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REVIEW

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Pregnancy in lupus: an updated consensus to guide best practice strategies

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Abstract

Background: Systemic lupus erythematosus is a multifaceted chronic relapsing autoimmune disease of unknown etiology. The disease has always been a serious diagnosis in women being a multisystem pathology that is classically encountered during the childbearing age posing serious systemic comorbidities with a potential impact on the functional performance, psychosocial status, and survival. In this article, we review critical issues related to the decision to conceive in female with lupus highlighting the impact of the diagnosis and disease activity status on the mother and the fetus, attempting to suggest a consensus to guide safe decision making for pregnancy with SLE.

Main body: The pleomorphic dysregulated immune nature of lupus in the presence of uncontrolled disease carries a higher risk of complicated pregnancy. Therefore, SLE pregnancies should be well planned and are usually encouraged if the disease is inactive (at least 6 months prior to conception) to ensure immune quiescence towards a safer outcome.

Conclusion: With the proper implementation of preconception counseling strategy, choice of the correct timing of conception, close monitoring of SLE flares with tight control, and the appreciation of the value of multidisciplinary management to best practice most young women with SLE can carry on successful pregnancies with favorable outcome.

Keywords: Systemic lupus erythematosus, Immune response in pregnancy, Pregnancy outcomes, Risk, Benefit, In vitro fertilization, Therapy

Background

Systemic lupus erythematosus (SLE) is a multifaceted chronic relapsing systemic inflammatory autoimmune disease of unknown etiology. The disease has always been a serious diagnosis in women being a multisystem pathology that is classically encountered during the childbearing age posing serious systemic comorbidities with a potential impact on the functional performance, psychosocial status, and survival [1]. Recent data have displayed growing evidence that the majority (almost 80%) of women with the diagnosis of lupus can carry on successful pregnancies with a fairly satisfying fetal outcome, a conditional consensus if conception is timely well planned to take place securely during periods of inactive disease and with monitoring by a competent multidisciplinary team of a rheumatologist and high-risk obstetrician/gynecologist and a neonatologist [2].

In this article, authors reviewed published original research including, peer-reviewed articles, systematic reviews, meta-analyses, publications on guidelines, recommendations on monitoring, and therapy as well as risk assessment for adverse pregnancy outcomes with lupus aiming to establish an evidence-based consensus on the management of lupus with pregnancy.

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Main text

Normal pregnancy is considered a potentially unique physiological challenge to the immune response during which the female immune system adopts a complex strategy to sustain immune quiescence via promoting maternal immune tolerance to fetal antigens while synchronously preserving the potential to combat foreign pathogenic invaders [3–5].

The strategy of the immune response during pregnancy

The local immune response within the female uterus undergoes phasic changes with each trimester to serve the purpose of safely growing the fetus. In the first trimester for example, the local immune system adopts a pro-inflammatory phase, with macrophages, dendritic cells, neutrophils, and natural killer (NK) cells participating in a coordinated, controlled inflammatory response. This proinflammatory response regulates trophoblast invasion, proliferation, tissue remodeling, and angiogenesis essential for implantation and placentation. Progressing to the second trimester there will be a shift towards an immunologically tolerant state with the anti-inflammatory Th2-dominating and regression of the Th1 and Th17 arms to promote fetal allograft tolerance and protect the trophoblasts from pathogens. Finally, in the third trimester, a regain of the pro-inflammatory state occurs to support myometrial contraction and delivery. The T regulatory cells (T regs) are critical players for sustenance of immune homeostasis and minimizing oxidative stress during pregnancy. All through pregnancy there is a synchronous increase in the T reg cell population to promote the initiation of an immune regulatory drive to an upregulated proinflammatory response to fetal antigens (allograft) especially during the first and second trimesters to suppress the undesirable actions of the dominating Th1, Th 2, and Th 17 cells. During pregnancy in female patients with SLE, there is a combination of defective T reg cell function and upregulation of the Th17 cytokine milieu (under the effect of estrogen) enhancing the productivity of IL-17 which is not downregulated with the rise in progesterone as observed with normal pregnancies [6–12]. This has been implicated in the causation of adverse maternal and fetal outcomes including preeclampsia, recurrent miscarriages, or preterm labors in addition to defective immune response to infections during pregnancy [12–15].

The immune nature of SLE and pregnancy outcome

The pleomorphic dysregulated Immune nature of lupus with the presence of uncontrolled disease carries a higher risk of complicated pregnancy. Conception in a patient with lupus is a challenge that is highly dependent on the disease status, autoantibody profile, and associated comorbidities; therefore, SLE pregnancies are encouraged only if the disease is inactive for at least 6 months before conception to secure safe outcome. A recommendation that strongly supports the need of counseling with planned pregnancy [16–19]. Several years ago in 1965, pregnancy outcomes and disease flares were considered remarkable, with pregnancy loss up to 43%, consequently, pregnancy with lupus was discouraged [20]. In 2003, studies reported a dramatic decline in pregnancy loss in patients with SLE to 17% [21–23]; yet, there are still reports supporting that pregnancy loss predicts future recurrent miscarriages with a likelihood of successful pregnancy around 10% [24–27]. Obstetric complications in pregnancy with lupus have been attributed to multiple factors notably attributed to uncontrolled disease. A positive lupus anticoagulant profile with or without complete antiphospholipid antibody syndrome for example are highly predictive of early fetal demise [24–27]. A high disease activity index, the presence of renal impairment or active lupus nephritis, a low serum complement, and a high anti ds-DNA were reported by Petri et al. as risk factors for preterm births in lupus [28, 29]. Active lupus nephritis, anti-Ro/SSA antibodies, antiphospholipid (aPLs) syndrome, systemic hypertension, Raynaud's phenomenon, active illness during conception, and refractory disease have been repeatedly confirmed in multiple wide scale studies as potential predictors of poor outcome with serious complications including preeclampsia, eclampsia, spontaneous abortion, thromboembolic illness, maternal hypertension, premature births, and postpartum infection [22, 29–31].

Lupus pregnancy

The story of pregnancy with Lupus is quite challenging to the rheumatologists and the patients owing to the high risk of morbidity and mortality, with data about maternal mortality risk reporting an estimate approximately 20 times greater with SLE compared to healthy women (325/100,000 live births-US data) [32].

Challenges with the ability to conceive

SLE imposes a significant burden on the potential of an afflicted female in her childbearing period to conceive. The conflict between the need for family planning with uncontrolled disease and the risk of infertility adds to the challenge. Andreoli and colleagues stressed in their study that family planning should be considered as early as possible following the diagnosis of SLE, though most women with inactive disease may be granted a healthy pregnancy, yet still serious precautions are warranted to lessen the chance of bad maternal or fetal outcomes [33]. Similarly, Phuti et al., in their study of 25 SLE females during pregnancy, reported that despite that females

with SLE in their childbearing period are always eager to conceive, the unpredictability of the disease behavior during pregnancy left a considerable population of SLE patients with little or no possibility of fulfilling these objectives adequately [34]. Carp et al. further confirmed in their study the impact of SLE on decreased fertility, increased risk of abortions, and miscarriage emphasizing the impact of age at onset, disease activity, severity of organ disease, and iatrogenic complications on the potential to conceive [34, 35]. The need for introducing potentially effective systemic immunosuppressive induction therapy with uncontrolled organ threatening disease to control and sustain quiescence is an additional threat to conception as some drugs affect ovarian function and/are teratogenic (cyclophosphamide, mycophenolate mofetil). Factors associated with fertility problems in females with lupus have included severe flares associated with secondary amenorrhea, chronic kidney disease with estimated glomerular filtration rate <60 mL/min, drug-induced ovarian failure following cyclophosphamide, and venous thromboembolism (especially women with ovarian hyperstimulation syndrome and/or other prothrombotic risk factors). Therefore, effective disease control, stratifying high-risk patients, pre-cycle counseling, and thromboprophylaxis are mandatory proactive measures in these patients [36].

Challenges during pregnancy

Pregnancy constitutes a major concern in women with lupus with recommendations to avoid in the vicinity of significant renal damage, non-renal major organ disease, and other disease-related predictors of poor outcome. In a broad prospective cohort study by Buyon et al., 2015 that included 385 pregnant women (49% of non-Hispanic origin) with inactive or mild to moderate stable SLE, an adverse pregnancy outcome (APO) was defined by the authors in their study as any of the following: fetal or neonatal death, birth before a 36-week gestation, placental insufficiency, hypertension, preeclampsia, and birthweight less than the fifth percentile. A positive lupus anticoagulant profile (LAC), antihypertensive use, Physician's Global Assessment score (PGA) greater than 1, and low platelet count were all predictors/risk factors of APOs. The authors found that 81 % of the studied population had non-complicated pregnancies. The rate of adverse pregnancy outcomes was 7.8% and as high as 58%, with fetal and neonatal mortality reaching 22% in the presence of identified risk factors. Adverse pregnancy outcomes (APOs) occurred in 19.0% of pregnancies, whereas fetal mortality happened in 4%, neonatal death in 1%, preterm birth in 9%, and SGA (small for gestational age) neonate was reported in 10% of cases. The study suggested that severe flares are uncommon in pregnant women with mild to moderately severe SLE in remission, and the prognosis is good in the absence of identifiable risk factors; however, the lack of inclusion of patients with severe disease activity is considered a limitation to this study [21, 37]. Liu et al., similarly, aimed to identify in their study of a population of pregnant Chinese women with SLE factors related to poor fetal and maternal outcomes. Premature births and small for gestational age occurred more significantly in the active SLE group compared to the inactive group (53.23 versus 8.8%, 40 versus 5.6%, P 0.001). Active disease preeclampsia/eclampsia, and thrombocytopenia were substantially linked to preterm delivery and a flare-up of maternal SLE, making them major predictors of fetal death and maternal SLE flare-ups. The study concluded that most women with SLE can have successful pregnancies. The study by Liu however concluded that even in pregnant women whose SLE is under good control, a sizable minority of patients still experience an increase in their disease activity [38]. An interesting prospective study by Lian et al. that aimed to address maternal and fetal outcome in pregnant SLE patients with new onset versus long standing lupus nephritis, the authors reported that contrary to individuals with new-onset LN, pregnant patients with pre-existing LN had a greater risk of composite poor fetal outcomes with comparable maternal outcomes [36].

Numerous studies further confirmed the association between SLE diagnosis and/or a seropositive profile in women and unfavorable pregnancy outcomes including preeclampsia, hypothyroidism, stroke, and infection as well as fetal structural myocardial complications other than heart block [39–41]. In one vast meta-analysis of 529,778 patients published in 2017 pooling studies from 2001 to 2016 on SLE outcomes in pregnancy, the researchers exhibited that the diagnosis of SLE had a considerably greater rate of cesarean deliveries (RR 1.85, 95% CI 1.63–2.10; $P = 0.00001$), because women afflicted by the disease were considerably more likely to develop preeclampsia and hypertension (RR 1.91, 95% CI 1.44–2.53; & RR 1.99, 95% CI 1.54–2.56; $P = 0.00001$), respectively. In addition, the SLE subgroup had significantly greater rates of spontaneous abortion, thromboembolic illness, and postpartum infection (RR 1.51, 95% CI 1.26–1.82; $P = 0.0001$), (RR 11.29, 95% CI 6.05–21.07; $P = 0.00001$), and (RR 4.35, 95% CI 2.69–7.03; $P = 0.00001$), respectively [31]. Smyth et al. in their systemic review and meta-analysis concluded that the presence of lupus nephritis and anti-phospholipid antibodies were associated with an increased risk of maternal hypertension/preeclampsia (16.3%) and premature births (39.4%) [22]. Another study on pregnant Saudi females with SLE further confirmed the observation with considerably greater rates of fetal loss, preterm births, and intrauterine growth

retardation (IUGR) [30]. The presence of preeclampsia was found to significantly contribute to a poor maternal and fetal outcome of maternal complications during pregnancy including, chances of stroke, renal failure, hepatic failure, and maternal deaths. Furthermore, the associated placental malfunction with preeclampsia might lead to IUGR, preterm delivery and low birth weight baby with an increased risk of fetal deaths [31, 42–46]. Additional factors "other than preeclampsia" were known to contribute to preterm labor with lupus which might affect up to 50% of pregnancies with SLE [44–48]. Among these factors, the estrogen levels are identified as crucial players as they are among the indicators of placental health which usually correlates with gestational age. The estrogen levels were found to be significantly lower than normal in pregnant patients with lupus [49–51]. Also, the presence of active immune inflammation either with uncontrolled disease or infection can induce early labor cytokines, prostaglandins, increased anti-dsDNA, and hypocomplementemia that act to further stimulate the drive of the hypothalamic pituitary axis towards early termination of pregnancy [52–55]. Furthermore, and regardless of the presence or extent of inflammation, the use of oral corticosteroids and azathioprine has been linked to premature delivery [56–58]. Early fetal loss was also estimated to reach 16.5% in a prospective cohort of 1000 SLE pregnancies by Cervera et al. [44].

Antibodies and pregnancy in lupus

The autoantibody network in lupus is a crucial player in defining the disease severity, phenotype, organ involvement, and response to therapy. This directly and indirectly reflects on the potential to conceive as well as on the outcome of the conception process in females with lupus.

Antiphospholipid antibodies

The most encountered autoantibodies in lupus broadly identified to affect fertility as well as safe accomplishment of pregnancy are the antiphospholipid antibodies. Antiphospholipid syndrome, which is marked by the presence of antiphospholipid (aPL) antibodies, is also commonly diagnosed in SLE women of childbearing age (20–35%) with an annual incidence of around 5/100,000 [59, 60]. Female patients with SLE/APS are at increased risk of pregnancy complications: recurrent abortions, gestational hypertensive disease (including pre-eclampsia and hemolysis elevated liver enzymes, low platelets, i.e., HELLP syndrome), venous and arterial thrombosis, and miscarriage. On the other hand, fetal complications that were related to a positive antiphospholipid profile have included prematurity, fetal growth restriction, stillbirth, neonatal lupus, and neonatal deaths [23, 31]. The unceasing efforts aiming at in-depth understanding of SLE/APS as a potential risk to successful pregnancy outcome and the recent development of the Joint European League Against Rheumatism, European Renal Association, and American College of Rheumatology (EULAR/ERA-EDTA/ACR) recommendations for the management of patients with SLE/APS with a pregnancy wish announced the new era towards best practice [33, 61, 62]. These guidelines considered preconception counseling as essential for safer pregnancies in SLE/APS patient recommending individualized decisions with the aid of experts and a multidisciplinary specialized team for decision making [23, 24]. The league highlighted that the use of a clinically targeted pathway is the basis for development of a multidisciplinary strategy for pre-pregnancy counseling adapted to SLE/APS patients [25].

Anti-Ro and anti-La antibodies

The isolate presence of maternal anti-Ro/SSA or anti-La/SSB antibodies (capable of breaching the maternal-fetal protective barrier) contributes to 1–2% risk of congenital heart block and neonatal lupus [37, 63, 64]. Neonatal lupus erythematous syndrome can affect up to 5% of the offspring born to lupus mother [42]. Clinical presentations other than heart block have included cutaneous lupus, cardiomyopathy, hepatobiliary disease, and hematologic diatheses [43]. This high risk of congenital heart block necessitates screening by ultrasound between 16 and 18 weeks of gestational age with follow up of antibody titer [44]. Lupus mothers with anti-Ro/SS-A autoantibodies who previously had children with complete heart block were found to have a likelihood of having complete heart block rising from 2 to 18% in subsequent pregnancies [65].

Antithyroid antibodies

The presence of antithyroid antibodies with or without an evident autoimmune thyroid disease is a frequent clinical encounter in women with SLE. The prevalence of thyroid disease was reported to be 21% in SLE women, while postpartum thyroiditis (PPT) might affect 5–10% [66–68]. The presence of uncontrolled disease and positive antiphospholipid profile are common associations [32, 69–72]. Interestingly, subclinical hypothyroidism and thyroid antibody positivity in euthyroid women have been linked to miscarriage, premature births, higher cesarean section rates, and lower IQ. Levothyroxine treatment in thyroid peroxidase antibody-positive

women in the first trimester supported decreased adverse outcomes [73–80].

Preconception risk assessment needs in women with SLE

The decision to conceive in a female with lupus must be preceded by careful assessment to ensure safety to the mother and fetus. Recommendations for proper assessment have included assessment of individual risk based on the present and past history of the disease, careful portray of the disease phenotype in each patient, assessment of the disease activity status, serological parameters, consideration of the frequency and patterns of flares, the presence of systemic disease related or non-related comorbidities, the extent of organ specific disease and damage index, the evaluation of the potential hazards of teratogenic drugs used to control disease activity while in need, and the list of available safe yet effective therapeutic options. The assessment needs to be followed by individual stratification regarding the risk with pregnancy and a plan for management of possible critical clinical situations in cases with flare during pregnancy in an individualized approach. For women with uncontrolled disease flares or frequent flares or significant organ disease or comorbidity, counseling for the essentiality of contraception is warranted [81–83].

The assessment needs and conception plan for a pregnant female with lupus should be structured on what we describe as "An individualized approach to preconception needs" with the following clinical considerations: Table 1, Figs. 1 and 2 illustrates pivotal assessment needs prior to conception.

Updated evidence-based consensus on drug risk versus benefit in pregnancy with lupus

The effect of the different therapeutic strategies on pregnancy and fertility with SLE is a matter of major concern in real life practice. Weighing the risk to benefit comes first when considering the adoption of a specific strategy of management. The risk to benefit policy applies to prenatal counseling, natal, and postnatal timelines. Data from different studies have elaborated the benefit of effective preconception disease control for at least 6 months with the safe continuation of DMARDs of proven potential benefit in sustaining disease remission while imposing no harm to the fetus. One of the potentially beneficial identified DMARDs is the antimalarial drug hydroxychloroquine (HCQ) sulfate. In a meta-analysis done by Liu et al. in 2021 [83], the risk of premature rupture of membranes, preeclampsia, intrauterine distress, gestational age at delivery, preterm birth, and postpartum hemorrhage were not increased by HCQ in 119 pregnancies neither did the treatment with HCQ 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). Another later meta-analysis by Clowse et al. in 2022, with 7 cohorts providing 938 pregnancies in 804 women, revealed that women who continue using HCQ through lupus 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 to 0.93) [71]. Research data about the effect of therapy and pregnancy-related complications in SLE clearly reported that the use of hydroxychloroquine may lower the risk of preeclampsia, spontaneous abortions, congenital abnormalities, and fetal deaths. The anti-inflammatory and immunomodulatory properties of hydroxychloroquine made it a popularly safe recommendation for the treatment of SLE. HCQ has been found to restore endothelial function in an animal model of severe SLE oxidative stress is believed to be a major factor in both the onset of preeclampsia and SLE. HCQ prevents

Table 1 Pivotal individualized preconception assessment needs in pregnancy with lupus

Previous gynecologic and obstetric history
Disease activity status current and within the past 6 months
Frequency and patterns of clinical disease flares
Disease and non-disease related comorbidities
The potential for an acute or chronic decline in renal function should be carefully considered in women with lupus nephritis
Serological profile (including the presence of positive antiphospholipid profile, or positive anti-Ro, anti-La, antiU1 RNP)
Disease damage index
Drug history relative to disease status
Current drug regimen and doses
Stratify individual risk
Tailor individual therapeutic options available for management of flares during pregnancy
Patient and family education and counseling

Female patients with SLE planning to conceive are advised to seek preconception counselling by an expert rheumatologist who has the competencies to assess individual risk based on an integrated approach incorporating a list of clinical and laboratory indices with a potential impact on pregnancy outcome.

1- Clinical Indices:

- History of current illness.
- Previous gynecological and Obstetric (prenatal, natal, and postnatal) history.
- History of thromboembolic Manifestations.
- History and patterns of Flares (duration since latest flare).
- Current disease activity status and within past 6 months.
- Organ Specific Clinical History especially nephritis.
- Disease damage index.
- Disease and /or drug related comorbidities.
- Acceptance and compliance to medications.
- Current drug regimen and doses.
- Response to therapy with flares.
- Weighing risk versus benefit for potentially teratogenic medications.
- Was successful disease free/ organ free remission affordable with therapy.

Laboratory Indices:

- Autoantibody Profile: Anti-dsDNA titer- Anti- Ro antibodies- Anti La antibodies- anti-thyroid antibodies- lupus anticoagulants- anticardiolipin antibodies- anti B2 glycoprotein-1 antibodies- anti-RNP.
- Serum Complement Status: Complement 3- Complement 4- Complement hemolytic CH-50.

Fig. 1 Proposed consensus on indices to guide preconception risk assessment and conception planning in women with SLE

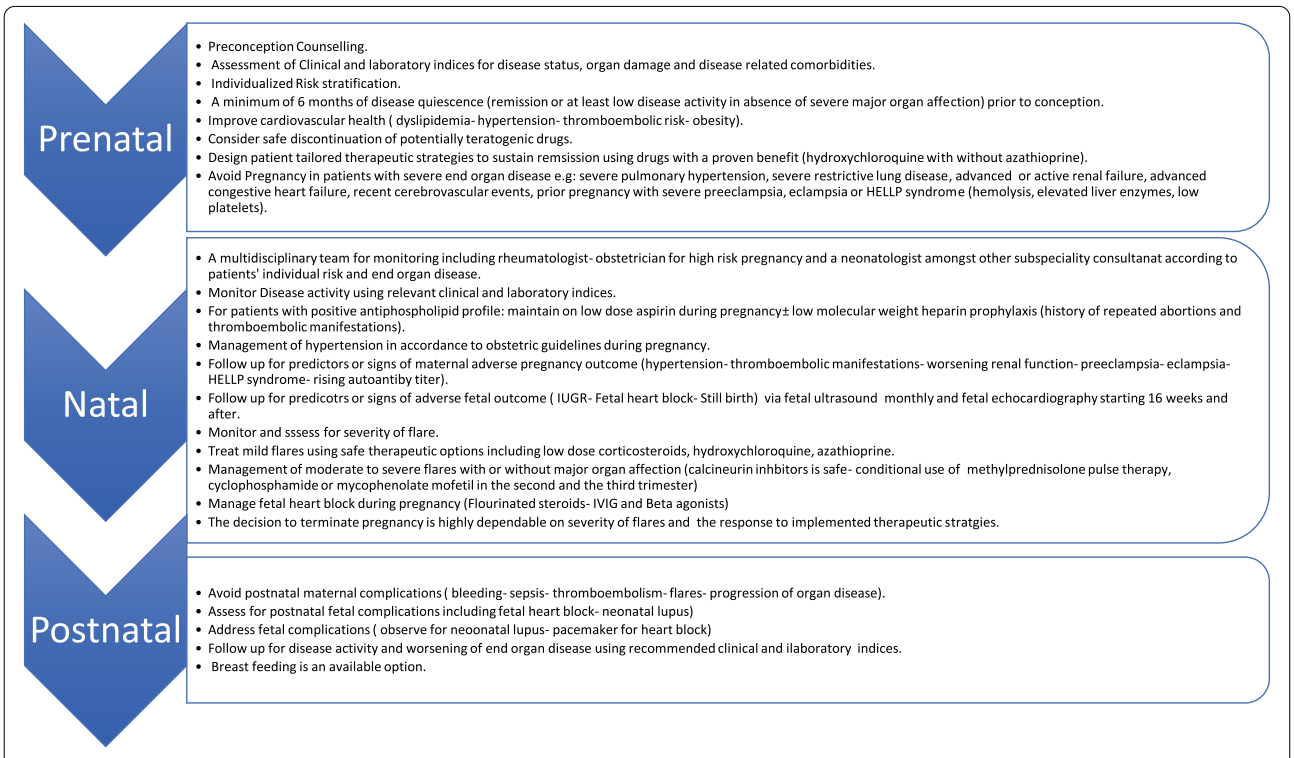

Fig. 2 Updated consensus on the management of lupus with pregnancy towards best clinical practice

the synthesis of reactive oxygen species, preventing tissue damage brought on by auto-oxidation and having subsequent anti-inflammatory actions. In women with SLE, HCQ may reduce the risk of maternal lupus flares, neonatal lupus syndrome, premature birth, and fetal growth restriction, preeclampsia, and preterm labor through these mechanisms [84–87].

On the other hand, preterm birth has been linked to 6-mercaptopurine (azathioprine and derivatives) use during pregnancy; however, unfavorable pregnancy outcomes such miscarriages, low birth weight, preterm birth, or adverse neonatal outcomes have not been clearly documented [88]. Despite the lack of sufficient evidence-based data, azathioprine is still considered to be safe during pregnancy as well because although few metabolites are detected in breast milk, and none was detected in the sera of newborns whose mothers breastfed while taking azathioprine [89–91].

Similarly, the use of corticosteroids during pregnancy is considered generally safe [89], and pregnant lupus patients on corticosteroids were found to experience lower rates of fetal morbidity and mortality [92]. Low-dose glucocorticoids in addition to the conventional treatment in pregnant patients with SLE have proven their safety efficacy and effectivity as evidenced by the majority of well-planned clinical studies. On the other hand, high dosages of steroids, considerably increase the incidence of maternal and fetal morbidities [43]. However, still the decision and choice of therapy must be weighted according to risk to benefit ratio.

The debate regarding the use of DMARDs and immune suppressive drug therapy during pregnancy and their impact on outcomes has been resolved to a great extent by real-life data that provided sound evidence for the possible risk versus potential benefit to a list of commonly prescribed medications in lupus. These data supported the justified introduction as well as the continuation of certain drugs during pregnancy marking them as safe to use based on risk versus benefit. The currently adopted evidence-based consensus regarding drugs safe to use during pregnancy have recommended that for glucocorticoids, the use of non-fluorinated corticosteroids (prednisolone, methylprednisolone, hydrocortisone) is considered a safe option for sustaining disease quiescence during pregnancy supporting the use of the least effective dose. As for fluorinated corticosteroids treatment with high-dose betamethasone 12 mg/week was found to potentially abort the direct effects of antibodies on cardiac function in fetal cardiac conduction problems [23]. Antimalarial drugs are generally another well-established safe disease-modifying drug during pregnancy and lactation, with successive reports confirming that the use of hydroxychloroquine during pregnancy has been associated with improved outcome and an observable risk reduction of fetal complications including congenital heart block and decreased risk of preeclampsia, while discontinuation might carry the risk of flare during pregnancy. The immune suppressive drug azathioprine/6-mercaptopurine crosses the placenta, yet the fetal liver lacks the enzyme required for drug activation and was not detectable in neonatal blood of lactating mothers which stratified the drug as being safe provided that its use is justified during pregnancy [23, 81–96]. Calcineurin inhibitors including cyclosporine, tacrolimus, and the recently approved voclosporin can be safely used in patients with nephritis at the least effective dose. The use of aspirin was associated with a decreased risk of preeclampsia in pregnant women with lupus and the prescription of a low dose of acetylsalicylic acid was significantly associated with a reduced incidence of miscarriage in patients with antiphospholipid syndrome; therefore, antiplatelets "Aspirin"/acetylsalicylic acid can be safely used during pregnancy. The analgesic drug acetaminophen is considered safe with pregnancy [81–96].

On the other hand, the updated consensus on the use of drugs that are considered unsafe and need to be discontinued during pregnancy have recommended that methotrexate need to be discontinued at least 3 months prior to conception, while folic acid supplementation is a must. However, if accidental pregnancy happens on the drug, this mandates discontinuation, folic acid administration, and referral to obstetrician for fetal assessment. For cyclophosphamide, the drug must be discontinued at least 3 months prior to conception and conditional use is allowed in the second and the third trimester with life-threatening and or organ-threatening flares. Mycophenolate mofetil must be stopped 1.5–3 months prior to conception; however, similarly the risk versus benefit consensus does not forbid the potential need for use with caution during the second and third trimester if disease flares occur. Non-steroidal anti-inflammatory drugs are considered unsafe and better avoided unless needed intermittently in the first and second trimester with absolute avoidance after 32 weeks of gestation. Antihypertensive drugs are known to increase the risk of congenital anomalies especially those of the cardiovascular system. ACE inhibitors can be continued until very early in pregnancy first positive pregnancy test after a missed menstrual period), and then, a switch to another first-line antihypertensive is recommended, and methyl dopa is usually the drug of choice in pregnancy with data supporting no proven evidence of human fetal abnormalities.

Finally, for the vaccines that are considered compatible and recommended while going through pregnancy

generally and in lupus, the measles, mumps, and rubella vaccines should be offered a month prior to conception to non-immunized women [81–96].

Managing difficulty to conceive with lupus

SLE women in remission who can go through safe pregnancy but failed to conceive spontaneously, in vitro fertilization might be an option with a careful watch to the possibility of flares and venous thromboembolism especially in the context of positive antiphospholipid profile or history of hypercoagulable status. In patients with APS, safer options including single embryo transfer and ovulation induction therapy need to be well implemented to minimize the risk of flares or avoidance of ovarian hyperstimulation syndrome [96–98].

Highlights on evidence about biologic experience in lupus pregnancy

The conundrum of the biologic therapy risk versus benefit in pregnant lupus patients remains a matter of great concern due to ethical considerations and paucity of data. In Lupus, the uncontrolled disease activity by itself especially in the presence of lupus nephritis or high damage index might contribute to serious maternal and fetal adverse events [30, 70]. A recent retrospective cohort study on 37 cases of pregnant SLE patients who used belimumab for uncontrolled disease by Ghalandari and colleagues 2022, including a total of 47 pregnancies, disposed the reported fetal and neonatal outcomes with either scheduled discontinuation of belimumab therapy from the first trimester group A (number= 37) or continuation of therapy group B (number= 10). The primary outcomes considered included the frequency of live births or deaths due to miscarriage or still birth, the rates of pre-term birth, low birth weight, and major congenital malformations (CMs). There were no statistical differences in fetal death rates between the two groups (46.4% A and 52.4% B, respectively; p value> 0.05), while there was an observable tendency towards increased incidence of pre-term births (43.2% A vs 40% B, $P > 0.05$) and low birth weight babies (24.35% A, 0.00 % B, respectively, $P > 0.05$) with discontinuation of belimumab in the first trimester though statistically insignificant. The study concluded that continuation of belimumab in patients already on treatment might contribute to a better pregnancy outcome with an acceptable safety margin, yet the small sample size remains a limitation [99].

Conclusion

The absence of remission for at least 6 months before conception, a preexisting active lupus nephritis, complement depletion, and a positive antiphospholipid antibody syndrome are well-recognized predictors for adverse pregnancy outcome. The consensus on the standard of care for pregnancy with lupus mandates the proper adherence to the implementation of preconception counseling strategy, planning for the correct timing of conception with a minimum of 6 months of disease-free remission prior to conception, stratifying patients according to individualized risk assessment, the close monitoring of SLE flares with tight disease control, and the appreciation of the value of multidisciplinary management to best practice and adopting patient tailored safe, yet effective therapeutic strategies are crucial [99, 100].

Abbreviations

SLE: Systemic lupus erythematosus; T reg: T regulatory cells; aPLs: Antiphospholipid syndrome; LAC: Lupus anticoagulants; IUFD: Intra-utrerine fetal death; SGA: Small for gestational age; PGS: Physician Global Score; APO: Adverse pregnancy outcomes.

Authors' contributions

The authors enlisted have contributed to the conception, writing, and revision of the manuscript. The authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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