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REVIEW ARTICLE

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Maternal and fetal outcomes of SLE in pregnancy: a literature review

Abdul Basit Sangah[a], Sidra Jabeen[a], Meklit Zenbabaw Hunde[b], Sunita Devi[a], Hassan Mumtaz[c] and Shazia Saleem Shaikh[a]

[a]Liaquat National Hospital and Medical College Karachi, Karachi, Pakistan; [b]Mekelle University College of Health Sciences, Mekelle, Ethiopia; [c]Senior Clinical Research Associate, Maroof International Hospital, Public Health Scholar, Health Services Academy, Islamabad, Pakistan

ABSTRACT

Systemic Lupus Erythematosus (SLE) is an auto-immune disease in which the immune system assaults its tissues. We aimed to analyse the maternal and foetal outcomes during pregnancy in SLE mothers. A literature search was conducted by two investigators to assess SLE's outcomes on maternal and foetal during pregnancies. We searched PubMed/Medline, Embase, and Google scholar to collect evidence from different research studies, draw the conclusion, and report it. In our investigation, we found out that SLE could cause a spectrum of complications during pregnancy, not only for the mother but also for the foetus. It could affect fertility and cause difficult pregnancies for the couple as well which includes certain complications such as: preterm labour and delivery, high blood pressure (preeclampsia), placental insufficiency, miscarriage or stillbirth, whereas in the foetus SLE can cause mortality, preterm birth, and neonatal lupus (a temporary condition in the baby caused by SLE-related antibodies) and structural abnormalities. The literature suggests that SLE could prove fatal for the foetus and induce many complications in the mother. However, this could be avoided if pregnancy is planned right from the start and proper management is provided to the mother during pregnancy and delivery.p

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Pregnancy; lupus; SLE; maternal outcomes in lupus; foetal outcomes in lupus; pregnancy and SLE

Introduction

Systemic Lupus Erythematosus (SLE), is a form of lupus. According to Centres for Disease Control and Prevention (CDC) SLE is an auto-immune condition where the immune system attacks its tissues (CDC 2022). SLE is a chronic inflammatory illness with an unclear origin and auto-immune pathophysiology, and its clinical symptoms might encompass various organs due to polymorphic biological alterations (Bălănescu *et al.* 2017). It may impact blood vessels, the brain, the lungs, the skin, and the joints and subsequently damage all these organs. SLE is a disease believed to be genetically linked, environmentally acquired, or caused by hormonal factors (CDC 2022).

It is noted that SLE often begins in early adulthood (Petri 2020). It is well established that SLE patients may have various symptoms, such as tiredness, skin rashes, fevers, and joint discomfort or swelling (CDC 2022). Some individuals may have flares of SLE symptoms every so often, perhaps even years apart, and then go into remission at other times (CDC 2022). There are various reasons for Lupus (SLE), including a drug-induced nature (Rubin 2005). Long-term treatment with over 40 drugs has been linked to drug-induced lupus (Rubin 2005). The drug-induced Lupus (SLE)'s clinical and analytical aspects are identical to systemic lupus erythematosus, except that individuals completely recover after discontinuing the offending medicine (Rubin 2005). Lupus (SLE) could also manifest as Lupus Mastitis (Cerveira *et al.* 2006). It can also present as the most prevalent type of cutaneous TB, which is lupus vulgaris (Sirka *et al.* 2021). Plaque-like, ulcerative, hypertrophic, vegetative, papular, and nodular forms are among the clinical types of lupus vulgaris (Pai *et al.* 2014). SLE can causes complications during pregnancy too (Derksen 1991). It has long been believed that pregnancy worsens the symptoms of maternal SLE by causing exacerbations (Derksen 1991).

Unexplained infertility affects 10% of infertile couples on average. Some of these instances are due to auto-immune illness (systemic lupus erythematosus, anti-phospholipid syndrome) (Deroux *et al.* 2017). While average life expectancy has increased in recent decades, the condition continues to have a great impact on the quality of life of the affected patients (Phuti *et al.* 2020).

Aim of study

In our literature review, we aim to explore the effects of systemic lupus erythematosus on fertility and pregnancy outcomes and how these outcomes are related to the therapy and disease activity and severity status according to the latest literature available.

CONTACT Hassan Mumtaz hassanmumtaz.dr@gmail.com Senior Clinical Research Associate, Maroof International Hospital, Public Health Scholar, Health Services Academy, Islamabad, Pakistan

Methods

Our review has been registered in Research Registry UK having UIN researchregistry1464 (11). Two independent investigators independently searched the literature from inception through July 2022 using PubMed/MEDLINE, Google Scholar, and the Cochrane library. These databases were searched using a strategy string that combined free text keywords with Medical Subject Heading (MeSH) phrases:

('lupus vulgaris' [MeSH Terms] OR ('lupus' [All Fields] AND 'vulgaris' [All Fields]) OR 'lupus vulgaris' [All Fields] OR 'lupus' [All Fields] OR 'lupus erythematosus, systemic' [MeSH Terms] OR ('lupus' [All Fields] AND 'erythematosus' [All Fields] AND 'systemic' [All Fields]) OR 'systemic lupus erythematosus' [All Fields]) AND ('pregnancy' [MeSH Terms] OR 'pregnancy' [All Fields] OR 'pregnancies' [All Fields] OR 'pregnancy s' [All Fields]) AND (('fetale' [All Fields] OR 'fetally' [All Fields] OR 'fetals' [All Fields] OR 'foetus' [MeSH Terms] OR 'foetus' [All Fields] OR 'foetal' [All Fields] OR 'foetal' [All Fields]) AND ('outcome' [All Fields] OR 'outcomes' [All Fields])) AND (('maternally' [All Fields] OR 'maternities' [All Fields] OR 'maternity' [All Fields] OR 'mothers' [MeSH Terms] OR 'mothers' [All Fields] OR 'maternal' [All Fields]) AND ('outcome' [All Fields] OR 'outcomes' [All Fields])).

Potential papers were found on Medline, Cochrane Central, and Google Scholar after a preliminary search of the three electronic databases; these studies were then filtered using the time filter of 10 years. The investigators excluded all articles for which full texts were unavailable and those in a language other than English. After exclusions, the remaining papers of interest underwent thorough full-text reviews, and pertinent information was incorporated into our literature review such as the information that was of interest to the literature review i.e. Maternal and foetal outcomes.

Fertility

A couple's fertility is defined as their capacity to get pregnant. Fertility (monthly likelihood of starting a pregnancy) in humans is difficult to measure. However, it is considered to be about 20%–30% (Boivin *et al.* 2007). The global 12-month rate of infertility (lack of pregnancy despite frequent unprotected sexual intercourse) is estimated to be 9%, with 56% of these couples consulting for this reason (Boivin *et al.* 2007). SLE puts a great burden during pregnancy. A study by L. Andreoli and colleagues mentioned that family planning should be considered as soon as feasible after a diagnosis. Most women may have healthy pregnancies, and precautions can be taken to lessen the chance of bad maternal or foetal outcomes (Andreoli *et al.* 2017). Extensive research by Phuti found that Most individuals desired pregnancy, delivery, and child raising. However, the unpredictability of SLE left some people with little or no possibility of fulfilling these objectives adequately (Phuti *et al.* 2020). According to the study, they collected obstetrics data from 25 SLE patients about pregnancy before SLE diagnosis, among which 2 experienced miscarriages, 2 had preterm births, 4 had Live, normal pregnancies, and birth. Furthermore, 4 participants experienced difficulty conceiving. Whereas after the diagnosis of SLE, difficulty in conceiving was experienced by 4 patients, 1 went termination of the pregnancy, 2 participants had a miscarriage, 1 had a premature birth, and 4 underwent the Caesarian procedure for the delivery. 1 participant had a successful normal delivery. Among these participants, 6 experienced the flares, making up about 24% of the participants who experienced some flares (Phuti *et al.* 2020). Nine out of ten people who became pregnant after receiving a diagnosis of SLE spoke of difficult pregnancies in which high blood pressure, discomfort, and arthritis necessitated long hospital stays, preterm deliveries, and heartbreak because of caesarean sections. They were often frightened, horrified, or despaired of having additional children due to these problems. In the narratives, women were described as having unpredictable, turbulent pregnancies and dealing daily with SLE. In the Phuti study, numerous individuals spoke of experiencing mental upheaval, including worry, melancholy, resentment, and the hardship of having lupus flares while pregnant. The end of close connections and the resulting emotional toll increased these negative sentiments (Phuti *et al.* 2020). It is very overwhelming for SLE patients to deal with and explain the complexities of SLE and pregnancies in SLE to their family and relatives. However, having a partner who understands the fertility problems and complexities of the SLE helps the patients cope with the overwhelming nature of things much better, as reported by the participants in the Phuti study.

Another research study by Carp states that there is a potential for SLE to cause reduced fertility. Multiple variables determine illness age of beginning, disease activity, degree and severity of visceral involvement, and therapy. Aside from the possibility of diminished fertility, there is a greater risk of miscarriage and pregnancy-related diseases, which are impacted by immunological variables, most notably the existence of anticardiolipin antibodies (Carp *et al.* 2012). The literature so far supports the idea that SLE could have a great impact on the fertility of SLE patients and make it troublesome for them to handle SLE-related issues as well as social issues.

Pregnancy outcomes in LUPUS (SLE)

Pregnancy is a big worry when a woman has systemic lupus erythematosus (SLE), which affects women of reproductive age (Buyon *et al.* 2015). Pregnancy has long been prohibited in SLE patients, especially when renal damage is evident (Moroni and Ponticelli 2016).

Jill P Buyon *et al.* conducted a prospective Cohort Study in which 385 women with inactive or stable SLE were taken as subjects. APOs (Adverse Pregnancy Outcomes) occurred in 19.0% of pregnancies, whereas foetal mortality happened in 4%, neonatal death in 1%, preterm birth in 9%, and SGA (Small for Gestational Age) neonate in 10% of cases. Lupus anticoagulant (LAC) usage, antihypertensive use, PGA (Polyglandular auto-immune syndrome) score greater than 1, and low platelet count were all predictors of APOs. The results showed that Severe flares are uncommon in pregnant women with mild to moderate SLE that is inactive or stable, and the prognosis is good in the absence of identifiable risk

factors. The barrier in the study was that patients with severe disease activity were not included (Buyon *et al.* 2015).

Another study was performed by Liu *et al.* to identify Chinese women with SLE who would have poor foetal and maternal outcomes. It turned out that the pregnancy outcome is similar in general to all the populations affected with SLE (Liu *et al.* 2012). Preeclampsia/eclampsia, active SLE, and thrombocytopenia were substantially linked to preterm delivery and a flare-up of maternal SLE, making them major predictors of foetal death. The conclusion although reported that Most women with SLE can have successful pregnancies. However, even in individuals whose SLE is under good control, a sizable minority of patients still experience an increase in SLE activity (Liu et al. 2012).

Xing ji lian *et al.* studied the results of active and chronic Lupus Nephritis (LN) in pregnant women for adverse maternal and foetal outcomes. Conclusion reported that Contrary to individuals with newly-onset LN, pregnant patients with pre-existing LN had a greater risk of composite poor foetal outcomes. However, the poor maternal outcomes for these two patient groups were comparable. After pregnancy, there were no differences in the long-term renal outcomes between these two groups (Lian *et al.* 2021).

Anita N Krishnan *et al.* concluded in a retrospective study that Foetuses of women with serologic or clinical evidence of SLE have structural cardiac abnormalities in addition to CHB (Congenital Heart Block) and myocardial dysfunction (Krishnan *et al.* 2008).

One case report by Moore *et al.* also shows that Systemic lupus erythematosus (SLE) and other connective tissue diseases in the mother are associated with (CHB) Congenital Heart Block in the child (Moore 1981).

Data from a prospective Cohort study by Arkema *et al.* show that pregnancies with SLE are more likely to have unfavourable mother and foetal outcomes. Preeclampsia, hypothyroidism, stroke, and infection were more prevalent maternal outcomes in SLE-affected women (Arkema *et al.* 2016).

A Meta-Analysis of studies from 2001 to 2016 on SLE outcomes in pregnancy exhibited that individuals with SLE had a considerably greater rate of caesarean deliveries. Women with SLE were also considerably more likely to develop preeclampsia and hypertension. In addition, the SLE subgroup had significantly greater rates of spontaneous abortion, thromboembolic illness, and postpartum infection (Bundhun *et al.* 2017).

Systemic Review and Meta-Analysis by Andrew Smyth *et al.* revealed that in patients with Lupus (SLE), both lupus nephritis and anti-phospholipid antibodies increase the risks for maternal hypertension and premature births (Smyth *et al.* 2010).

Pregnancy outcomes are more likely unfavourable in SLE patients with active lupus nephritis, anti-Ro/SSA antibodies, (aPL) Antiphospholipid Syndrome, hypertension, Raynaud's phenomenon, active illness during conception, and SLE exacerbations (Al Arfaj and Khalil 2010). According to a study conducted in Saudi Arabia by Al Arfaj *et al.*, patients with the disorders mentioned earlier or SLE exacerbations experienced considerably greater rates of foetal loss. Preterm births occurred far more often. Intrauterine growth retardation (IUGR) in neonates was more prevalent (Al Arfaj and Khalil 2010).

Outcomes in the present era are luckily improving with the correct timing of conception, close monitoring of SLE flares, and the idea of multidisciplinary management. Advancements in medicine are resulting in declined morbidity and death. Hence, most young women with SLE can carry out one or more pregnancies (Lazzaroni *et al.* 2016). Pregnancy should be carefully planned, and seasoned rheumatologists and obstetricians should evaluate SLE patients during pregnancy and after giving birth (Al Arfaj and Khalil 2010).

Researcher Benito studied if microRNAS play any role in pregnancy showing evidence that microRNAs (miRNAs) play a part in a range of pregnancy-related problems, such as preeclampsia and foetal growth limitation. The placenta expresses the majority of the roughly 1880 miRNAs that have been found to exist in humans. The development of non-invasive techniques for the detection of cell-free nucleic acids in maternal circulation, including miRNAs from the embryo-placental compartment, has been popular in recent years. An early assessment of miRNA circulating levels (i.e. between the 12th and 16th weeks) may be able to distinguish between pregnant women whose pregnancies are developing properly and those who may later experience difficulties because of placental insufficiency. Data suggested that C19MC microRNAs may be involved in preeclampsia pathogenesis (Chiofalo *et al.* 2017).

In order to control potential negative outcomes, enhance successful normal delivery, term newborns, and decrease congenital anomalies in children delivered to moms with SLE, extra attention and therapies should be provided to those women (Bundhun *et al.* 2017).

In light of the current literature about the effects of Lupus (SLE) in pregnancy, we took an approach to explain the outcomes mentioned above and the effects of the therapy on disease activity and severity status according to the latest good evidence published in the field.

Maternal outcomes

Preeclampsia. Compared to 3.4% of all pregnancies in the United States, preeclampsia can afflict up to 30 percent of SLE pregnancies (Chakravarty *et al.* 2005, Ananth *et al.* 2013, Mehta *et al.* 2019). It is found to be the most common complication in SLE-afflicted 1000 mothers in a prospective cohort of 1000 mothers (Cervera *et al.* 2015). Natural killer cells (NKCs) and endothelial progenitor cells (EPCs) when present in the bloodstream can be employed as markers in the early stages of preeclampsia diagnosis. Antonio Simone's analysis of the study suggests that this may be regarded as a useful screening for the early detection of women at risk of developing pre-eclampsia. According to growing evidence, NK cells may be crucial in orchestrating the pro-inflammatory microenvironment in the decidua of healthy pregnancies. Conversely, if this cell population is not sufficiently activated, the decidual artery remodelling will be poor and the risk of preeclampsia will increase (Laganà *et al.* 2017).

The chances of stroke, renal failure, hepatic failure, and death in mothers are increased by preeclampsia. The related placental malfunction increases the risk of foetal problems, such as IUGR and foetal death. Neonates are exposed to risks from preterm birth because preeclampsia frequently requires preterm delivery. Preterm birth affects up to 50% of pregnancies in women with SLE, making it three times more frequent than births in women without SLE (Jakobsen *et al.* 2015, Bundhun *et al.* 2017, Lateef and Petri 2017). Preeclampsia was the primary cause of preterm birth in one SLE cohort, followed by foetal impairment and maternal disease activity, and 70% of these preterm births were medically necessary (Eudy *et al.* 2018).

The effective SLE medication hydroxychloroquine (HCQ) does not raise the risk of congenital abnormalities, spontaneous abortion, or foetal death when used during pregnancy. These results have increased its usage during pregnancy (3,4). The significance of (3,4) is that usage of hydroxychloroquine (HCQ) is safe from the risk of congenital abnormalities, spontaneous abortion, or foetal death when used during pregnancy. The European League Against Rheumatism and other experts have advised continuing HCQ for SLE during pregnancy (Lateef and Petri 2017, Do *et al.* 2020). HCQ reduced the number of pregnancy problems in SLE-affected women, including maternal lupus flares, neonatal lupus syndrome, premature birth, and foetal growth restriction (Leroux *et al.* 2015). New research indicates that HCQ may lower the risk of preeclampsia (Seo *et al.* 2019).

In a recent study, we discovered that preeclampsia mediated up to 28% of the relationship between SLE and medically indicated premature births. Antimalarial medication HCQ has anti-inflammatory and immunomodulatory properties, making it popular for treating SLE (Simard *et al.* 2019). Endothelial dysfunction is also linked to preeclampsia, and HCQ has been found to restore endothelial function in an animal model of severe SLE (Gómez-Guzmán *et al.* 2014). Additionally, it is believed that oxidative stress is a major factor in both the onset of preeclampsia and SLE (Abd Rahman *et al.* 2018). HCQ prevents the synthesis of reactive oxygen species, preventing tissue damage brought on by auto-oxidation and having subsequent anti-inflammatory actions (Miyachi *et al.* 1986). In women with SLE, HCQ may reduce the risk of preeclampsia and preterm delivery through these mechanisms.

In a meta-analysis done by Liu *et al.* (2021) premature membrane rupturing, preeclampsia, intrauterine distress, gestational age at delivery, preterm birth, and postpartum haemorrhage risk were not increased by HCQ in 119 pregnancies. Treatment with HCQ did not significantly reduce the risk of preeclampsia. Additionally, the meta-analysis revealed a similar finding that the rate of preeclampsia was not substantially reduced by HCQ (RR = 0.61, 95% CI = 0.34–1.11). However, another meta-analysis by Clowse *et al.* (2022), with 7 cohorts providing 938 pregnancies in 804 women, revealed that women who continue using HCQ through Lupus (SLE) pregnancy experience less lupus activity and have healthy pregnancies. This study supports existing recommendations to maintain HCQ throughout pregnancy since it shows that the drug is safe and its usage reduces SLE activity. (OR: 0.53; 95% CI: 0.31–0.93).

Preterm birth has been linked to azathioprine or 6-mercaptopurine use during pregnancy (Nørgård *et al.* 2007). However, unfavourable pregnancy outcomes such as miscarriages, low birth weight, preterm birth, or adverse neonatal outcomes have not been documented (Shim *et al.* 2011, Francella *et al.* 2003). Despite the lack of research, a few indicate that azathioprine is usually safe (Saavedra *et al.* 2015) when nursed because few metabolites are detected in breast milk (Sau *et al.* 2007). Moreover, none are detected in the sera of newborns whose mothers breastfed while taking azathioprine (Gardiner *et al.* 2006).

In well-planned clinical studies, it is necessary to confirm the effectiveness of low-dose glucocorticoids in addition to conventional treatment in patients with SLE. On the other hand, high dosages of steroids considerably increase the incidence of maternal and foetal morbidities, making their use contraindicated (Riancho-Zarrabeitia *et al.* 2022).

Hypothyroidism. Miscarriage and premature birth have been linked to subclinical hypothyroidism (Allan *et al.* 2000, Abalovich *et al.* 2002) and thyroid antibody positivity in euthyroid women, respectively (Stagnaro-Green 2009, Chen and Hu 2011). The study by Benhadi *et al.* showed that stimulating thyroid hormone (TSH) levels increased even within the normal range, increasing the risk of unfavourable pregnancy outcomes, defined as miscarriage and foetal or neonatal death (Benhadi *et al.* 2009). Minor changes in thyroid function have been associated with breech presentations at term, higher caesarean section rates (Sahu *et al.* 2010), and lower IQ5(Toijonen *et al.* 2020). Negro *et al.* have shown that levothyroxine treatment of thyroid peroxidase antibody-positive women in the first trimester of pregnancy with TSH exceeding 2.5mU/l had decreased adverse outcomes compared to women who were not treated in a prospective randomised trial in a region of mild iodine deficiency (Negro *et al.* 2010). Additionally, postpartum thyroiditis (PPT) affects 5–10% of all women (Nguyen and Mestman 2019, Stagnaro-Green 2012, OTHMAN *et al.* 1990) and 20–25% of women with Type 1 diabetes mellitus (Maleki and Tavosi 2015, Nicholson *et al.* 2006). A thyroid condition affects about 5% of all pregnant women (subclinical or overt hypothyroidism or hyperthyroidism) (Arbib *et al.* 2017). Miscarriage and PTD are more common in SLE-affected women, especially when the disease is active and antiphospholipid antibodies are present (Clowse *et al.* 2005, Petri 2020). Children of SLE-affected mothers are more likely to experience heart block and frequently require care in a newborn intensive care unit (Tincani *et al.* 2006). Furthermore, mortality rates are higher among SLE-affected pregnant mothers (Petri 2007, Clowse *et al.* 2008). Hypothyroidism and auto-immune thyroid disease (AITD), defined as the presence of thyroid antibodies with or without thyroid dysfunction, are also more common in women with SLE. The prevalence of thyroid disease was 21% in SLE women and 10% in controls in case-control research using a questionnaire ($p = .02$). However, it is uncertain how

common hypothyroidism and AITD are in pregnant SLE women (Yuen *et al.* 2008).

- Stroke. Systemic lupus erythematosus (SLE) can cause various problems that affect the central nervous system (CNS). Therefore, it is improbable that a single pathogenic process accounts for all brain anomalies linked to the condition. Antiphospholipid, antineuronal, anti-P, anti-endothelial, other as-yet-undescribed autoantibodies, and inflammatory byproducts of compliment or platelet activation, may all be involved in the process (D'Cruz *et al.* 1999, Ornoy *et al.* 2003). Thrombosis in arteries or veins is primarily related to antiphospholipid antibodies. The cerebral circulation is one of the most often described locations of arterial thrombosis, leading to stroke or transient ischaemic attacks (TIA AS). Strokes and TIAs are uncommon side effects of SLE. Therefore, the contribution of antiphospholipid antibodies to CNS Lupus (SLE) is minimal if these are the only effects of antiphospholipid antibodies in the brain. Although antiphospholipid antibodies may only have a little impact on CNS Lupus (SLE), they provide autoantibodies more 'creditability' in the pathophysiology of the illness. Antiphospholipid antibodies are among the few autoantibodies whose functional effects in vitro have been easily demonstrated. More crucially, there is growing evidence from animal models that these autoantibodies have a direct role in thrombosis and miscarriage (Ornoy *et al.* 2003). The CNS symptoms of SLE can range widely in severity and prognostic significance. In addition to non-specific symptoms like headache and cognitive impairment, patients with SLE may also encounter life-threatening symptoms, including memory loss, seizures, and stroke. An evidence-based therapy regimen is available for some characteristics of the neurologic manifestation of SLE, particularly those connected to coagulopathy. However, nothing is known about how it manifests cognitively and emotionally. Its pathophysiology has been linked to several immunological effectors, including cell-mediated inflammation, cytokines, and brain-reactive autoantibodies. Other brain-intrinsic factors significantly facilitate it, including local microglia, the blood-brain barrier, and other neurovascular interfaces (Schwartz *et al.* 2019). Neurologic symptoms of SLE, however, are thought to have several causes and probably even several different aetiologies because no comprehensive model has yet been identified. This variation poses a barrier for physicians who have historically used empirical judgement to select treatment methods for individuals with NPSLE. Additional strategies for treating this condition may become available with a better knowledge of this SLE symptom.

Additionally, women with SLE experience greater pregnancy-related medical issues compared to healthy women. Compared to the non-SLE group, the risk of maternal mortality was approximately 20 times greater (325/100,000 live births). The actual mortality rate for all SLE pregnancies was 0.32%, which equates to an average of 11 maternal fatalities annually in the US. The risk of maternal mortality for women with SLE was still significantly higher after accounting for maternal age (OR 17.8, CI 7.2–44) (Clowse *et al.* 2008).

Infection. SLE is characterised molecularly by a chronic inflammatory state harmful to various organs, including the skin, joints, kidneys, serous membranes, central nervous system, and blood. This chronic inflammation is brought on by dysregulations of the adaptive immune system and the overproduction of various autoantibodies (Habibi *et al.* 2011). Viral, bacterial, parasite or fungal infections may cause an aberration of the immune system's physiological and defense mechanisms in genetically susceptible individuals. Although a person's genetic history increases their risk of developing a condition, neither it is necessary nor the cause of SLE. According to a number of studies, the results of an autoimmune process may be influenced by the combination of genetic and viral variables. However, this idea still needs to be debated, and further study is required to comprehend the dynamic interaction between genetics and infections fully. The illness discordance rate between monozygotic twins raises the possibility that environmental variables play a part in developing autoimmune diseases (Rigante and Esposito 2015). Since SLE is an immunodeficient state (Sawada *et al.* 2019) and pregnancy is also a state of weaker immunity (Lahita 1992), it is conclusive that the chances of infections during pregnancy in an SLE patient increase multiple folds.

Foetal outcomes

Foetal mortality. In a prospective cohort of 1000 SLE pregnancies by Cervera *et al.*, early pregnancy loss affected 16.5% of the pregnancies, making it the most prevalent maternal complication. There may be a connection between SLE activity, renal illness, antiphospholipid antibodies, and the likelihood of foetal loss in SLE. The prognosis for pregnancies in people with active nephritis is poor. Although pregnancy loss is only 10% common in persons with mild renal illness, it is 60% common in those with moderate or severe nephritis (Petri 1994). In research by Smyth *et al.*, the rate of induced abortion was 5.9%, and when foetal problems were taken into account, they included spontaneous abortion (16.0%), stillbirth (3.6%), neonatal mortality (2.5%), and intrauterine growth retardation (12.7%). 23.4% of pregnancies failed, while 39.4% of babies were born prematurely (Smyth *et al.* 2010).

- Preterm birth. Preterm birth, which denotes birth before 37 weeks of gestation, is of particular concern among perinatal problems since it substantially contributes to perinatal morbidity (Goldenberg *et al.* 2008). In a multicentre prospective cohort study of individuals with SLE, unfavourable pregnancy outcomes occurred in 19.0% of cases, and preterm delivery was 9% of the time if first-trimester pregnancy losses were excluded (Buyon *et al.* 2015). Preterm birth may result from systemic inflammation or inadequate placental development. A recent article in the literature about patients with SLE and lupus nephritis showed that the preterm birth rate was significantly higher at 39.4% (95% confidence interval (CI), 32.4%–46.4%) among all live births. Many studies aim to elucidate the impact of SLE on pregnancy outcomes (Smyth *et al.* 2010).

Even a few weeks before term, preterm delivery is linked to the newborn's delayed growth, lung immaturity, and worse long-term results (Dong and Yu 2011). The following factors may be the major causes of SLE patients having higher preterm births. (1) Placental corticotropin-releasing hormone increases when the maternal or foetal hypothalamus-pituitary axis is activated, which also triggers labour by increasing the synthesis of prostaglandins and cortisol (Voltolini *et al.* 2013). (2) Local and systemic inflammation from infections can cause labour to be induced by cytokines, prostaglandins, increased anti-dsDNA, and hypocomplementemia (Park *et al.* 2005). (3) Oestrogen levels are correlated with gestational age at birth and have been utilised for decades as a gauge of placental health (Nagata *et al.* 2006, Kramer *et al.* 2013). Oestradiol levels in pregnant women with SLE are often lower than those in the general population, according to research (Doria *et al.*, 2002). One study found that low oestradiol levels may signify premature birth in women with mild to moderate disease activity (Clowse *et al.* 2013). (4) Finally, oral prednisone may be linked to premature delivery regardless of the inflammation it is treating (Namazy *et al.* 2013, Wei *et al.* 2017). In conclusion, factors that cause premature birth include clinical or subclinical inflammation, autoantibodies, hormonal imbalance, immunological abnormalities associated with Lupus (SLE), and medications used to manage disease activity. Preterm births are more common when there is disease activity during conception because of increased clinical inflammation, autoantibody, immunological alterations from lupus, and medication usage (Clowse *et al.* 2005, Ko et al. 2011).

SGA (Small for gestational age) neonate and intrauterine growth retardation (IUGR). In addition to being linked to a higher frequency of obstetric difficulties, including stillbirth, abortion, preterm, and intrauterine growth restriction (IUGR), maternal lupus has also been linked to newborn issues such as congenital heart block and neonatal lupus (Molad *et al.* 2005, Khamashta 2006, Lateef and Petri 2017). The prognosis for the foetus and newborn is particularly bad in moms with elevated SLE activity, lupus nephritis, hypertension, and positive antiphospholipid and anti-Ro/SS-A antibodies. In addition to aPL, it has been suggested that the existence of ANAs during pregnancy may impact the outlook for the perinatal period (Coleman *et al.* 2005). Antibodies to Ro/SS-A and La/SS-B, particularly, were linked to congenital heart block and neonatal lupus2 but not to stillbirth, abortion, or premature delivery (Brucato *et al.* 2002).

Many women with lupus take medicines while pregnant. Using steroids during pregnancy is generally considered safe (Khamashta 2006). It has been shown that moms with lupus who used steroids experienced lower rates of foetal death and morbidity (Mintz *et al.* 1986). However, Molad *et al.* (2005) observed in 2005 that in addition to high lupus activity, lupus moms might also be at risk due to hypoalbuminemia, proteinuria, the presence of ANAs, and a history of using medicines such as steroids and hydroxychloroquine.

In research by Kim and Lee (2008), it was shown that the incidence of SGA was greater in the lupus group. However, birth weight and gestational age were lower in the lupus group because the pregnancy was sustained to full term by providing prenatal treatment for various obstetrical issues.

Compared to healthy pregnant women, lupus mothers have a worse perinatal outcome. Therefore, careful assessment and treatment of the neonates are necessary, even if the pregnancy may be maintained until full term, by avoiding obstetrical issues that could emerge during pregnancy and delivery.

Structural cardiac abnormalities in addition to congenital heart block (CHB) and myocardial dysfunction. As a kind of passively transmitted autoimmunity from mother to child, the presence of anti-Ro/SS-A autoantibodies is substantially related to the risk of developing neonatal lupus erythematosus (Scott *et al.* 1983, Lee 2005). Maternal anti-Ro/SS-A autoantibodies penetrate the placenta frequently and cause cardiac conduction system impairment in neonatal lupus, a congenital disease (Scott *et al.* 1983, Lee 2005). Neonate lupus patients can get full heart block, which needs pacing to survive. Foetal myocarditis is related to foetal complete heart block (Saleeb *et al.* 1999). Even if a pregnant woman does not have SLE, circulating anti-Ro/SS-A antibodies can cause neonatal lupus to manifest. Patients with anti-Ro/SS-A and asymptomatic Sjogren syndrome patients are candidates for this option (Buyon *et al.* 1998). According to studies, maternal autoantibodies that cross the placenta to the foetus are thought to be the secondary cause of between 60% and 90% of all occurrences of congenital heart block (Jayaprasad *et al.* 2006, Friedman *et al.* 2007). Anti-Ro/SS-A antibodies may harm the baby, but they do not increase the risk of heart block in adults. According to several recent investigations, the QTc interval is longer in adults with anti-Ro/SS-A, and certain ventricular arrhythmias may be more frequent in adults with these autoantibodies (Lazzerini *et al.* 2004, Lazzerini *et al.* 2007, Bourré-Tessier *et al.* 2011). An anti-Ro/SS-A association was shown to be related to a mean QTc of 445 ms as opposed to 419 ms in individuals missing the autoantibody, according to one study (Lazzerini *et al.* 2004). This research illustrates that anti-Ro/SS-A autoantibodies may cause a modest type of conduction disorder in adults.

The difference between neonatal and adult conduction disease is difficult to understand. One theory is that an unidentified prenatal component enhances the action of anti-Ro/SSA autoantibodies. Immune complexes aimed towards the foetal conduction system have been seen, which provides evidence in favour of this (Litsey *et al.* 1985). However, in the presence of anti-Ro/SS-A antibodies, only 2% of foetuses get congenital heart block (Brucato *et al.* 2001). Additionally, epidemiological research does not conclusively demonstrate the existence of a harmful prenatal component. The likelihood of future kids getting full heart block increases from 2% to 18% if a woman has anti-Ro/SS-A autoantibodies and has previously had children with total heart block (Julkunen and Eronen 2001). However, congenital heart block is discordantly developed in monozygotic twins of women with circulating anti-Ro/SS-A antibodies, indicating that the aetiology of neonatal total heart block is complicated and

does not just depend on the existence of antiRo/SS-A and an unidentified foetal component. Another option is that certain autoantibodies only harm the developing cardiac conduction system, maybe due to the foetus being exposed to particular antigens; however, monozygotic twin discordance renders this scenario less plausible. Furthermore, genetically identical newborns may have discordant phenotypes due to minute variations in the uterine environment or the maturing immune system, but this has not yet been proven. Treatment with corticosteroids can occasionally stop the progression of irreversible total heart block from incomplete heart block (Hutter *et al.* 2010). Despite reducing circulating autoantibodies, postnatal development of heart block has been described in certain case reports (Geggel *et al.* 1988). Given the severe, sometimes fatal implications of neonatal lupus, it is crucial to inform pregnant women who are known to have anti-Ro/SSA antibodies about this risk. Hydroxychloroquine usage by mothers may lower the chance of reoccurring neonatal lupus in subsequent pregnancies (Izmirly *et al.* 2012).

Limitations

One limitation of our study is that it only looked at 10 years of available literature, which may not provide a comprehensive understanding of the topic being studied as it could miss the initial data from the years before 10 years ago. Additionally, the study only included English articles, which may exclude valuable perspectives and findings from non-English sources. This could potentially lead to biases and limitations in the conclusions drawn from the study. A limited time frame and language scope of the research might not be able to capture the complete picture of the topic under study, leading to incomplete or inaccurate findings.

Future implications

The future implications of our research study regarding maternal and foetal outcomes of SLE in pregnancy include the potential for further research to be conducted with an even longer time frame to provide more robust and comprehensive findings. Additionally, including non-English articles in future studies would also be beneficial in order to gain a more complete understanding of the topic. The research could also be used to guide clinical practice and inform the development of guidelines for the management of SLE during pregnancy to improve maternal and foetal outcomes. The study could also be used to identify areas where more research is needed, such as in the long-term outcomes of SLE in pregnancy, and to inform the development of interventions to improve these outcomes.

Conclusion

Systemic Lupus Erythematosus is an auto-immune condition where the antibodies attach to their own body. After reviewing extensive literature on the effects of SLE in pregnancy, it would be sufficient to say that SLE could create numerous problems during pregnancy for the mother and the child. However, the problems related to SLE during pregnancy could be avoided if the pregnancy is well-planned, well-managed, and the delivery is well-executed. Medicines like hydroxychloroquine can help reduce oxidative stress and could be used as a supportive therapy. However, most of the literature supports the idea of planning a pregnancy well in order to avoid unwanted or detrimental events during pregnancy.

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ORCID

Abdul Basit Sangah http://orcid.org/0000-0001-5676-5756
Sidra Jabeen http://orcid.org/0000-0002-9697-1113
Hassan Mumtaz http://orcid.org/0000-0003-2881-2556

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