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Maternal, Fetal and Neonatal Outcomes in Pregnant Women with Systemic Lupus Erythematosus: A Comprehensive Review Study

Fatemeh Zahra Karimi[1], Masumeh Saeidi[2], Masoumeh Mirteimouri[3], *Nahid Maleki-Saghooni[3]

[1]Assistant Professor of Reproductive Health, Department of Midwifery, Evidence-Based Health Care Research Center, School of Nursing and Midwifery, Mashhad University of Medical Sciences, Mashhad, Iran.
[2]Students Research Committee, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran.
[3]Associate Professor, Department of Obstetrics and Gynecology, Patient Satety Research Center, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
[4]PhD Student of Reproductive Health, Students Research Committee, School of Nursing and Midwifery, Mashhad University of Medical Sciences, Mashhad, Iran.

Abstract

Background: Systemic lupus erythematosus (SLE) is an autoimmune disease with multiple organ involvement and periods of relapse and remission that mainly affects young women of childbearing age. In this regard the reproductive health is an important issue. Although diagnosis, treatment and management of pregnancy in SLE women have been improved recently, but the main concern is effects of SLE on maternal, fetal and neonatal outcomes. This study aimed to investigate the maternal, fetal and neonatal outcomes in pregnant women with SLE.

Materials and Methods: The databases of PubMed, Medline, Scopus and Web of Science as well as domestic database (Persian) such as SID, Magiran, Irandoc, and Google Scholar were searched with using keywords such as" Systemic lupus erythematosus"; "Pregnancy"; "Neonatal lupus"; "maternal, fetus or neonatal outcome"; and equivalent Persian words. Included were all Persian and English articles, published between 2000 and May 2017. Finally, a total of 77 studies were included.

Results: Adverse perinatal outcomes increase in pregnancies with lupus. Outcomes include respiratory, cardiovascular, blood and skin disorders in mothers; stillbirth, spontaneous, and recurrent abortion in fetuses and neonatal lupus, prematurity, intrauterine growth restriction (IUGR), and small for gestational age (SGA) in neonates, respectively.

Conclusion: Pregnant women with SLE are at high risk due to increased complications for both mother and fetus. It seems broad control of the women before fertilization, so that they be at full remission in the beginning of pregnancy and the disease activity be in complete control, it can help to improve outcomes of pregnancy and so better results can be expected.

Key Words: Fetus, Neonate, Pregnancy, Outcome, Systemic lupus erythematosus.

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Corresponding Author:

Nahid Maleki-Saghooni, School of Nursing and Midwifery, Mashhad University of Medical Sciences, Mashhad, Iran.

Email: malekisn931@mums.ac.ir

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1- INTRODUCTION

Systemic Lupus Erythematosus (SLE) is an inflammatory, autoimmune, chronic, multi-organ disease with remitting and relapsing periods (1, 2). Etiology of the disease is unknown; and has different clinical and laboratory manifestations (3). Although the origin of SLE is unknown, increasing evidence suggests that it caused by a combination of genetic, immune, hormonal and probably environmental factors (4). The disease manifestations might be limited to one organ from the beginning and other systems may be involved with the progression of the disease. Common findings include malaise, fever, arthritis, rash, pleuropericarditis, sensitivity to light, anemia and cognitive dysfunction. At least half of the patients had kidney involvement. Lupus is a disease that primarily affects the joints, skin and various internal organs like lungs, heart, kidneys, and central nervous system (CNS) (5). In this disease, tissues and cells are affected by antibodies and pathogenic immune complexes (6). In fact, lupus has a complex pathogenesis that creates an abnormal immune response. Immune system disorder is manifested in the form of overactive B cells producing auto-antibodies. Consequently when the autoantibodies or immune complexes are against one or more of the cell nucleus, cellular and tissue damage occurs. The disease is not cured and complete remission is rarely achieved (7). American College of Rheumatology criteria's are used as standard for the diagnosis of SLE around the world so that, if four or more than four criteria are present at each stage of the disease course, SLE can be diagnosed with specificity of 75%, and sensitivity of 95% **Table.1.**

Table-1: American College of Rheumatology criteria's (7).

Criteria	Description
Malar rash	Erythema (malar).
Discoid rash	Erythematous skin patches, scaling, follicular tubules.
Photosensitivity	Contact with ultraviolet rays can cause rash.
Oral/nasal ulcers	Ordinary painless ulcers of the mouth and nasopharynx.
Arthritis	Non-erosive and affects two or more peripheral joints and is associated with sensitivity, swelling or oppression.
Serositis	Pleuritis or pericarditis.
Renal disease	Proteinuria more than 0.5 grams per day or more than 3+ in the urine sample, or cell casts.
Neurological disorders	Seizures, Psychosis.
Hematologic disorders	Hemolytic anemia, Leukopenia, Lymphopenia, thrombocytopenia.
Immune disorders	Anti-dsDNA or anti-Sm antibodies, false-positive VDRL, abnormal levels of anti-Cardiolipin IgM, or IgG antibodies or anti-coagulant lupus.
Anti-nuclear antibodies	Abnormal increase in ANA titers.

VDRL: Venereal Disease Research Laboratory test; Anti-dsDNA: anti-double stranded DNA; IgM: Immunoglobulin M; IgG: Immunoglobulin G; ANA: Antinuclear Antibody.

Lupus has wide geographical distribution in different parts of the world, and many manifestations differences are seen among different ethnic and geographical groups. The prevalence of lupus in Iran, according to a large study of community-based study of rheumatic diseases control at the Rheumatology Research Center, is estimated to be 40 individuals per 100,000 populations (8). Although lupus can occur at any age and affect both genders; nevertheless, the ratio of affected women to men is around 9:1 and mainly affects young women in the reproductive age group (9). In fact, the disease is more common in women and the most common age of first referred patients was during the first, second, third or fourth decade of lifetime (4). The prevalence of lupus in women of reproductive age is about 1 in 500. For this reason the disease is relatively common during pregnancy. Therefore, the issue of reproductive health, including contraception is major topics of the patients. Pregnancy creates special problems for patients with SLE. A flare-up may occur during pregnancy. As a result, underlying organ damage or SLE treatment drugs may cause or aggravate pregnancy complications in mothers (4).

Several studies also have suggested that pregnant patients with SLE are at high risk due to increased complications for both the mother and fetus (1, 5, 6, 10). Maternal disease that appears during pregnancy can affect the fetus directly or indirectly. Autoantibody-mediated diseases can have direct consequences on fetus and newborn, because these auto-antibodies usually are from Immunoglobulin G (IgG) type that can cross the placenta and enter the fetal circulation (11). In the past, due to the frequent reports of severe relapses during pregnancy, and poor obstetric outcomes, the pregnancy was not supported in these women and therefore the termination of pregnancy was often recommend (1, 2). In recent decades, diagnosis, treatment strategies, and subsequent management of pregnancy in women with SLE has been greatly improved, but the main concern in these patients is effects of pregnancy on maternal disease as well as the SLE impact on midwifery and fetal outcomes (12).
Since awareness of the effects of lupus during pregnancy on maternal, fetal and neonatal outcomes plays a very important role for its management by the medical team (13), and since that previous studies have contradictory results, in order to increase the success rate in managing lupus-associated pregnancy and plans for better management of pregnancy, the researchers aimed to investigate the effect of lupus during pregnancy on maternal, fetal and neonatal outcomes.

2-MATERIALS AND METHODS

In this comprehensive review databases of PubMed, Medline, Scopus and Web of Science as well as domestic database (Persian) such as SID, Magiran, Irandoc, and Google Scholar were searched by two authors with keywords such as "Systemic lupus erythematosus"; "Pregnancy"; "Neonatal lupus"; "Maternal, fetus or neonatal outcome"; and equivalent Persian words using bulletin index such as AND, OR. Included were: all Persian and English articles which have the mentioned keywords in the title and abstract and related to the purpose of the research, published between Jan. 2000 to May 2017.

Articles with incomplete data, and also from other languages were excluded. In the initial review, 1,086 articles were found from those, 700 articles were extracted using the keywords of lupus and pregnancy, and 386 articles were extracted using the keywords of the lupus and maternal, fetal and neonatal outcomes. Of the collected articles, 1,009 documents were excluded in several steps by processes of article selection 600 and 64 articles removed by reviewing the title and abstract and 345 articles removed because

of irrelevant results or duplicate. A total of 77 studies were ultimately included in this review (**Table.2**). We extracted all information related to purpose of this study by the data extraction form. This form was designed by the research team and two researchers independently extracted data from the articles; any disagreements about data extraction were resolved through discussion between the assessors. The procedure of the search and selection of studies is appeared in **Figure.1.**

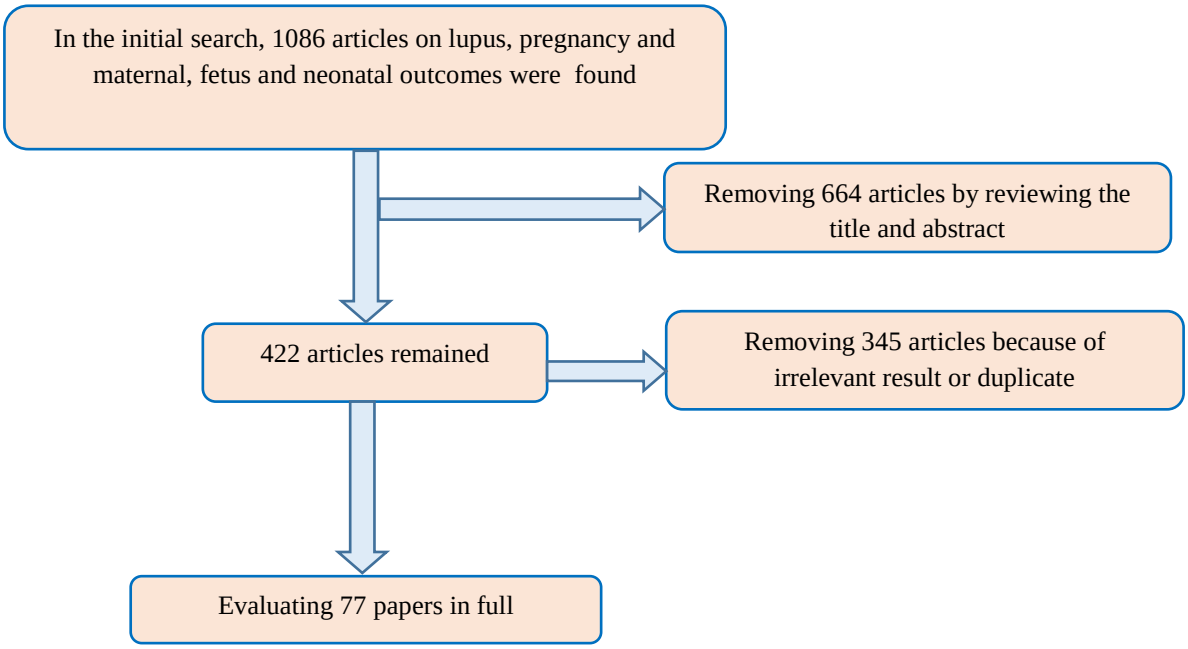

Fig.1: PRISMA flowchart of present study.

3- RESULTS

Since lupus mainly affects young women of childbearing age (14), pregnancy and its consequences are the main issues of these patients. In the past, pregnancy was not supported in these women due to frequent reports of severe recurrence of illness during pregnancy and poor outcomes, and therefore pregnancy termination was often recommended (1, 2). In recent decades, diagnostic, therapeutic, and consequently, management strategies for pregnancy have greatly improved in women with SLE, but the main concern in these patients is the effects of pregnancy on maternal disease and the impact of SLE on the midwifery, fetal, and newborn outcomes (12). Important factors affecting the pregnancy outcome include: active or inactive status of the disease at the start of pregnancy, age and parity, coexisting of other medical or obstetric disorders, and the presence or absence of antiphospholipid antibodies.

3-1. Maternal consequences

The activation or flare-up of SLE in pregnancy is maternal complications that is associated with the negative consequences of pregnancy, and have been mentioned by numerous studies (10, 15-39). In contrast to previous studies, the results of a retrospective cohort study conducted by Feld et al., on SLE pregnant patients, revealed that none of the patients developed a flare of illness during pregnancy and adverse outcomes of pregnancy occurred in 35.6% of pregnancies (40). Similarly, Aggarwal et

al. (2011) in a retrospective study examined 71 pregnant women with SLE in India, where no cases of relapse occurred (41). Disease activity in pregnancy or in its previous months (from both clinical and serological aspects), is an important predictor of not only complications of midwifery and childbirth, but also the maternal outcomes, and the flare-up of SLE during pregnancy. Indeed, active SLE during pre-gestation is associated with a high risk of flare-up during pregnancy, and therefore special attention should be paid to the type of the organ involved, because active organ involvement, especially the kidney, hematologic and dermatologic, in 6 months before fertilization, anticipates a similar involvement during pregnancy (5, 20, 25, 41, 42).

In this regard, Jesus et al. (2015), in a review study of pregnant mothers with lupus found that the risk of lupus flare-up depends on the disease activity in mothers 6-12 months before fertilization, and in women with a history of recurrent, discontinuation of drug therapy and active nephritis is higher (43). In a retrospective study in South Korea, Park et al. (2015) examined the outcomes of 62 pregnancies in women with lupus. Reported cases included erythematosus lupus. Renal involvement was one of the most common causes of lupus recurrence during pregnancy. Lupus recurrences during pregnancy are strongly affected by pre-pregnancy proteinuria (odds ratio [OR] = 30.28; P = 0.024), and antiphospholipid antibodies (OR = 6.62; P = 0.47) (44). Hypertensive complications include hypertension, preeclampsia, eclampsia, Hemolysis, Elevated Liver enzymes, and Low Platelet count (HELLP) syndrome, and chronic hypertension in several studies as major outcomes and concerns for pregnant women with SLE, especially acute promyelocytic leukemia (APL) or Antiphospholipid syndrome (APS) positive patients and Lupus Nephritis (10, 15, 16, 18-20, 22, 24, 26-32, 34-36, 38, 39, 41, 42, 45-58). Miyamoto et al. (2016) in a case report study in Japan stated that a SLE differential diagnosis of preeclampsia was difficult in the third trimester (54). In a cohort study on pregnant women with lupus in Mexico, Leaños-Miranda et al. (2015) showed that the risk of preeclampsia with early onset (< 34 weeks) or late (≥ 34 weeks) is higher than normal pregnancies in these patients (52). Diabetes mellitus is other maternal outcomes reported by Molad et al. (2005), in a prospective study on 22 women with Lupus (10) among other maternal outcomes were blood disorders such as thrombocytopenia and anemia. In this regard, Miyamoto et al. (2016), in a case report study, described the outcomes of pregnancy-induced SLE in a 32-year-old Japanese primeval woman who had a progressive thrombocytopenia and progressive anemia (54).

In another systematic review study on 77 pregnancies with lupus, Xu et al. (2015), found the incidence of thrombocytopenia and blood disorders increased in these individuals (38). Haddad et al., also found in a cohort study on patients with lupus in Toronto that although thrombocytopenia incidence is increased in these individuals it was not associated with a risk of complications of childbirth and thrombotic events (59). Similarly, Liu et al. reported thrombocytopenia (2012), in a retrospective study in China on pregnant women with lupus (60). Thromboembolic events are another important consequence in patients with lupus that were confirmed by the results of several studies, including Bleau et al. (2016), in a retrospective cohort study on a group of American women with autoimmune diseases, including lupus found that the risk of Venous Thromboembolism (VTE) is high in these individuals, and therefore concluded that most autoimmune diseases significantly increased the risk of VTE

(61). Similarly, Lee and Pope and Bundhun et al. (2017) pointed to the risk of thromboembolic events in their meta-analytic studies and found that in ten studies on pregnant women with SLE, cumulative incidence of VTEs is 7.29% (95% confidence interval [CI]: 5.82% to 8.75%), and concluded that inflammatory rheumatologic diseases are associated with high rates of VTEs (three times higher than the general population) (47, 62). Similarly, Chighizola et al. (2015), in a systematic review study showed that the prevalence of antibodies to phospholipids (APL) in pregnant women suffering from lupus with complication deep vein thrombosis (DVT) was 10%, but the positive relationship between APL and this clinical outcome was not supported by all studies (48).

The results another longitudinal study by Shand et al. (2012), which was conducted in Australia on 675 pregnant women with SLE, referred to thromboembolic events (63). Chung et al. also conducted a cohort study in Taiwan and found that in people with SLE, both pregnant and non-pregnant, the risk of DVT and pulmonary embolism is 12.8 times, and 19.7 times, and concluded the incidence of DVT and pulmonary embolism (PE) is significantly higher in these patients (64). Finally, Makhdoomi et al., reviewed pregnancy outcomes in individuals with lupus in a retrospective study in Urmia and found evidence of DVT (29). Another possible consequence that was referred to in a systematic review study by Chighizola et al. (2015), was that the prevalence of APL in women with Myocardial Infarction (MI), and stroke was 11% and 14%, respectively. But the positive relationship between APL and these clinical outcomes was not supported by all studies (48). Renal involvement in forms of lupus nephritis, decreased albumin and proteinuria is other outcomes reported in these individuals. For example, Miyamoto et al. (2016), in a case-report study described the renal impairment in patients with SLE (54). Moroni et al. (2016) in a prospective study on pregnant women with lupus nephritis in Italy reported a number of outcomes such as renal lupus erythematosus during or after pregnancy, and indicated that a high BMI is associated with late recurrence (31). Lupus nephritis has been reported in several other studies (34, 35, 53, 57, 64). Soubassi et al. (2004) reported proteinuria (35), and Park et al. (2015), renal involvement and proteinuria and considered their occurrence before pregnancy as the most common causes of lupus recurrence during pregnancy (44). Aggarwal et al. (2011) observed in a retrospective study in India the outcomes such as renal manifestations (41). In a cohort study in the United States, Andrade et al. (2011) found that complications occurred in 63.7% of 102 pregnancies with SLE, and renal involvement was independently associated with adverse pregnancy outcomes (OR = 5.219) (65).

Lv and Wang (2015), and Yang et al. reported kidney damage, decreased albumin and renal involvement in pregnant women with lupus (27, 39). Respiratory problems such as lupus pneumonia and acute respiratory distress were reported in a case study on a pregnant woman with lupus in Taiwan, by Chen et al., but the respiratory function of the mother was improved after cesarean section and basic treatment (66). Inflammatory complications such as arthritis and arthralgia were reported in 60% of patients by Aggarwal et al. (2011), and Bruceton et al. (2011), as maternal outcomes(41, 67), respectively. Several recent studies indicated an increase in cesarean section and the need for emergency cesarean section as a maternal outcome, which is higher in pregnant women with lupus (24, 36, 47, 54, 55, 66). Postpartum complications are other findings observed in mothers with lupus. For example

Bundhun et al. (2017), referred to postpartum infection (P =0.009), in a meta-analysis study (47). In a retrospective cohort study, Nili et al. (2013), reported postpartum hemorrhage, need for blood transfusion and postpartum fever (55). In another study, Aggarwal et al. (2011), examined 71 pregnant women with SLE in India and referred to infectious diseases and arthritis in 60% of patients (41). Ultimately, Yang et al., in a systematic review study, reported recurrence of the disease during the period (39). Increasing mortality and maternal mortality were other outcomes referred to by some studies. For example, Soubassi et al. (2004) reported increased maternal mortality in a cohort study in Greece (35). Maternal mortality was reported by Makhdoomi et al., in a retrospective study on 20 pregnant women with lupus in Urmia (29). Also, in a longitudinal study in Australia, Shand et al. (2012), found that perinatal mortality was increased (63); but contrary to previous studies, a retrospective study in Ghana was carried out by Dey et al. (2016), on pregnant women with lupus and no cases of maternal mortality was reported (19).

3-2. Fetal outcomes

Premature birth is one of the fetal outcomes that many studies (10, 18, 23, 24, 28, 29, 32, 34-39, 42-45, 47, 49, 50, 57, 58, 60, 66, 68-71) acknowledged its increased risk in people with lupus. In this regard Feld et al. Found in a cohort study of SLE pregnant patients that the average weekly birth weight of all pregnancies under study was 31.8 weeks (40). In a prospective study on pregnant women, Clowse et al. reviewed a preterm labor with mild to moderate degrees of SLE, and found that 23.7% of pregnant women with mild to moderate SLE had preterm labor and disease activity, ferritin levels, estradiol and uric acid may predict preterm delivery in the mid-stages of pregnancy (69). In a study in the United States, Wagner et al. (71), found that the outcomes of early delivery in women with lupus nephritis are greater than those without renal involvement. In a retrospective study in South Korea, Park et al. (2015), identified the preterm labor as a maternal outcome and proteinuria was a predictor of its incidence during pregnancy (OR = 12.50; P = 0.032)(44). Smyth et al. (34), in a review study and meta-regression analysis showed that there is a positive and significant relationship between preterm labor and active nephritis and the increase in blood pressure in people with active lupus nephritis or the history of nephritis(34). Contrary to previous studies, Fatemi et al. (2013), in a previous study in Iran examined 72 pregnant women with SLE, and reported no cases of preterm labor (20).

Loss of the fetus as a spontaneous abortion (10, 17-20, 23-25, 27, 31, 32, 34-39, 42, 44, 50, 57, 58, 60, 62), recurrent abortions (29, 45, 57), and abortion therapy (44, 58), are other fetal outcomes referred to by several studies. In this regard, Pelusa et al. (2016), in a retrospective study on 24 Argentinian women with recurrent abortions before the 10th week of pregnancy, found that there was a significant relationship between lupus anticoagulants, Anti-cardiolipin antibodies (ACA) and premature or recurrent abortions (73). In another study in Saudi Arabia, Al Jameil et al. (2015), found that in patients with recurrent abortions, the prevalence of antiphospholipid antibodies, such as and lupus anti-coagulants, was 42.68%(45). In a study by South Korea, Park et al. (2015), reported that proteinuria during pregnancy with lupus is a predictor of undesirable outcomes (OR = 12.50; P = 0.032), such as spontaneous abortion and abortion therapy (44). Intrauterine fetal death (IUFD), and stillbirth as other fetal outcomes were referred to in a large number of studies (17, 19, 23, 28, 29, 32, 34, 35, 38, 42, 44,

45, 47, 49, 57, 58, 60, 62, 68, 71, 74). In this regard, Zhan et al. (2017), in a retrospective study, examined the fetal outcomes and related factors in 263 pregnant women with lupus in China, and reported fetal mortality, and introduced hypertension, Hypoalbuminemia, reduction of complement, and antiphospholipid antibodies as predictors of this negative outcome (75). Also, Dhar et al. (2005), found in a descriptive analytical study on lupus pregnant women that the probability of stillbirth in the lupus group was increased compared to the control group (OR= 4.84, 95% CI= 1.72, 11.08), and the risk of stillbirth in maternal severe disease with the involvement of the Central nervous system (CNS) significantly increases (49).

Fetal developmental disorders such as Intra Uterine Growth Retardation (IUGR), and Small for Gestational Age (SGA), are other fetal outcomes that have been studied in several studies (10, 16, 19, 24, 29, 34, 40, 47-50, 57, 69, 74, 76). Zhan et al. (2017) reported in a retrospective study of pregnant women with lupus that intrauterine growth restriction and predictors of adverse pregnancy outcomes included hypertension, hypoalbuminemia, lower complement, and positive antiphospholipid antibodies (75).

Studies referred to heart problems such as congenital fetal heart block (35, 57, 77-79), Atrioventricular (AV) block (64, 66), fetal bradycardia (66), Tetralogy of Fallot and Atrial Septal Defect (ASD) as other fetal outcomes (60). In this regard, Roy et al., in a retrospective study in India investigated 11 cases of complicated pregnancy complications by Complete congenital heart block (CCHB) in women with Anti-Sjögren's-syndrome-related antigen A, (Anti-Ro/SSA) autoantibodies and found that the average gestational age at diagnosis of the fetus with CCHB, was 24.5 weeks, and in some mothers with lupus, the prognosis of fetuses has led to IUFD, and neonates required a permanent pacemaker (80). Similarly, Madhusudan et al. (2015) in a prospective study in India on patients with SLE, showed that there is a relationship between CCHB and maternal Anti-Ro/SSA, Sjögren syndrome antigen B (Anti-La/ SSB), and ANA antibodies (79). Other fetal outcomes included fetal anomalies (22, 60), fetal distress (74), and Oligohydramnios (43) which were confirmed in previous studies.

3-3. Neonatal and childhood outcomes

Neonatal Lupus Syndrome (NLS) is one of the major outcomes of infants born to mothers with lupus that has been mentioned in numerous studies (24, 37, 41, 50, 57, 64, 69). This syndrome is an acquired autoimmune passive disease mediating to maternal antibodies, which is reported in about 1-2% of infants born to mothers with autoimmune disease with Anti-RO/SSA, and Anti-La/SSB antibodies (64). However, some cases occur in children of mothers who have the same autoantibodies but have no symptoms of SLE, and no other autoimmune disease during pregnancy (75). The pathogenesis of the disease is not completely clear, but is likely to be greater than the simple passage of paired antibodies. Neonatal lupus manifestations are from benign conditions, such as skin manifestations and asymptomatic elevations in liver function tests, to central nervous system involvement and life-threatening cardiac manifestations. Other neonatal outcomes reported in several studies (18, 23, 30, 32, 38, 51, 60) include infant mortality rates. Growth disturbances such as IUGR at birth (66, 68, 81, 82), small baby for gestational age (SGA) (27, 43, 55, 60), low birth weight (LBW) (18, 23, 24, 26, 27, 29, 30, 37, 42, 55, 74, 76), very low birth weight (VLBW)(49, 83), and extremely low birth weight (ELBW) (49, 65), are the neonatal outcomes reported in numerous studies. Premature infants are another neonatal outcome

referred to by several studies (17, 26, 30, 37, 43, 55, 81, 83). Other neonatal cases included respiratory distress in various forms, including neonatal asphyxia (38), increased need for neonatal resuscitation, respiratory distress syndrome, pulmonary dysplasia, bronchopulmonary dysplasia (55) that was presented in the previous studies. According to studies, cardiovascular outcomes in these infants include congenital heart block (CHB) (24, 26, 31, 50, 55, 57, 64, 82-84), cardiac septum deficiency (24), and open arterial duct (55). In this regard, Llanos et al. found that the incidence of endocardial fibro elastosis (EFE), low ventricular ejection, cardiac block and dilated cardiomyopathy was increased in a study on 325 infants born to lupus mothers (72).

In a review study, Zuppa et al., reported non-cardiac neonatal lupus manifestations, including skin rash and cutaneous lupus erythematosus, cholestasis, mild hepatomegaly and sometimes splenomegaly, giant cell hepatitis, neutropenia and thrombocytopenia, hydrocephalus, white matter non-specific changes, calcification of basal complexes and vessels in radiography (85). According to previous studies, other neonatal outcomes include hydrops (85), blood manifestations such as anemia, neutropenia, thrombocytopenia(69, 70), non-specific brain abnormalities in the absence of clinical neurological symptoms, intraventricular hemorrhage (IVH)(55, 83), rash (64, 69, 82), multiple congenital anomalies (32, 61), retinopathy of premature infants (55), fetal uncertainty condition, emergency cesarean section (83), and long hospitalization (30).

The outcomes of children born to mothers with lupus are referred to as case by case in the following studies: In a case report study, Khodapanahandeh and Hadizadeh Kharrazi (2005), presented manifestations of a 9-year-old child with lupus, which included localized febrile seizure that occurred after several hours during a day; pale face rashes on cheeks, occasional headaches, academic failure, agitation and somewhat depression, and did not find any pathological case in systemic examinations, examination of the nervous system and urine tests, and eventually the patient developed nausea, vomiting, and decreased conscious levels shortly after the onset of prednisolone therapy and died with a deep coma (86).

In a prospective study, Moradinejad (2007), examined the lupus outcomes in 55 children and reported chronic and persistent migraine headaches, tension headache, hypertension, of which 35% of the children were APL positive, and 96% of the ANA positive (87). In a case study, Aghighi et al. described the effects of lupus outcomes on a 10-year-old girl, which included unexplained neurological manifestations such as headache, depression, seizure and mood disorders over a period of more than one year (88). In a case study, Bason et al. (2016) described the effects of lupus on 13-year-old black Italian boy and referred to congenital heart block and sensory neural hearing loss (89). Finally, Buyon et al. in a case study in the United States reported a number of children with congenital heart block, advanced heart block, and life-threatening cardiomyopathy in women with lupus (90).

4- DISCUSSION AND CONCLUSION

Lupus is a heterogeneous autoimmune disease with complex pathogenesis, which causes some kind of abnormal immune response (7). Many studies Considered interactions of disease and pregnancy and pregnancy on fetus, which were also discussed in the present study. Generally, the pregnancy and its termination can lead to renewed activity or manifestation of latent disease. The end of pregnancy in lupus is not so pleasant. Lupus can be risky for both the mother and the newborn.

Women with lupus are at high risk of many midwifery complications. Adverse perinatal outcomes increase in pregnancy with lupus. The adverse effects referred to in the studies include spontaneous abortion, recurrent abortion, abortion therapy, preterm delivery, fetal developmental disorders such as IUGR and SGA, respiratory, cardiovascular, blood, skin disorders, brain abnormalities, stillbirth, and neonatal lupus. Reasons that are at least partly responsible for adverse fetal outcomes include decidual vasculopathy associated with placental infarction and reduction of pair perforation. Anti-RO/SSA and Anti-La/SSB antibodies may also damage the heart and its regulatory system and cause the death of the baby (29, 36, 40, 46).

Maternal outcomes include hypertension, preeclampsia, eclampsia, HELLP syndrome and chronic hypertension, renal disorders, thromboembolic events, blood disorders such as thrombocytopenia and anemia, increased cesarean section and emergency cesarean section, postpartum hemorrhage and peripheral infections, and increased maternal mortality, and morbidity. However, studies have shown that the severity of disease activity in pregnancy affects the risk of flare-up of SLE symptoms and other complications during pregnancy (29, 36, 39, 46).

Although no definitive treatment has ever been found for lupus, conservative treatment goals, including reducing inflammation, suppressing the immune system and accurate clinical follow-up of patients in order to identify the characteristics of the disease is important. Also lupus may flare up at any time during pregnancy. Therefore, it is recommended that all pregnant women with lupus should be considered at risk and closely monitored. The best maternal and fetal prognosis is when pregnancy occurs at least 6 months after the complete remission, and the normal kidney function is normal or near normal. Mother's health and embryo development must be monitored regularly, and pregnancy and delivery should be planned under fully controlled conditions. It is also necessary that all lupus patients who decide to have a pregnancy should be screened for Anti-RO/SSA, and Anti-La/SSB. Identifying mothers at risk allows quick treatment before or after birth. In fact, clinical precautions in pregnancies associated with SLE should be the same as high risk pregnancies.

In this regard, it is essential to accurately determine the gestational age at the beginning of pregnancy. Periodic sonography is performed to evaluate fetal development after seven days from 18 to 20 gestations. Pre-natal monitoring (such as non-stress test [NST], biophysical profiles, etc.) should begin in the third trimester to confirm fetal health. Also, due to the higher congenital heart disease compared to the general population in these fetuses, the fetal heartfelt echo should be carried out.

Although studies have indicated a higher rate of cesarean section, SLE is not in itself an indication for cesarean section; and delivery method should be selected based on appropriate midwifery indications (69, 70, 74, 76, 79, 81, 90). Ultimately, although pregnancy is risky in patients with SLE due to increased maternal, fetal and neonatal morbidity, it seems that complete control of the patient before fertilization, so that the patient be in full remission at the onset of pregnancy and the disease activity in pregnancy is completely controlled, it can help to improve the outcome of pregnancy and also better outcomes can be expected for it.

5- CONFLICT OF INTEREST

All the authors declare that they have no conflict of interest.

6- ACKNOWLEDGMENTS

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Table-2: Characteristics of 77 studies included in thisComprehensive Review.

Ref	Author	Year	Country	Study Design	Sample Size	Disease	Tool	Result
31	Moroni et al.	2016	Italy	Prospective	61	LN	Counselling visit screening visit	Maternal adverse events: flares (19.7%), pre-eclampsia (8.4%) HELLP (2.8%).
30	Mbuli et al.	2015	South Africa	Retrospective	61	SLE	Survey	Poor pregnancy outcomes.
10	Molad et al.	2005	Palestine	Prospective	29	SLE	Fallow up evaluation	High rate of obstetrical complications and postpartum lupus flare-up.
12	Andreoli et al.	2012	Italy	Review	-	SLE	Patient counselling	Flare during pregnancy.
13	Whitelaw et al.	2008	South Africa	Retrospective	47	LN	History and documents	Maternal, fetal and neonatal outcome.
71	Wagner et al.	2009	USA	Retrospective	58	LN	Medical records	Higher incidence of maternal complications (57% vs 11%) and fetal complications.
49	Dhar et al.	2005	USA	Case-control	148	SLE	Records	Poor fetal outcomes.
14	Huong et al.	2001	France	Retrospective	32	SLE	History	Pregnancy need not be discouraged in women with a history of SLE nephritis.
15	Aoki et al.	2014	Japan	Case-control	71	SLE	Clinical courses and laboratory findings	Severe SLE flare and severe preeclampsia.
70	Moroni et al.	2005	Italy	Review	-	LN	-	Reports emphasized a high fetal and maternal risk such as: Renal flares, Pre-eclampsia.
16	Buyon et al.	2015	USA	Cohort	385	SLE	Physician's Global Assessment	In patients with inactive or stable mild/moderate SLE, severe flares are infrequent.
17	Carvalheiras et al.	2010	Portugal	Retrospective	43	SLE	Medical records	No cases of maternal mortality occurred. No cases of fetal malformation were recorded.
18	Cavallasca et al.	2008	Argentina	Retrospective	61	SLE	Records	No patient acquired the disorder during gestation.
19	Dey et al.	2016	Ghana	Retrospective	-	SLE	Medical records	Eclampsia, early fetal losses, mild flares, No maternal mortality, No cases of CHB.
20	Fatemi et al.	2013	Iran	Retrospective	72	SLE	Clinical and laboratory evaluations	Absence of LN was in favor of prevention of SLE flare and preeclampsia.

21	Galappatthy et al.	2017	Sri Lanka.	Descriptive	71	SLE	History	Low live births, Fetal loss, pre-maturity, low birth weight, Unplanned pregnancies.
22	Gladman et al.	2010	Canada	Prospective	193	LN	Follow-up	Fetal complications: Stillbirth, LBW, Congenital malformations. Maternal complications: hypertension, lupus flares, renal disease.
23	Imbasciati et al	2009	Italy	Retrospective	113	LN	Renal biopsy	Renal flares, progressive decline of glomerular filtration rate.
24	Jakobsen et al.	2015	Denmark	Cohort	39	SLE	Medical records	SLE pregnancies were mostly successful.
25	Ko et al.	2011	Korea	Retrospective	183	SLE	Medical records	Pregnancies with APLs, active disease at conception and SLE flares are at a higher risk of adverse outcomes.
26	Lin et al.	2014	USA	Retrospective	56	SLE	Medical record	SLE patients with a history of pre-eclampsia had a higher rate of subclinical CVD.
27	Lv et al.	2015	China	Retrospective	52	LN	Laboratory data	Pregnancy in LN patients should be monitored before and during pregnancy because of poor fetal and maternal outcomes.
28	Madazli et al.	2014	Turkey	Retrospective	65	SLE	History and Laboratory data	Cases with uterine artery Doppler abnormalities had significantly poorer obstetric outcomes.
32	Saavedra et al.	2016	Mexico	Retrospective	180	SLE	Medical records	Pregnancy in women with childhood-onset SLE should not be contraindicated if the disease is well controlled.
33	Wong et al.	2006	Taiwan	Retrospective	17	SLE	Medical records	Proteinuria, preeclampsia, disease flare up, stillborn, fetal loss, Neonate: congenital atrioventricular block, intrauterine growth retardation and preterm deliveries.
34	Smyth et al.	2010	USA	Systematic review	37	SLE	-	Lupus nephritis and anti-phospholipid antibodies increase the risks for maternal hypertension and premature births.
35	Soubassi et al.	2009	Greece	Cohort	22	LN	Records	Pregnancy is not contraindicated in women with lupus nephritis, but is associated with significant fetal and maternal risks.
36	Teh et al.	2016	Malaysia	Retrospective	86	SLE	Records	Lupus pregnancies remained as high-risk pregnancies with significant maternal and foetal complications.
37	Wei et al.	2011	China	Retrospective	86	SLE	Clinical analysis	Planned pregnancy during stable stage, appropriate treatment in pregnancy and close monitoring can improve the security of pregnancy.

38	Xu et al.	2015	China	Systematic review	73	SLE	-	Thrombocytopenia in SLE during pregnancy indicates higher pregnancy loss.
39	Yang et al.	2014	China	Case-control	155	SLE	Clinical features, laboratory findings	SLE patients with a flare history and serological activity at the time of conception were at an increased risk of disease flares during pregnancy and puerperium.
29	Makhdoomi et al.	2012	Iran	Retrospective	20	SLE	Medical records	The probability of maternal and fetal outcomes in the pregnancy of women with remission is high.
40	Feld et al.	2014	Palestine	Cohort	35	SLE	Medical records	An adverse pregnancy outcome had occurred in 35.6% of the pregnancies.
41	Aggarwal et al.	2011	India	Retrospective	35	SLE	Records	A better pregnancy outcome can be expected if clinical remission is achieved.
42	Barnado et al.	2014	USA	Case- control	220	SLE	Socioeconomic and pregnancy records	Maybe a pre-disease state predisposes to adverse pregnancy outcomes.
44	Park et al.	2014	Korea	Retrospective	62	SLE	Medical records	High rate of live births and flares in pregnant lupus patients.
45	Al Jameil et al.	2015	Saudi Arabia	Cross-sectional	82	SLE	History	There is strong correlation between number of abortions and the level of LA.
46	Bramham et al.	2011	UK	Retrospective	107	SLE	Records	In SLE, preterm deliveries are more frequent and preeclampsia occurs earlier.
47	Bundhun et al.	2017	China	Meta-analysis	11	SLE	-	SLE to indeed have a high impact on maternal and fetal outcomes following pregnancy.
48	Chighizola et al.	2015	Italy	Systematic review	81	SLE	-	The positive association between APL and clinical outcomes is not supported by every study.
50	Hendawy et al.	2011	Egypt	Prospective	48	SLE	Laboratory data	Pregnancy in SLE patients is associated with a higher risk of obstetric complications.
51	Ideguchi et al.	2013	Japan	Retrospective	41	SLE	Records	Because of complicated pregnancy Women with APS should be regarded with particular attention.
52	Leaños-Miranda et al.	2015	Mexico	Nested case–control	42	SLE	Labrotary analysis	SLE precedes the onset of preeclampsia in pregnancies.
53	Mecacci et al.	2009	Italy	Retrospective	62	APS	Medical records	Fetal outcomes were similar to APL-negative patients or to standard treated APS.
54	Miyamoto et al.	2016	Japan	Case report	1	SLE	Labrotary analysis	New-onset SLE should be suspected and an autoimmune workup should be performed as soon as possible when symptoms of preeclampsia persist.
55	Nili et al.	2013	Iran	Cohort	97	SLE	Medical records	Mothers with SLE have an increased risk of Caesarean section, postpartum hemorrhage, and blood transfusion.

56	Simard et al.	2016	Sweden	National population-based	742	SLE	Records	Women with SLE are at increased risk of early-onset preeclampsia.
57	Singh et al.	2014	USA	Review study	-	SLE	-	Pregnant patients with SLE should be followed in a high-risk obstetric clinic.
58	Tedeschi et al.	2016	USA	Cohort	149	SLE	Medical records	A higher risk of adverse pregnancy.
59	Haddad et al.	2015	Canada	Case-control	-	SLE	Clinical test	Thrombocytopenia was not associated with a higher risk for obstetrical complications.
60	Liu et al.	2012	China	Retrospective	105	SLE	Medical records	Pregnancies can be successful in most women with SLE.
61	Bleau et al.	2016	Canada	Cohort	43/523	SLE	Health Care database	Risk of VTE was high in pregnant women with SLE.
62	Lee et al.	2014	Canada	Meta-analysis	25	SLE	-	Rheumatologic diseases all associated with high rates of VTEs.
63	Shand et al.	2011	Australia	Cohort	675	SLE	Hospital records	Women with SLE are at high risk of adverse pregnancy outcomes.
64	Chung et al.	2014	Taiwan	Cohort	13 084	SLE	Health Insurance database	The risks of DVT and PE are significantly higher in SLE patients.
67	Brucato et al.	2011	Italy	Prospective	-	SLE	Laboratory analysis	Early detection of fetal abnormalities high risk of recurrence CHB.
65	Andrade et al.	2008	USA	Cohort	102	SLE	Records	Renal involvement, the maximum dose of glucocorticoids was associated with adverse pregnancy outcomes.
66	Chen et al.	2014	Taiwan	Case report	1	Lupus	Laboratory analysis	Newborn had an extremely low birth weight.
86	Khodapanahandeh et al.	2006	Iran	Case report	1	SLE	Laboratory tests	Prolonged focal seizure.
87	Moradinejad	2007	Iran	Prospective	55	SLE	History	Data highlights probable correlation between ApL, ANA, an anti-double stranded DNA (anti-dsDNA), and lupus headache.
88	Aghighi	2014	Iran	Case report	1	SLE	Clinical and laboratory evaluation	Unexplained neuropsychiatric presentations such as headache, depression or seizures in an adolescent girl should raise the suspicion of systemic lupus erythematosus.
89	Bason	2017	Italy	Case report	1	CHB	Cardiological evaluation ELISA test	Autoimmune CHB is related to the presence of anti-Ro antibodies in mothers' serum.
85	Zuppa et al.	2017	Italy	Review study	50	SLE	Specific diagnostic program	CCHB anemia, neutropenia, thrombocytopenia.

72	Llanos et al.	2010	USA	Cohort	77	Mothers with SLE and anti-SSA/Ro antibody	Laboratory tests	Cutaneous NL in infant.
76	de Jesus et al.	2017	Brazil	Cohort	135	SLE	History	26% SGA, 40% premature, Preeclampsia 9 cases, IUFD 2 cases
69	Clowse et al.	2013	USA	Cohort	39	SLE	SLEPDAI, PGA, Laboratory and delivery data	Ferritin, estradiol and uric acid levels at mid-gestation may predict preterm birth.
74	Saavedra et al.	2012	Mexico	Prospective	92	LN	Medical records	Higher rate of maternal complications.
75	Zhan et al.	2017	China	Retrospective	251	SLE	Medical records	Lupus was still at high risk of APOs in terms of pregnancy loss and preterm delivery.
43	Jesus et al.	2015	Brazil	Review	-	SLE	-	SLE especially with nephritis has poorer pregnancy outcomes, such as preeclampsia, fetal loss, prematurity, IUGR and SGA.
78	Fujioka et al.	2012	Japan	Case report	1	SLE	-	SLE flare and Severest SGA, sever early-onset circulatory collapse, severe cytopenias, and chronic lung disease in newborn.
79	Madhusudan et al.	2016	India	Prospective	13	SLE	Blood test , aneuploidy screening, anomaly scan, fetal echocardiography and Maternal and fetal characteristics	Fetal congenital heart blocks are associated with maternal Anti-Ro/SSA and Anti-La/SSB and ANA antibodies.
83	Yu et al.	2015	china	Retrospective	25	NLE	History and physical examination, Laboratory test	22% CCHB, 88% CNLE Children with NLE have an excellent outcome when only skin lesions are present.
84	Arai et al.	2016	Japan	Case report	1	SLE	Serological examination	Infant developed a NRFS and IVH, the condition of the fetus should be carefully monitored during and after long-term maternal steroid treatment.
80	Roy et al.	2014	India	Retrospective	11	SLE	Medical records	Fetal CCHB is associated with maternal Anti-Ro/SSA.
90	Buyon et al.	2009	USA	Review study	-	SLE	-	Mothers with anti-SSA/Ro antibodies having a child with CHB.
81	Al Arfaj et al.	2010	Saudi Arabia	Retrospective	176	SLE	Medical records	SLE patients with active lupus nephritis, anti-Ro/SSA antibodies, APL, hypertension, Raynaud's

								phenomenon, active disease at conception and SLE exacerbations are at a higher risk of adverse pregnancy outcomes.
82	Leroux et al.	2015	France	Cohort	118	SLE	Obstetric history, SLEDAI score, Biological test	HCQ, reduces neonatal morbidity prematurity and IUGR.

SLE: Systemic lupus erythematosus; APS: antiphospholipid syndrome; RA: rheumatoid arthritis; LN: lupus nephritis; CVD: cardiovascular disease; PRL: pregnancy-related lupus; LA: Lupus anticoagulant; APL: antiphospholipid antibodies; VTE: Venous thromboembolism; DVT: deep vein thrombosis; PE: pulmonary embolism; ANA: anti-nuclear antibody; Anti-ds-DNA: anti-double strand DNA; NL: Neonatal lupus; SLEPDAI: SLE pregnancy disease activity index; PGA: physician's global assessment; SGA: small for gestational age; CCHB: congenital complete heart block; CHB: congenital heart block; HCQ: Hydroxychloroquine; ECG: electrocardiogram; CNLE: Cutaneous; neonatal lupus erythematosus; NRFS: non-reassuring fetal status; IVH: intraventricular hemorrhage; RDS: respiratory distress syndrome; AVB: atrioventricular block.
IUFD: intrauterine fetal death.