 (52.4%) received cesarean section due to PIH/HELLP syndrome. Four women (19.0%) received cesarean section due to SLE, 2 (9.5%) due to uterine scars, 1 fetal distress, 1 low-lying placenta and 1 rheumatic heart disease, respectively, as demonstrated in Figure 1.

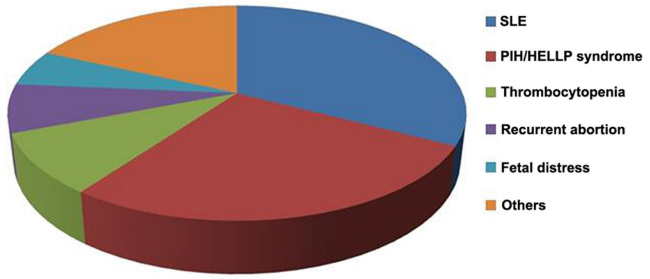

Figure 1. Graph illustrating the surgical indications of cesarean section.

3.7 Effect of medication on pregnancy outcomes

Patients who were positive for SSA/Ro antibody and SSB/La antibody and complicated with rash were supplemented with oxychloroquine. Those complicated with APS, recurrent pregnancy loss or significant increase in D-dimer levels was administered with aspirin, and low-molecular-weight heparin when necessary. The incidence rate of pregnancy loss, preterm labor and full-term labor did not significantly differ among groups E, F and G (all $P>0.05$).

3.8 Effect of history of adverse pregnancy on pregnancy outcomes

Among 83 SLE pregnant women, 43 (51.2%) had a medical history of adverse pregnancy including abortion and still birth, *etc*. The incidence rate of pregnancy loss, preterm labor and full-term labor did not significantly differ between women with and their counterparts without a medical history of adverse pregnancy (all P>0.05).

4 Discussion

SLE can theoretically cause autoimmune ovary injury and ovary dysfunction, lead to hypothalamic-pituitary-ovarian axis changes and ovarian reserve decline. All these changes make SLE woman infertile. However, multiple studies have demonstrated that the conception probability does not significantly differ between SLE women and their healthy counterparts (Yang et al., 2014). The status of status exerts effect upon the maternal and neonatal outcomes. Alternative researches have indicated that the prevalence of preterm labor and pregnancy loss in SLE women is significantly higher compared with that of normal counterparts. The prevalence of preterm labor in SLE pregnant woman fluctuates between 12.1% and 54% (Saito et al., 2010; Moroni & Ponticelli, 2014), and 3%-36% for the incidence of fetal lose (Aluvihare et al., 2004; Dardalhon et al., 2010). In this study, the incidence of PIH, pregnancy loss and preterm labor significantly differs between the pregestational active and stable SLE groups, suggesting that pregestational active status of SLE probably increases the incidence of PIH, pregnancy loss and preterm labor. In addition, the incidence of PIH, FGR, pregnancy loss and preterm labor also considerably varies between the gestational active and stable SLE groups, indicating that gestational active SLE status could enhance the risk of PIH, FGR, pregnancy loss and preterm labor.

Among women with stable SLE, the active rate of SLE attained to 35% after conception, and 83% for those with active SLE. For pregnant women with active LN, the kidney disease was further aggravated in approximately 50%-60% of patients after conception. For patients with pregestational stable SLE for 3-6 months, merely 7%-10% of them suffered from the recurrence or exacerbation of SLE after conception (Ruiz-Irastorza & Khamashta, 2004; Sarter et al., 2013). In this study, 9 among 55 women (16.4%) with pregestational stable SLE presented with active SLE during pregnancy. Twenty-nine women with pregestational active SLE all had active SLE during pregnancy, suggesting that pregnancy exerts a certain effect upon the recurrence of SLE.

During conception, the status of SLE (active or stable) is intimately correlated with gestational complications and pregnancy outcomes. The active status of SLE during conception may lead to adverse maternal and neonatal outcomes. A multi-center research of 56 SLE pregnant women have found that pregnant women with pregestational stable SLE for > 6 months obtain relatively favorable maternal and neonatal outcomes (Ruffatti et al., 2011). Compared with pregnant women with active SLE, the pregnancy rate, delivery rate and full-term delivery rate in their counterparts with stable SLE for at least 6 months are significantly enhanced, whereas the incidence of gestational complications and the recurrence and aggravation of postpartum SLE are considerably declined (Narin et al., 2008). In this study, the percentage of pregnancy loss and preterm labor in the pregestational stable SLE group was significantly lower compared with that in the pregestational active SLE group. Therefore, SLE women are recommended to prepare for pregnancy when the SLE remains stable for at least 6 months. Whether it is applicable for those with stable for 4-6 months remains to be further validated.

SLE is not an absolute indication of cesarean section. Nevertheless, it is recommended to perform cesarean section to terminate pregnancy for pregnant women who are complicated with fetal abnormality and severe gestational complications. In this study, 73 among 84 SLE women were successfully pregnant and 55 patients (75.3%) received cesarean section at a gestational age of 30 to 39+6 weeks. The percentage of full-term delivery via cesarean section was 61.8% (34/55), and the proportion of preterm labor via cesarean section was 38.2 (21/55). In terms of surgical indications of cesarean section, SLE was documented in 18 women (32.7%), PIH/HELLP syndrome in 15 (27.3%), and complications induced by active SLE accounted for 43.7%. In this investigation, a majority of SLE patients selected cesarean section for the termination of pregnancy. Merely approximately 1/3 of pregnant women who were complicated with SLE alone chose to receive cesarean section.

PIH is a common obstetrics complication with a national prevalence of approximately 9.4% in China, and approximately 7%-12% reported worldwide. SLE patients are likely to suffer from PIH during gestation period. The prevalence of preeclampsia in SLE pregnant women is around 7.5%-22% (Wagner et al., 2009), approximately 3% higher compared with that in their healthy counterparts (Moroni & Ponticelli, 2003). In this study, the incidence rate of PIH in SLE women was calculated as 27.4%

(23/84). The incidence of PIH in the pregestational active SLE group was significantly higher than that in the pregestational stable SLE group. The prevalence of PIH in the gestational active SLE group was considerably higher compared with that in the gestational stable SLE group. Consequently, the severity of SLE is correlated with the risk of both pregestational and gestational PIH. Approximately 50%-70% of SLE patients suffer from varying degree of kidney injury, and almost all patients present with pathological changes confirmed by renal biopsy. In this study, 7 SLE patients were complicated with LN. Among them, 3 women were complicated with severe preeclampsia and received the termination of pregnancy at the gestational age of 17, 22^{+6} and 16^{+4} weeks, respectively. One patient was complicated with severe preeclampsia and HELLP syndrome and fetal death was identified at the gestational age of 22^{+6}, and she had to receive the termination of pregnancy. Due to the small sample size of LN cases, whether LN pregnant women are more likely to suffer from preeclampsia remains to be subsequently validated.

Anti-phospholipid syndrome is an inflammatory autoimmune disease, which is characterized with recurrent onset of arterial and/or venous thrombosis, natural abortion and/or still birth, thrombocytopenia and positive anti-phospholipid antibody (APA) (Yamamoto & Aoki, 2016). In this study, 6 SLE women were complicated with APS, aged 23-35 years, had a medical history of at least twice embryo damage. Among them, 5 women obtained full-term delivery, and 1 had fetal death at the gestational age of 22^{+6} weeks. She was complicated with HELLP syndrome and chorion amnionitis. All 6 patients were positive for ACA. Positive ACA is a vital parameter for the clinical diagnosis of APA. It is intimately associated with adverse pregnancy outcomes, such as recurrent abortion, embryo damage and still birth, *etc*.

In this study, 13 among 84 pregnant women complicated with SLE were detected positive for SSA/Ro antibody and 5 were positive for SSB/La antibody. One newborn presented with skin rash. All women were followed up for 3 months to 6 years. Eighteen infants were not complicated with LN. A prospective study has suggested that 40 infants among 186 pregnant women are diagnosed with congenital heart block. No case presents with congenital heart block when the range of maternal serum titer of anti-SSA/Ro antibody is 8-49 U/mL. Six cases (15%) are diagnosed with congenital heart block when the titer of anti-SSA/Ro antibody is 50-100 U/mL. Thirty-four cases (85%) suffer from congenital heart block when the titer of anti-SSA/Ro antibody exceeds 100 U/mL (Jaeggi et al., 2010). To avoid the incidence of embryo congenital heart block, active measures should be taken to reduce the maternal serum titer of anti-SSA/Ro antibody. Heart ultrasound is recommended to make an early diagnosis and deliver effective interventions.

5 Conclusion

SLE pregnant women have a high risk of adverse pregnancy outcomes and SLE recurrence. Nevertheless, they can obtain high pregnancy rate if joint intervention and treatment are delivered from multi-disciplinary departments. The status of SLE (active or stable) is intimately correlated with maternal and neonatal outcomes. SLE patients are recommended to prepare for conception during stable SLE stage to enhance the success rate of pregnancy and decrease the risk of obstetrics complications. PIH is a major complication of active SLE, and significantly associated with adverse pregnancy outcomes. SLE can lead to congenital embryo damage, especially heart block. Early screening and timely intervention should be implemented. Taken together, multi-disciplinary department coordination should be performed for SLE pregnant women, aiming to improve the maternal and neonatal outcomes.

Conflict of interest

The authors declare that they have no conflict of interests.

Funding

None.

References

Aluvihare, V. R., Kallikourdis, M., & Betz, A. G. (2004). Regulatory T cells mediate maternal tolerance to the fetus. *Nature Immunology*, 5(3), 266-271. http://dx.doi.org/10.1038/ni1037. PMid:14758358.

Carmona, F., Font, J., Cervera, R., Muñoz, F., Cararach, V., & Balasch, J. (1999). Obstetrical outcome of pregnancy in patients with systemic Lupus erythematosus: a study of 60 cases. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, 83(2), 137-142. http://dx.doi.org/10.1016/S0301-2115(98)00312-1. PMid:10391522.

Carvalheiras, G., Faria, R., Braga, J., & Vasconcelos, C. (2012). Fetal outcome in autoimmune diseases. *Autoimmunity Reviews*, 11(6-7), A520-A530. http://dx.doi.org/10.1016/j.autrev.2011.12.002. PMid:22198431.

Chen, S., Sun, X., Wu, B., & Lian, X. (2015). Pregnancy in women with systemic lupus erythematosus: a retrospective study of 83 pregnancies at a single centre. *International Journal of Environmental Research and Public Health*, 12(8), 9876-9888. http://dx.doi.org/10.3390/ijerph120809876. PMid:26295404.

Dardalhon, V., Anderson, A. C., Karman, J., Apetoh, L., Chandwaskar, R., Lee, D. H., Cornejo, M., Nishi, N., Yamauchi, A., Quintana, F. J., Sobel, R. A., Hirashima, M., & Kuchroo, V. K. (2010). Tim-3/galectin-9 pathway: regulation of Th1 immunity through promotion of CD11b+Ly-6G+ myeloid cells. *Journal of Immunology*, 185(3), 1383-1392. http://dx.doi.org/10.4049/jimmunol.0903275. PMid:20574007.

Eliasson, H., Sonesson, S. E., Sharland, G., Granath, F., Simpson, J. M., Carvalho, J. S., Jicinska, H., Tomek, V., Dangel, J., Zielinsky, P., Respondek-Liberska, M., Freund, M. W., Mellander, M., Bartrons, J., & Gardiner, H. M. (2011). Isolated atrioventricular block in the fetus: a retrospective, multinational, multicenter study of 175 patients. *Circulation*, 124(18), 1919-1926. http://dx.doi.org/10.1161/CIRCULATIONAHA.111.041970. PMid:21986286.

Gladman, G., Silverman, E. D., Yuk-Law, Luy, L., Boutin, C., Laskin, C., & Smallhorn, J. F. (2002). Fetal echocardiographic screening of pregnancies of mothers with anti-Ro and/or anti-La antibodies. *American Journal of Perinatology*, 19(2), 73-80. http://dx.doi.org/10.1055/s-2002-23555. PMid:11938480.

Jaeggi, E., Laskin, C., Hamilton, R., Kingdom, J., & Silverman, E. (2010). 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. *Journal of the American College of Cardiology*, 55(24), 2778-2784. http://dx.doi.org/10.1016/j.jacc.2010.02.042. PMid:20538173.

Ku, M., Guo, S., Shang, W., Li, Q., Zeng, R., Han, M., Ge, S., & Xu, G. (2016). Pregnancy outcomes in chinese patients with Systemic Lupus Erythematosus (SLE): a retrospective study of 109 pregnancies. *PLoS One*, 11(7), e0159364. http://dx.doi.org/10.1371/journal.pone.0159364. PMid:27442513.

Llanos, C., Izmirly, P. M., Katholi, M., Clancy, R. M., Friedman, D. M., Kim, M. Y., & Buyon, J. P. (2009). Recurrence rates of cardiac manifestations associated with neonatal lupus and maternal/fetal risk factors. *Arthritis and Rheumatism*, 60(10), 3091-3097. http://dx.doi.org/10.1002/art.24768. PMid:19790064.

McCarty, D. J., Manzi, S., Medsger, T. A. Jr., Ramsey-Goldman, R., LaPorte, R. E., & Kwoh, C. K. (1995). Incidence of systemic lupus erythematosus. Race and gender differences. *Arthritis and Rheumatism*, 38(9), 1260-1270. http://dx.doi.org/10.1002/art.1780380914. PMid:7575721.

Moroni, G., & Ponticelli, C. (2003). The risk of pregnancy in patients with lupus nephritis. *Journal of Nephrology*, 16(2), 161-167. PMid:12768062.

Moroni, G., & Ponticelli, C. (2014). Rapidly progressive crescentic glomerulonephritis: early treatment is a must. *Autoimmunity Reviews*, 13(7), 723-729. http://dx.doi.org/10.1016/j.autrev.2014.02.007. PMid:24657897.

Narin, C., Ege, E., Orhan, A., & Yeniterzi, M. (2008). Repair of coarctation-related aortic arch aneurysm and ventricular septal defect in an adolescent. *Texas Heart Institute Journal*, 35(4), 466-469. PMid:19156244.

Petri, M., Howard, D., & Repke, J. (1991). Frequency of lupus flare in pregnancy. The Hopkins Lupus Pregnancy Center experience. *Arthritis and Rheumatism*, 34(12), 1538-1545. http://dx.doi.org/10.1002/art.1780341210. PMid:1670196.

Pons-Estel, G. J., Alarcon, G. S., Scofield, L., Reinlib, L., & Cooper, G. S. (2010). Understanding the epidemiology and progression of systemic lupus erythematosus. *Seminars in Arthritis and Rheumatism*, 39(4), 257-268. http://dx.doi.org/10.1016/j.semarthrit.2008.10.007. PMid:19136143.

Ruffatti, A., Tonello, M., Visentin, M. S., Bontadi, A., Hoxha, A., De Carolis, S., Botta, A., Salvi, S., Nuzzo, M., Rovere-Querini, P., Canti, V., Mosca, M., Mitic, G., Bertero, M. T., Pengo, V., Boffa, M. C., & Tincani, A. (2011). Risk factors for pregnancy failure in patients with anti-phospholipid syndrome treated with conventional therapies: a multicentre, case-control study. *Rheumatology*, 50(9), 1684-1689. http://dx.doi.org/10.1093/rheumatology/ker139. PMid:21652586.

Ruiz-Irastorza, G., & Khamashta, M. A. (2004). Evaluation of systemic lupus erythematosus activity during pregnancy. *Lupus*, 13(9), 679-682. http://dx.doi.org/10.1191/0961203304lu1099oa. PMid:15485102.

Saito, S., Nakashima, A., Shima, T., & Ito, M. (2010). Th1/Th2/Th17 and regulatory T-cell paradigm in pregnancy. *American Journal of Reproductive Immunology*, 63(6), 601-610. http://dx.doi.org/10.1111/j.1600-0897.2010.00852.x. PMid:20455873.

Sarter, K., Janko, C., Andre, S., Muñoz, L. E., Schorn, C., Winkler, S., Rech, J., Kaltner, H., Lorenz, H. M., Schiller, M., Andreoli, L., Manfredi, A. A., Isenberg, D. A., Schett, G., Herrmann, M., & Gabius, H. J. (2013). Autoantibodies against galectins are associated with antiphospholipid syndrome in patients with systemic lupus erythematosus. *Glycobiology*, 23(1), 12-22. http://dx.doi.org/10.1093/glycob/cws120. PMid:22887862.

Smyth, A., Oliveira, G. H., Lahr, B. D., Bailey, K. R., Norby, S. M., & Garovic, V. D. (2010). 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; CJASN*, 5(11), 2060-2068. http://dx.doi.org/10.2215/CJN.00240110. PMid:20688887.

Stojan, G., & Baer, A. N. (2012). Flares of systemic lupus erythematosus during pregnancy and the puerperium: prevention, diagnosis and management. *Expert Review of Clinical Immunology*, 8(5), 439-453. http://dx.doi.org/10.1586/eci.12.36. PMid:22882219.

Wagner, S. J., Craici, I., Reed, D., Norby, S., Bailey, K., Wiste, H. J., Wood, C. M., Moder, K. G., Liang, K. P., Liang, K. V., Rose, C., Rozkos, T., Sitina, M., Grande, J. P., & Garovic, V. D. (2009). Maternal and foetal outcomes in pregnant patients with active lupus nephritis. *Lupus*, 18(4), 342-347. http://dx.doi.org/10.1177/0961203308097575. PMid:19276302.

Yamamoto, Y., & Aoki, S. (2016). Systemic lupus erythematosus: strategies to improve pregnancy outcomes. *International Journal of Women's Health*, 8, 265-272. http://dx.doi.org/10.2147/IJWH.S90157. PMid:27468250.

Yang, H., Liu, H., Xu, D., Zhao, L., Wang, Q., Leng, X., Zheng, W., Zhang, F., Tang, F., & Zhang, X. (2014). Pregnancy-related systemic lupus erythematosus: clinical features, outcome and risk factors of disease flares--a case control study. *PLoS One*, 9(8), e104375. http://dx.doi.org/10.1371/journal.pone.0104375. PMid:25118692.