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RESEARCH

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Egyptian recommendations for treating to target of lupus nephritis: an evidence-based consensus on clinical practice recommendations for the management of lupus nephritis and pregnancy

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Abstract

Background: Nephritis is known to be one of the most serious complications of lupus and a strong predictor of poor outcome. This study was carried out aiming at setting up an up-to-date recommendation for the management of women living with lupus nephritis and planning for a family throughout conception, pregnancy, and the postpartum period.

Ten key clinical questions were identified by the scientific committee according to the Patient/Population, Intervention, Comparison, Outcomes and Timing (PICOT) approach. The literature review team performed a systematic review to summarise evidence advocating the benefits and harms of available pharmacologic and nonpharmacologic therapies for women living with lupus nephritis (LN) and planning for a family. Subsequently, recommendations were formulated. The level of evidence was determined for each section using the Oxford Centre for Evidence-Based Medicine (CEBM) system. A 2-round Delphi process was conducted with 24 experts. All rounds were conducted online. A consensus was achieved on the direction and the strength of the recommendations.

Results: An online questionnaire was sent to an expert panel who participated in the two rounds (response rate 100%). At the end of round 2, a total of 20 recommendation items, categorised into 10 domains to address the main LN with pregnancy categories, were obtained. The percentage of those who agreed with the recommendations (rank 7–9) ranged from 88.5 to 100%. On the phrasing of all the clinical standards defined by the scientific committee, a consensus was reached (i.e., 75% of respondents strongly agreed or agreed). An algorithm for the management of LN with pregnancy has been suggested.

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Conclusion: These recommendations provide an updated consensus on the pharmacological treatment of LN with pregnancy and strategies to reach optimal outcomes for both the mother and newborn in common clinical scenarios, based on a combination of evidence and expert opinion. Best treatment decisions should be tailored to each individual patient's situation.

Keywords: Lupus nephritis, Pregnancy, Antiphosholipid syndrome, Fertility, Maternal outcome, Obstetric outcome, Foetal outcome, Preeclampsia

Background

Systemic lupus erythematosus (SLE) is a multi-organ autoimmune disorder that affects principally women in their reproductive age. Worries about conception, pregnancy, and fertility as well as flare-ups of the disease activity are major components of the standard day-to-day care of SLE patients. Nephritis has been recognised as one of the major complications of SLE and a predictor of poor outcome [1]. However, its impact on the patient's mortality has lessened in recent studies [2, 3], and a rising number of women with lupus nephritis aim for having a family and getting pregnant.

Hormonal and immunologic changes in pregnancy may help understanding how pregnancy changes some of the body's fundamental systems. Hormones of pregnancy not only affect the SLE disease activity in general, but also the kidney functions. Earlier data revealed an increased risk of lupus nephritis (LN) flare during pregnancy [4–6]. In a recent meta-analysis, rates of LN flare among SLE pregnant women ranged from 1.5 to 83%, with a random-effect rate of LN flare estimated at 25.6% (17.4–33.8%) [7]. Given the substantial risk of maternal and newborn morbidity associated with active LN [8], as well as the high likelihood of flare [9], management of LN together with close monitoring of disease activity are highly recommended [10].

Previously, these risks, combined with a lack of information about medication compatibility and the appropriate administration of medications during pregnancy, prompted several treating healthcare providers to advise their SLE patients against being pregnant. However, in recent years, a better knowledge of the course of SLE disease and the best ways to manage SLE/LN patients during pregnancy has opened the road for better maternal and foetal outcomes. The objective of this study was to develop an up-to-date recommendation for the management of women in their reproductive years who have LN during conception, pregnancy, and the postpartum period. This would be helpful not just for health care professionals who deal with acute autoimmune inflammatory disorders in general, but also for regulatory authorities, health-related organisations, and patient groups/people. This project was carried out under the CEG (Consensus, Evidence-based, Guidelines) initiative set up in Egypt which aims at promoting evidence-based practice in rheumatology by developing treat-to-target (T2T) clinical practice guidelines addressing relevant clinical problems.

Methods

Study design

The study design and procedures were developed using a qualitative synthesis of scientific evidence and consensus based on clinical experience and current scientific evidence. The manuscript followed the recommendations for preferred reporting items in systematic reviews and meta-analysis [11].

Study teams

Core team

To supervise, coordinate, and help in the development of the project's scope, and initial key clinical questions based on Patient/Population, Intervention, Comparison, Outcomes and Time (PICOT) approach. For each PICOT question, the core team pre-identified outcomes as critical for the systematic literature review. They also nominated the expert panel and drafted the manuscript.

Literature review team

To perform the literature search, data abstraction, and evidence quality assessment. Following data abstraction, evaluation of published recommendations, and quality of evidence rating [12, 13], the professionals in charge of the literature review offered a comprehensive list of proposals for lupus/LN management based on available research evidence and their own clinical competence. The Oxford Centre for Evidence-based Medicine (CEBM) approach was used to establish the degree of evidence for each section [13].

Expert panel

Those were selected by the core team. The participants should have professional knowledge, training, and experience in the field of lupus, with active participation in scientific research in this field.

Data sources and search strategies

The search strategy was planned to capture all studies in which the study population were adults living with lupus nephritis. The PICOT questions were used to conduct the literature search. Literature search strategies were carried out to locate randomised clinical trials evaluating conception, pregnancy and pregnancy outcomes in patients with lupus nephritis.

Study selection

Relevant studies were chosen using inclusion and exclusion criteria applied to the literature found using the search methodologies.

Inclusion criteria

Systematic reviews, randomised controlled trials (RCTs), uncontrolled trials, observational studies such as cohort, case-control, and cross-sectional studies, and economic evaluations were among the articles included.

Exclusion criteria

Commentaries, conference abstracts and nonevidence-based narrative/personal reviews, and manuscripts lacking an English version were excluded.

Delphi process

The Delphi method is an organised strategy for gathering essential information about a certain issue. It is predicated on the premise that group projections are more accurate than individual forecasts. The Delphi method's goal is to build consensus forecasts from a group of experts in a structured iterative manner. Its methodology is based on a sequence of "rounds" of questionnaires sent to experts. The anonymity of participants and regulated feedback are two key components of this strategy [14].

Delphi rounds

This is the consequence of two rounds of an online survey.

- The first round: the participants were asked to rate key clinical questions identified by the systemic literature review, as well as identify additional items that may have been overlooked and clarify those that were unclear.
- The second round: Participants were asked to score statements generated in view of each key clinical question, which was based on the results of the first round. The participants were encouraged to give their comments.

Voting process

Voting was done via the internet in several rounds, each with a strict time limit. All task force members were invited to participate and were given advance notice of the start and end times of each round of voting. We gathered and processed anonymous votes. Comments on rephrasing, potential ambiguity, and unidentified overlaps were obtained and reviewed for each statement. The task force members were the only persons who could vote on the statements.

Rating

Each statement was assessed on a scale of 1 to 9, with 1 representing "total disagreement" and 9 representing "full agreement". 1–3, 4–6, and 7–9, respectively, signify disagreement, uncertainty, and agreement. "Inconvenience concerning the accuracy of the recommendation" is represented by the "uncertainty" vote. There was no necessity for members to vote on all statements, and they were encouraged to abstain if a statement was outside their expertise. All statements allowed for the submission of comments, which the scientific committee assessed following each round of voting. In each round of voting, the same scenario was used, and members were encouraged to make comments wherever they voted in disagreement. This allowed the panel to spot a case of statement misinterpretation and invalidate the vote on that statement.

Definition of consensus

Prior to data analysis, a definition of consensus was established. It was determined that consensus would be obtained if at least 75% of the participants agreed (scoring 7–9) or disagreed (score 1–3) [6–9]. If a statement has a mean vote of less than 3 or a "poor" degree of agreement, it is retired. In light of the feedback, statements with an uncertainty score of 4–6 were changed. If all votes on a statement fell into the agreement bracket after the second round of voting, the level of agreement on that statement was characterised as "high" (7–9) [15].

Chronogram of Delphi rounds

The first round took place between 29 Jan and 1 Feb 2022 (4 days). The aspects about which respondents did not reach consensus in this first round were revised in view of the comments and included in the second round. The second round took place on 4 Feb 2022 (3 days after the first round) and lasted for 9 days (till 9 Feb 2022).

Target audience

The guideline has been developed to assist healthcare professionals who treat and manage patients with lupus and lupus nephritis. The guideline should also provide a helpful resource for patients and those responsible for commissioning care for patients with lupus/LN in the National Health Service.

Ethical aspects

This study was performed in accordance with the Helsinki Declaration. The Clinical, Evidence-based, Guidelines (CEG) initiative protocol was approved by the local ethical committee: ethical approval code: 34842/8/21, ethical board Tanta University. Written ethics approval from the experts sharing in this work was deemed unnecessary according to national regulations. All the participants were kept anonymous, in compliance with data protection regulations.

Results

Literature research and evidence selection

By using a search strategy, 2863 potential relevant studies were found during the study selection phase. 385 duplicates were excluded, while 2330 were excluded through title and abstract screening (studies did not examine population or intervention of interest, did not match study design of interest, or did not report outcome measures of interest). As a result, 148 studies were selected for full article evaluation. One hundred twenty-seven papers were removed because their citations did not match a PICOT; as a result, only 21 studies were included in this study (Fig. 1).

Expert panel characteristics

The Delphi form was sent to expert panel (n=24), of whom 24 (100%) completed in the two rounds. The respondents were drawn from different governorates and

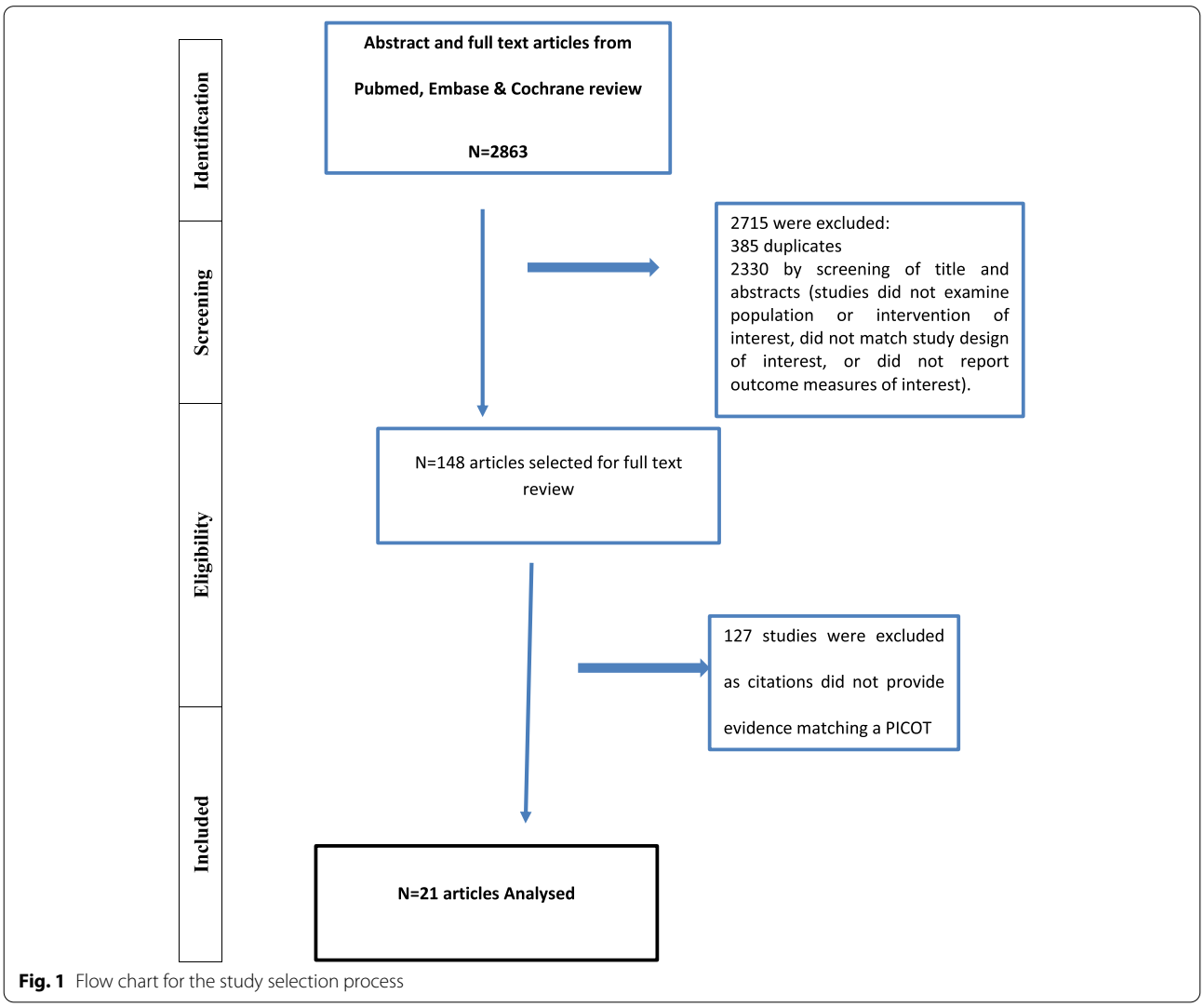


Fig. 1 Flow chart for the study selection process

health centres across Egypt: Ain Shams University (*n*=4, 16.6%), Cairo University (*n*=7, 29.2%), Tanta University (*n*=2, 8.3%), Benha University (*n*=2, 8.3%), South Valley University (*n*=1, 4.15%), Alexandria University (*n*=1, 4.15%), Fayoum University (*n*=1, 4.15%), Sohag University (*n*=1, 4.15%), Zagazig University (*n*=1, 4.15%), Assuit University (*n*=1, 4.15%), Minia University (*n*=1, 4.15%), Ministry of Health (*n*=1, 4.15%), in addition to (*n*=1, 4.15%) international expert from UK. 83.4% of the expert panel (20) were rheumatologists and 16.6% (4) were nephrologists.

Delphi process

An online survey was distributed to the expert panel members who took part in the two rounds (response rate 100%).

The key clinical question formed of 18 questions stratified under 10 domains (Table 1). Each domain entails one or more elements. Consensus was reached on the domains (as ≥80% of respondents strongly agreed or agreed), only one question was added about self-management, whereas all the suggested questions were accepted by the panel and no questions were retired.

The response rate for round 2 was 100% from the expert panel (24/24). Wording modifications were suggested for 5 statements (1 in the investigations, 2 in the treatment, and 2 in the outcomes). The statements were modified and amended. For the rest of the statements, the consensus was reached (as ≥ 80% of respondents strongly agreed or agreed).

Based on those results, this document was written, containing recommendations for the planning, monitoring and management of LN during and after pregnancy. Algorithm for the management of lupus nephritis during pregnancy has been suggested (Fig. 2).

Recommendation 1: Pregnancy planning in LN patients (Evidence: 3, Grade: C)

The presence of active SLE/LN at the time of conception is the strongest predictor of poor pregnancy outcomes. As a result, all pregnancies in women with SLE/LN should ideally be scheduled during illness control periods.

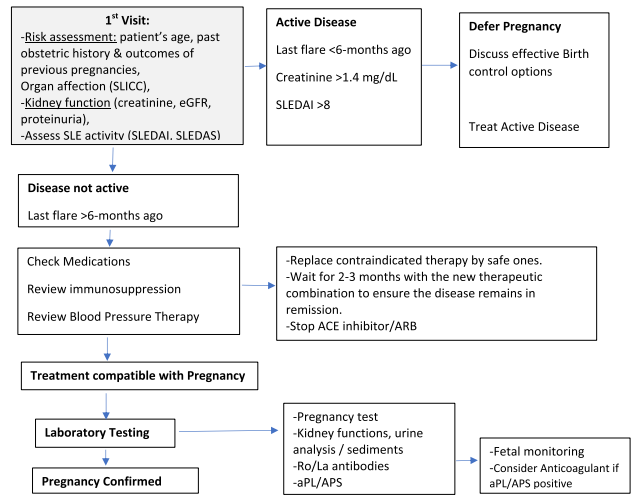
Natural and barrier methods of contraception have a high failure rate and may not be sufficient in a patient with active disease.

Contraceptives that contain progesterone only must be taken with caution. Long-term usage of depot preparations, in particular, has a detrimental impact on bone mineral density.

Table 1 Key clinical questions for treating to target lupus nephritis with pregnancy

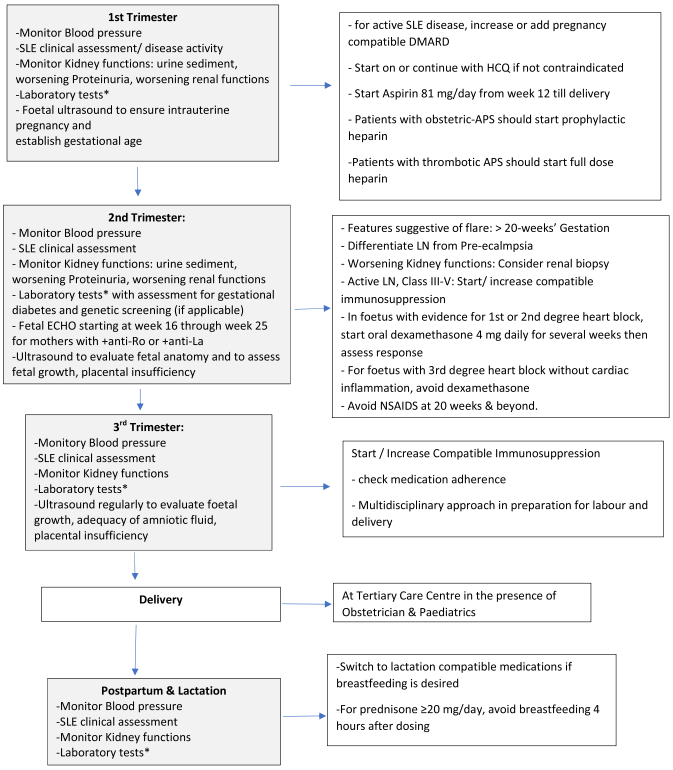
Domain	Key clinical questions
1. Pregnancy planning	- Is it possible for LN patients to have a successful pregnancy? - When it is the right time to conceive and what should you do before becoming pregnant?
2. Preconception evaluation	- What are the parameters to be assessed before the pregnancy in patients with lupus nephritis?
3. Pregnancy counselling	- What is the Influence of pregnancy on SLE with nephritis? - How can you identify the symptoms of SLE/LN flare during pregnancy?
4. Pregnancy	How pregnancy lupus patients with nephritis are monitored? - First Trimester - Second Trimester - Third Trimester
5. Patient's care:	
Antepartum care	How to set up a multidisciplinary team for patient's care during pregnancy?
Delivery	- What is the most appropriate method of delivery? - Is it possible for lupus patients to have a normal vaginal delivery?
Post-partum and lactation	- What should mothers with lupus nephritis do after the delivery of the baby? - Is it possible for a mother with lupus/LN to breastfeed her baby?
6. Pregnancy outcomes	What is the influence of SLE with nephritis on pregnancy? - Maternal outcomes - Foetal outcomes - Neonatal outcomes - What are the biomarkers predictive of pregnancy outcomes?
7. Antiphospholipid syndrome	What is the Influence of secondary APS on LN pregnancy?
8. Medications	- Which lupus medications can be safely used during pregnancy? - What is the Influence of SLE/LN-related medication?
9. Supplement therapy	- What is the most important supplement therapy to be considered for LN patients during pregnancy?
10. Shared decision-making	- What is the role of shared decision making in the management of LN during pregnancy?

SLE systemic lupus erythematosus, *LN* lupus nephritis, *APS* anti-phospholipid syndrome



SLE, systemic lupus erythematosus; HCQ, hydroxychloroquine; NSAIDS, nonsteroidal anti-inflammatory drugs; ECHO, echocardiogram. ARB: Angiotensin receptor blockers

a: Algorithm of an approach to the management of patients with lupus nephritis during pregnancy.



*Laboratory tests to be assessed: complete blood count (CBC), Kidney functions, metabolic profile, urinalysis and morning urine protein to creatinine ratio, anti-double stranded DNA (dsDNA) antibodies, complement levels (CH50, or C3 and C4), serum uric acid ± organ specific investigations.

SLE, systemic lupus erythematosus; HCQ, hydroxychloroquine; NSAIDS, nonsteroidal anti-inflammatory drugs; ECHO, echocardiogram. ARB: Angiotensin receptor blockers

b: Algorithm of an approach to the management of patients with lupus nephritis during pregnancy.

Fig. 2 Algorithm of an approach to the management of patients with lupus nephritis during pregnancy

For many patients with SLE, the intrauterine contraceptive device is still a viable and safe alternative.

Antiphospholipid antibodies (aPL) patients are at an increased risk of thrombosis and should avoid oestrogen-containing contraceptives [16, 17].

Recommendation 2: Preconception evaluation (Evidence: 3, Grade: C)

All SLE/LN patients who wish to get pregnant should have a preconception visit, during which the treating physician evaluates the risks associated to the pregnancy, current medications and whether there is any that is contraindicated during pregnancy and if it is the best moment for the patient to get pregnant according to underlying disease activity and possible complications. The goal of a preconception evaluation is to form a bond with the patient and work together to improve her health before becoming pregnant. Every woman with LN planning for a family should be assessed before considering getting pregnant for:

Major organ function

Advice against pregnancy if severe organ affection

Contra-indications to pregnancy

Severe pulmonary hypertension (systolic pulmonary artery pressure > 50 mmHg)
Severe restrictive lung disease (forced vital capacity < 1 L)
Advanced renal insufficiency (creatinine >2.8 mg/dL)
Advanced heart failure and previous severe pre-eclampsia or HELLP despite therapy

Disease activity status

Assess disease activity:

Stable: proceed
Active: defer pregnancy

Pregnancy should be deferred:

- Severe disease flare within the last 6-months
- Active lupus nephritis
- Stroke within the last 6 months

Lab

Assess for kidney function status, obtain autoantibody profile for risk evaluation especially aPL and anti-Ro antibody.

Medication

Review medications to check for compatibility with pregnancy, consider an alternative that is safe with pregnancy and adjust to achieve optimal control on a safe drug before pregnancy

Recommendation 3: Pre-pregnancy counselling (Evidence: 4, Grade: C)

A planned pregnancy is essential to allow enough time for medical care and disease control. In LN patients desiring pregnancy, inactive disease activity state for >6 months is the expected goal to achieve before attempting for pregnancy.

Preconception assessment

- For lupus nephritis, a preconception examination is necessary to determine whether pregnancy poses a high maternal or foetal risk.
- To optimise maternal and foetal outcomes, women with active lupus nephritis should be advised to postpone pregnancy till the disease is inactive for at least six months.
- Interventions should be initiated to control disease activity and to adjust medications to those that are safe for the foetus.
- Data from the renal biopsy should be included in the counselling session [18].
  LN classes I, II, and V, according to the World Health Organization, have low activity and chronicity indices, but classes III and IV are more aggressive and are linked to more LN flares [19, 20].
- Medication review:
  - Teratogenic immunosuppressives should be switched to ones that are safe for pregnancy before attempting to conceive.
  - Antihypertensives, such as angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, known to have adverse foetal effects should be switched to ones that are safe for pregnancy.

Patient advice

- Renal function should be stable for at least 6 months on a medication regimen that is safe to continue during pregnancy [21] without evidence of an ongoing LN flare.

Table 2 stratifying individual patient risk: pre-pregnancy counselling: assessment of the lupus nephritis risks and laboratory investigations

Risk assessment	Laboratory investigations
- Assessment of SLE disease activity - Assessment of kidney function status as well as major organ involvement - hypercoagulability status - Concurrent medical disorders that may impact pregnancy. - Previous obstetric outcomes should be reviewed - Attention should be paid to history of small for gestational age foetus, preeclampsia, stillbirth, miscarriage, and preterm birth.	- Anti-Ro/SSA and anti-La/SSB antibodies - Renal function (creatinine, urinalysis with urine sediment, spot urine protein/creatinine ratio, 24-hour urine protein) - Complete blood count (CBC) - Liver function tests - Anti-double-stranded DNA (dsDNA) antibodies - Complement (CH50, or C3 and C4) - aPLs (lupus anticoagulant [LA], immunoglobulin G [IgG] and IgM anticardiolipin [aCL] antibodies, and IgG and IgM anti-beta2-glycoprotein [GP] I antibodies).

dsDNA anti-double-stranded DNA, *aPL* anti-phospholipid antibodies, *C3* complement, *CBC* complete blood count, *dsDNA* anti-double-stranded DNA, *LA* lupus anticoagulant, *IgG* immunoglobulin G, *aCL* anticardiolipin antibodies, *GP* anti-beta2-glycoprotein

- Active SLE at the time of conception is linked to poor maternal and obstetrical outcomes.
- Women should be advised of the increased risk of lupus flare and pregnancy complications should they discontinue the medications prescribed to control their disease activity.
- Ideally, only medications which are compatible with pregnancy should be advised to women considering conception. The patients should continue taking these therapies during pregnancy.
- A history of lupus nephritis or current lupus nephritis during pregnancy is linked to an increased risk of maternal and foetal problems.
- For women with renal insufficiency, counselling should comprise an evaluation of the risk of a permanent or temporary decline in renal functions [8, 22]

Risk assessment and laboratory investigations

All patients should be assessed for major risks associated with pregnancy in women with lupus/lupus nephritis. In addition to the standard preconception labs, other laboratory tests are recommended to identify the maternal and foetal risks of complications. These are summarised in Table 2.

Risk stratification

- Renal function status/ proteinuria
- Disease activity
- Blood pressure
- Anaemia
- Thrombosis risk
- Diabetes mellitus/ Gestational Diabetes mellitus risk
- BMI
- Comorbidities
- Infection risk
- Smoking
- Nutrition
- Obstetric history

Additional advice:

- Maternal-foetal medicine obstetrics
- Genetics, anaesthesia, other
- Reproductive/fertility medicine

Biomarkers predictive of pregnancy outcomes

Lupus nephritis women planning for a family should be tested for:

Table 3 Pre-pregnancy counselling checklist for day-to-day standard practice

- Key question: Are you planning for a family or getting pregnant in the near future?
- Meeting with the patient and her husband (preferable)
- For women who are not planning for a family, discuss different birth control methods
- Ensure both SLE disease activity as well as LN are controlled for at least 6 months (advise to delay the pregnancy and discuss methods of birth control if the disease activity is moderate to severe)
- Review the patient's current medication and identify whether they are safe during pregnancy and breastfeeding
- Blood tests for: anti-Ro/SSA, anti-La/SSB antibodies, antiphospholipid antibodies as well as lupus anticoagulant
- Assess for the presence of comorbidities (e.g. diabetes, hypertension, renal disease, cardiovascular events) and whether they are controlled
- Multidisciplinary approach with a team including a rheumatologist, Obstetrician, nephrologist, as well as neonatologist/paediatric cardiologist

LN lupus nephritis

- Kidney functions
- Antibodies predict serious pregnancy problems, these include:
- Anti-Ro/SSA, anti-La/SSB
- Antiphospholipid antibodies (e.g. lupus anticoagulant, anticardiolipin IgM and IgG, b2-glycoprotein-I IgM, and IgG) [23, 24].

Table 3 shows a checklist for the pre-pregnancy counselling phase for use in standard clinical practice.

Recommendation 4: Pregnancy monitoring: (Evidence: 3, Grade: B)

After conception, antenatal management of pregnant SLE/LN patients mandates close collaboration between the treating rheumatologist, obstetrician and nephrologist. Clinical and laboratory evaluations specific for each trimester should be carried out for every SLE/LN woman who gets pregnant, in order to identify disease activity/flare up, pregnancy complications as well as situations that increase the risk of foetal complications.

First Trimester

- The first visit should include a physical examination, measurement of the BP, body weight and height. Baseline laboratory testing should be repeated at the first prenatal visit and should be done regardless if no preconception counselling was provided.
- Unless, otherwise indicated, every four weeks, women should be evaluated. However, the frequency of following prenatal and/or rheumatology clinic visits is determined by the individual patient's risks, as well as any obstetric history and the occurrence of any complications during the current pregnancy.
- Venous thromboembolism (VTE) risk should also be assessed at the patient's first visit and throughout pregnancy; those at high risk should receive thromboprophylaxis with low molecular weight heparin (LMWH) and be educated about deep venous thrombosis/pulmonary embolism symptoms [25]
- Proteinuria may rise during pregnancy in patients with permanent significant protein loss due to previous lupus nephritis due to increased renal blood flow, without indicating current nephritis [26]. This may be particularly noticeable in patients who discontinue ACE medications and/or angiotensin II receptor blockers before or during pregnancy. In early pregnancy, proteinuria can double from baseline levels [27]. If there is significant proteinuria, LMWH thromboprophylaxis may be required; previous results imply a threshold of protein: creatinine ratio (PCR) >100–200 mg/mmol or 24-h collection >1–2g/day during pregnancy [28, 29].

Second trimester

- Monthly prenatal visits are recommended, with laboratory testing frequency varying based on the severity of SLE/LN.
- To monitor foetal growth, regular foetal ultrasound examinations are recommended.
- Each visit should include blood pressure, dipstick urinalysis, symphysial-fundal height, and foetal heart rate, as well as the presence or absence of flare or pre-eclampsia symptoms.
- Starting at 12 weeks of pregnancy, all women with SLE/LN should take low-dose aspirin (81 mg) to lower their risk of preeclampsia [30, 31].
- Women taking steroids or who have had gestational diabetes in the past should be screened for gestational diabetes at 16 weeks, and if negative, at 26–28 weeks. Random blood glucose, glycosylated haemoglobin (HbA1c), oral glucose tolerance test, or finger prick blood sugar test are all options for blood sugar monitoring [32].
- In patients with active disease or previous complex obstetric histories, ultrasound scanning should be used to monitor foetal growth and well-being (amniotic fluid assessment, Doppler measurements of foetal blood flow): a standard approach might be a late second trimester (26–28 weeks) and mid-third trimester (34–36 weeks) scan. Ultrasound scans may be performed every 2–4 weeks if there are specific concerns or evidence of foetal impairment, with weekly (or more frequent) monitoring of amniotic fluid and Doppler and interaction with a foetal medicine consultant. Similarly, ultrasound scans may be sought in the case of a problem such as lupus flare or preeclampsia, or in the event of clinical concerns regarding foetal growth or well-being (lower symphysial-fundal height, or diminished foetal movements) [18].

Third trimester

- Women should be checked every 2 weeks from 28 to 34 weeks and every week after that.
- Each visit should include blood pressure, urinalysis, symphysial-fundal height, and foetal heart rate, as well as the presence or absence of flare or preeclampsia symptoms.
- Each visit, evaluate for intrauterine growth restriction

Table 4 How to differentiate between pre-eclampsia and flare of lupus nephritis in SLE patients (quoted with permission from [34])

	Pre-eclampsia	Lupus nephritis
Clinical		
	- After 20 weeks of gestation	- Any time during pregnancy
- Blood pressure: Hypertension (BP: 140/90 mmHg)	- Present	- Variable
- Other organ affection	- Occasionally CNS	- Evidence of non-renal active lupus
Laboratory investigations		
Standard blood testing		
- Platelets	- Low–normal	- Low–normal
- Creatinine	- Normal to raised	- Normal to raised
- Uric acid	- Elevated	- Normal
Immunology testing		
- Complements	- Normal–low	- Low
- Anti dsDNA	- Absent or unchanged	- Rising titers
Urine testing		
- Urinary sediment	- Inactive (uniform pattern, reflect renal damage, no correlation with clinical course)	- Active (urine sediment reflect lupus nephritis histopathlogy)
- 24-h urine calcium	- < 195mg/dl	- >195mg/dl
Management:		
Response to steroid therapy	No response	Good response

BP blood pressure, *dsDNA* double-strand DNA, *CNS* central nervous system

– Doppler sonography should continue at regular intervals

Recommendation 5: Patient's care during pregnancy (Evidence: 3, Grade: B)

Multidisciplinary team

Lupus nephritis pregnancies are high-risk pregnancies, therefore, it is vital to set up a collaborative approach to monitor these patients during pregnancy

It is highly recommended that a multidisciplinary team, including a rheumatologist, an obstetrician (optimally a maternal foetal medicine specialist), and a nephrologist should monitor and manage pregnant SLE patients with LN throughout pregnancy. Patients with a history of LN should be managed antepartum to treat both active disease and the avoidance of an LN flare. Pregnancy can affect different organ systems differently; musculoskeletal flares are less prevalent, while renal and hematologic flares are more common. The vast majority of pregnancy flares are mild to moderate, with only a tiny minority of patients experiencing severe flares. Active disease in the six months before conception, a history of lupus nephritis, and stopping antimalarials all raise the risk of flares during pregnancy. Given the added concerns about the growing foetus, the pregnancy-related safety and efficacy of the medical therapy typically used to treat LN should be carefully considered.

Ante-natal challenges

– Women with SLE/LN still have higher risks of different organ affection. Renal failure, pulmonary hypertension, and thrombophilia (thrombophilia predominantly due to anti-phospholipid syndrome (APS) are the most prevalent.
– There is also a higher chance of serious infections whether sepsis or pneumonia. Anaemia, thrombocytopaenia, and a higher need for blood transfusions are all hematologic problems. In concordance, the risk of thrombotic events such as DVT, PE, and stroke is more than tenfold higher in women with SLE. The risks of antepartum and postpartum haemorrhage, on the other hand, have been reported to be lower [29].

Preeclampsia is more likely in pregnant women with SLE/LN. Preeclampsia can affect up to 23% of women, which is 2–4 times more than the general population [29, 31]. Patients with lupus nephritis, chronic hypertension, and renal impairment, and women on high-dose oral steroids (steroids are likely to be indicative of disease activity, although steroids do increase blood pressure) after adjustment for maternal age may be at an even higher risk [7, 33, 34]. Table 4 shows how to differentiate between pre-eclampsia and flare of lupus nephritis in SLE patients.

Renal biopsy

- Renal biopsy should be considered in individuals with worsening proteinuria, worsening renal functioning, active urinary sediment, or serologic activity if the laboratory assessment is nondiagnostic.
- In patients with good blood pressure control and normal coagulation markers, a biopsy can be performed safely to get a clear diagnosis and inform therapy decisions [35].

After 32 weeks of pregnancy, a renal biopsy is not recommended.

With obstetrical and neonatal providers, the risks and benefits of biopsy versus delivery should be discussed.

- Gross haematuria occurs in 16.7% of renal biopsy patients, and perirenal hematoma occurs in 4.4% [36]. Recent studies, however, show that LN complications are similar in pregnant and non-pregnant women [37–39].
- Renal biopsy may make it easier to start disease-specific treatment rather than empirical treatment, which can be advanced postpartum to include immunosuppressive therapies that would normally be inappropriate during pregnancy.
- Empirical therapy should be undertaken only in rare clinical situations, such as in individuals with active urine sediment, proteinuria, and serological abnormalities, who have either had a previous kidney biopsy with a confirmed diagnosis of LN or who refuse to have the procedure done.
- Depending on the severity of the disease and the stage of the pregnancy, extra or repeated lab tests may be required. If a patient develops deep venous thrombosis during pregnancy while having negative antiphospholipid antibodies, they should be evaluated again.

Labour and delivery

- Women with SLE/LN are more likely to give birth prematurely.

Decisions for delivery date and mode should be made in consultation with an obstetrician who has experience managing labour in the presence of renal illness.

- In cases when there is evidence of thrombocytopenia or coagulation problems, an anaesthesiologist should be consulted about intrapartum analgesia.
- If a patient is anticipated to deliver before 37 weeks of pregnancy, it may be desirable to deliver in a tertiary care centre with neonatologists on staff.
- A lady in premature labour with a cephalic presentation should expect a vaginal delivery spontaneously.

If the foetus is between 24 and 34 weeks gestation, two maternal intramuscular steroid injections (betamethasone or dexamethasone) should be administered >24 h but no more than 7 days before delivery to enhance foetal lung development. This is independent of any maternal steroids, because prednisolone only reaches the foetus in trace amounts (10% maternal dose) due to placental metabolism. There is evidence that magnesium sulphate may have foetal neuroprotective benefits if the gestational age is less than 32 weeks (it may also be given to women with severe preeclampsia to prevent eclampsia) [18].

Women using conventional prophylactic LMWH doses "once daily" should cease taking them when spontaneous labour begins, or the night before induced labour or an elective caesarean section. Twelve hours following the last dose of LMWH, they can receive regional anaesthesia (epidural or spinal). Women using high prophylactic or therapeutic LMWH doses "twice daily" should stop taking them at the onset of spontaneous labour or 24 h before an induced labour or Caesarean section. They are eligible for regional anaesthesia 24 h following the last LMWH dose.

A patient-controlled analgesia opiate pump may be utilised as an alternate analgesic option for patients who are not within a safe post-LMWH time frame for regional anaesthesia and require further pain management, depending on the specific patient's kidney function status.

LMWH can be restarted 4 h after a spinal injection or after an epidural catheter has been withdrawn if the lady is hemodynamically stable. After the most recent LMWH injection, the epidural catheter should be removed >12 h later [25].

If the pregnant lady is on long-term oral steroids, intravenous hydrocortisone will be needed to deal with the physiological stress of labour and delivery. There is no perfect system. Standard procedure is to administer 50–100 mg intravenous hydrocortisone every 8 h (50 mg tds if taking 7.5–20 mg prednisolone; 100 mg tds if taking 20 mg prednisolone) [18].

Postpartum

- Mothers are at increased risk for thrombosis and disease flares during the postpartum period.

- Anticoagulation should continue for at least 6–12 weeks after parturition for those patients who have APS.
- Postpartum depression is prevalent, and it is easy to confuse it with neuropsychiatric lupus.
- If the mother has SLE/LN and tests positive for anti-Ro/SSA or anti-La/SSB, the newborn should be checked for cutaneous lesions. Cutaneous neonatal lupus can develop a few weeks after birth and go away on its own after a few weeks or months. These rashes are photosensitive; sun protection will help the rash resolve faster.
- These lab tests are recommended at 1 month after an uncomplicated delivery:
  - Urine analysis, urine protein/urine creatinine ratio
  - Renal function if the urinalysis is abnormal
  - CBC

Breastfeeding

- The benefits of breastfeeding (especially for preterm infants) may outweigh the theoretical risks of adverse effects on infants; therefore, breastfeeding options should be considered well before delivery.
- Many medications used for SLE disease during pregnancy can be continued during lactation, however, consideration should be given to the safety of immunosuppressive medications for the infant.
- Big doses of aspirin should be avoided in nursing mothers.
- Non-steroidal anti-inflammatory drugs (NSAIDs) are contraindicated in nursing mothers with jaundiced neonates.
- Prednisone, prednisolone, and hydroxychloroquine are compatible with breastfeeding.
- Breast feeding should not be contemplated in mothers who are taking cytotoxic agents such as cyclophosphamide, azathioprine, cyclosporin A, and methotrexate [40].

Recommendation 6: Pregnancy outcomes (Evidence: 3, Grade: B)

Maternal outcomes

Maternal morbidity

- The risk of maternal morbidity is increased in the setting of active LN, including an increased risk of hypertensive disorders of pregnancy [8].
- The risk of severe morbidity, such as eclampsia, stroke, and maternal death, approached 1%, though only maternal death reached statistical significance [7].
- The majority of deaths occurred in patients with active renal illness, with infection and SLE complications being the leading cause [41].
- This emphasises the importance of careful pregnancy planning, appropriate immunosuppressive medication use, and expert monitoring.

Pregnancy complications Pregnancy in the context of SLE is linked to an increased risk of complications, such as maternal mortality, preeclampsia, preterm labour, thrombosis, infection, and hematologic disorders, as compared to normal women.

Obstetric outcomes

- When compared to patients with new-onset LN, individuals with pre-existing LN had a considerably greater rate of preterm delivery (81.0% vs. 46.7%) and caesarean section (55.3% vs. 34.3%) [42].

Higher risks of foetal death, preterm birth, intrauterine growth restriction (IUGR), and newborn lupus syndromes are the main obstetric problems in SLE pregnancy. Lupus nephritis and active disease raise the risk of foetal loss and other negative effects. Other poor indicators of foetal survival include proteinuria, hypertension, thrombocytopenia, and the presence of anti-phospholipid antibodies. Preterm births and the morbidity that comes with them are the most common complications of SLE pregnancy. Premature birth can occur in up to half of all pregnancies. In SLE pregnancy, thyroid dysfunction is linked to a greater risk of preterm birth.

Foetal outcomes

All patients with pre-existing LN had at least one episode of a composite adverse foetal outcome, and this rate was significantly higher than that in patients with new-onset LN (97.4% vs. 80.0%) [42].

Foetal loss Pregnancies with SLE were more than twice as likely as non-SLE pregnancies to result in foetal death [43].

– Antiphospholipid antibodies, lupus nephritis, renal insufficiency, and increased lupus activity in the 6 months prior to or during pregnancy are all risk factors for pregnancy loss [44].

Foetal growth restriction

– Foetal growth restriction and small-for-gestational-age newborns affect roughly 10% to 30% of pregnancies in women with SLE, compared to about 10% of pregnancies in the general obstetric population.
– Women with SLE are more likely to have lower birth weight at all stages of pregnancy.
– Foetal growth limitation in the setting of lupus nephritis or pregnancies complicated by hypertension, APS, or pre-eclampsia [45].

Congenital heart block

- Reported in association with maternal anti-Ro/La autoantibodies. Antibodies cross the placenta and destroy the Purkinje system.
- It occurs in 2–3% of foetuses of women with the anti-Ro/La antibody and there is a recurrence rate of 16% in subsequent pregnancies [46].
- The clinical presentation is a fixed foetal bradycardia of 60–80 beats per minute on ultrasound scan.
- It is associated with significant perinatal morbidity and mortality, with about half of infants requiring pacing by the first year of life.
- Congenital heart block develops between 18 and 28 weeks of gestation and foetal echocardiography should be performed around this period to detect it.

Preterm delivery

This is more common in pregnancies complicated by active SLE or LN and often results in obstetric intervention and a leaning to deliver once the foetus is mature [42].

- Common causes for preterm delivery include pre-eclampsia, foetal distress as well as foetal growth restriction. Premature rupture of membranes is also more frequent in pregnant SLE women.
- SLE women on steroid therapy have been reported to have a greater risk [47].

Neonatal lupus syndromes (NLS) It is a type of passively acquired foetal autoimmunity caused by maternal antibodies such as anti-Ro and anti-La antibodies. The majority of the symptoms, such as dermatitis, hematologic, and hepatic abnormalities, are associated with maternal antibodies in the neonatal circulation. They usually disappear after six to eight months of life, after the antibodies have been cleared. Cardiovascular problems, on the other hand, are caused by maternal antibodies permanently damaging the foetal cardiac conduction system.

Conduction abnormalities, structural abnormalities, cardiomyopathy, and congestive heart failure are all cardiac symptoms of NLS. Congenital heart block is the most prevalent problem (CHB). CHB causes a significant rate of foetal mortality; rates of 15–30% have been documented. The majority of survivors require pacemakers, which adds to the high mortality rate. About 2% of children born to primigravid women with anti-Ro antibodies develop CHB. However, after the delivery of an afflicted child, the risk increases to roughly 16–20% in consecutive pregnancies.

Higher levels of maternal antibodies, maternal hypothyroidism, and foetal genetic variations have all been suggested as risk factors.

Recommendation 7: Co-existing APS (Evidence: 3, Grade: C)

The presence of aPL was reported in about one-quarter of lupus pregnancies [7]. The correlation between the number of positive tests for aPL and the risk of pregnancy loss; highlighted the importance of screening of all pregnant LN patients for the presence of these antibodies during the initial evaluation visit [48].

Obstetric APS is defined by: 1. three or more consecutive spontaneous abortions before 10 weeks of gestation, 2. one or more unexplained foetal loss beyond 10 weeks of gestation, or 3. one or more premature births of a morphologically normal neonate before 34 weeks of gestation due to eclampsia or preeclampsia [49]. The presence of aPL must occur on two or more occasions, separated by at least 12 weeks.

Thrombotic APS (T-APS) is defined by: one or more episodes of arterial, venous, or small vessel thrombosis in any tissue or organ

The occurrence of prior thrombotic or obstetric complications is important for risk stratification and management of APS during pregnancy [50–52].

The mainstay of management is anticoagulation, which seems to improve both maternal and foetal outcomes. Immunosuppressant therapies are reserved for patients who, in addition to APS, have active SLE.

Pregnant women with obstetric APS: it is advised to give low-dose aspirin with prophylactic doses of heparin

Table 5 Medication used during pregnancy

Drugs	Comments	Recommendations
Non-steroidal anti-inflammatory drugs (NSAIDS)	First trimester use may be associated with higher risk of congenital malformations, foetal renal impairment and premature closure of ductus arteriosus with use in the last trimester	• Use with caution during the first and second trimester • Discontinue during last trimester
Corticosteroids • Prednisolone/pulse methyl prednisolone • Flourinated compounds (betamethasone/dexamethasone)	• High doses can lead to higher maternal complications • Some association with impaired neuro-psychological development of the child	• Use the lowest possible dose Pulse therapy can be used for acute flares • Limit to one course, for foetal lung maturation
Antimalarials • Hydroxychloroquine	Reduced risk of disease flares, CHB and NLS	Should be continued in all lupus pregnancies
Immunosuppressants • Azathioprine • Calcineurin inhibitors (cyclosporine/tacrolimus)	Used in a large number of transplant recipients. Recent report of late developmental delays in offsprings with azathioprine	• Limit azathioprine dose to 2mg/kg/day • Explain the probability of late effects in the child to mother
Anti-hypertensives • Methyldopa • Labetalol • Nifedipine • Hydralazine	Concerns about growth retardation with labetalol and impaired utero-placental blood flow with hydralazine	Generally safe and preferred drugs for hypertension during pregnancy

SLE systemic lupus erythematosus, *LN* lupus nephritis, *aPL* anti-phospholipid antibodies, *NLS* neonatal lupus syndromes, *CHB* congenital heart block, *NSAIDS* non-steroidal anti-inflammatory drugs

(usually low molecular weight heparin). Continue anticoagulation for 6–12 weeks postpartum, as this is a vulnerable period for clotting.

Pregnant women with Thrombotic-APS should be prescribed aspirin and therapeutic dose of heparin throughout pregnancy and postpartum.

Hydroxychloroquine (HCQ) may help reduce the risk for thrombosis and APS-related poor outcomes.

There is not enough evidence to show that prednisone, intravenous immunoglobulin, or higher doses of heparin will help APS-related outcomes.

Women with a history of APS and arterial thrombotic events should be advised against pregnancy due to the significant risk of pregnancy loss, stroke, and maternal morbidity and mortality [53].

Oocyte retrieval should only be done during illness remission since it exposes women to large quantities of oestrogen, which can raise the risk of flare [54].

Recommendation 8: Medication used during pregnancy (Table 5) (Evidence: 2, Grade: B)

Discussion of the use of appropriate medications during pregnancy is an essential part of pre-pregnancy counselling.

Non-steroidal anti-inflammatory drugs (NSAIDS) were considered safe during the first and second trimesters. However, there has now been some evidence of a link between NSAID use in the first trimester and particular birth abnormalities. After 20 weeks of pregnancy, there is also an increased chance of foetal renal dysfunction. As a result, when using NSAIDs during early pregnancy, caution is recommended. Continued usage after the 32nd week of pregnancy increases the risk of premature ductus arteriosus closure by about 15 times and should be avoided. The data on cyclooxygenase 2 inhibitors in pregnancy is limited, hence they should be avoided during pregnancy.

Steroid exposure should be limited to a minimum during the pregnancy. High doses are linked to an increased risk of diabetes, hypertension, pre-eclampsia, and early membrane rupture during pregnancy. Short courses of large dosages (1–4 weeks) and/or intravenous pulse methylprednisolone can be administered in the case of illness flares. Stress dosages should be given to patients on long-term steroid therapy at the time of birth. In situations of premature delivery, the use of fluorinated drugs such as dexamethasone and betamethasone should be confined to a single course for foetal lung maturity. Repeated use has been linked to a child's neuro-psychological development being impaired later in life, so it should be avoided.

Hydroxychloroquine should be continued in all pregnant women with SLE. With use during pregnancy, disease activity was reduced with no adverse effects on the infant, whereas withdrawal resulted in an increase in disease flares. With continued usage of HCQ, the risk of CHB and neonatal lupus syndromes was considerably reduced in at-risk pregnancies.

Azathioprine is one of the only few immunosuppressive agents that has documented safety during pregnancy. To avoid foetal cytopaenias and immunological suppression, the dose should be kept to a maximum of 2mg/kg/day.

The calcineurin inhibitors, tacrolimus, and cyclosporine are other immunosuppressive medicines that have not been linked to an increased risk of foetal death.

Most other agents, such as cyclophosphamide, methotrexate, and mycophenolate, are contraindicated during pregnancy and should be discontinued at least 3 months before conception. The data on biologics like rituximab or belimumab during pregnancy is relatively limited, thus they should be stopped before getting pregnant. During pregnancy, the majority of regularly used antihypertensive medications must be avoided or taken with considerable caution. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers can produce ACE-inhibitor fetopathy, which is a type of foetal deformity. There have also been reports of newborn arterial hypotension, renal failure, and death. Beta-adrenergic blockers have been linked to foetal bradycardia and intrauterine growth retardation. Diuretics can cause maternal volume depletion and uteroplacental perfusion to be decreased. As a result, the safe weapons against hypertension during pregnancy are fairly limited, with medications like hydralazine, methyldopa, nifedipine, and labetalol among the options.

Anti-platelet therapy

Low-dose aspirin as a safe antiplatelet agent during pregnancy and should be taken from the 12th week of pregnancy till delivery. Data on other antiplatelet agents are limited.

Therapeutic anticoagulation

Heparin does not cross the placenta and is the anticoagulant of choice during pregnancy. Unfractionated heparin and low-molecular-weight heparin (LMWH) have similar efficacy and safety. LMWH has replaced UFH due to its simplicity of administration, greater antithrombotic to anticoagulant ratio, and consistent bioavailability. Due to the danger of warfarin embryopathy syndrome, warfarin should be avoided during pregnancy, especially during the first trimester. The data on fondoparinux, a direct factor Xa inhibitor, is limited yet promising. It does not cross the placenta and could be an alternative for women who are intolerant to heparin.

Recommendation 9: Supplement therapy (Evidence: 4, Grade: C)

- *Calcium supplementation* should be routinely provided to all pregnant women with SLE, especially those receiving corticosteroids and heparin. Vitamin D deficiency during pregnancy is linked to increased pregnancy morbidity, such as gestational diabetes, pre-eclampsia, and small-for-gestational-age newborns. Supplementing with vitamin D during pregnancy, on the other hand, did not consistently or significantly reduce the risk. Although recommendations vary, supplementing vitamin D during pregnancy in high-risk women is considered the safest option. Bisphosphonates should be stopped 6-12 months before conception.
- *Anaemia management:* anaemia of chronic illness is managed by disease activity control, hemolytic anaemia could be managed by high dose corticosteroids, and iron deficiency anaemia could be managed by iron supplements.

Recommendation 10: Shared decision-making of the patient's care (Evidence: 5, Grade: D)

Treatment of lupus nephritis with immunosuppressive medications is complex, especially for young women, and carries risks of infertility, teratogenicity, and serious infections. Many patients face difficult decisions, necessitating clear patient–provider communication and shared decision-making. Furthermore, Patient participation in decision-making not only ensures that treatment plans are consistent with patients' values but also can improve outcomes including medication adherence [55]. Therefore, shared decision-making plays an important role in tailoring the decision-making to the individual patient's requirement and should be part of the standard practice.

Management algorithm

In standard day-to-day practice, clinicians need a clear and readily accessible management approach that is applicable for standard practice. Such an approach should include information on appropriate evaluation, the required investigations, advised options for therapy as well as other interventions that should be offered to ensure optimum mother and foetus outcomes. Figure 2 shows a flow diagram of an approach of the management of lupus nephritis patients during pregnancy.

Discussion

Renal physiology changes significantly during pregnancy. A physiologic hydronephrosis can arise from progesterone-induced smooth muscle relaxation and constriction of the ureters by the expanding uterus, predisposing the pregnant woman to pyelonephritis and symptomatic urolithiasis. The glomerular filtration rate (GFR) increases by 50% to 60%, resulting in a 30% increase in creatinine clearance. A pregnant woman's serum creatinine level is lower than that of a non-pregnant woman, and

it fluctuates each trimester. As a result, a serum creatinine of 0.9 mg/dl may indicate the presence of underlying renal disease (16, 17). Pregnancy may be accompanied by an increase in proteinuria and the development of new or worsening hypertension in patients with pre-existing renal illness [18]. Pre-eclampsia, a pregnancy-specific illness clinically defined by hypertension and proteinuria, and its severe version, HELLP syndrome, are characterised by haemolysis, elevated liver enzymes, and low platelet count.

Systemic lupus erythematosus is a disease of reproductive-aged women; hence, it is important to set management recommendations for this cohort of patients particularly in association with organ affection such as nephritis. The work presented an evidence-based approach for the management of LN patients during pregnancy, developed and agreed upon by a consensus of experts. Results identified 7 main domains covering pregnancy planning, pre-conception evaluation, Pre-pregnancy counselling, maternal, foetal and neonatal outcomes, biomarkers Predictive of Pregnancy Outcomes, pregnancy monitoring, co-existing antiphospholipid syndrome, medication during pregnancy and post-partum care as management targets. This agrees with the outcomes of previously management recommendations published by the American College of Rheumatology (ACR) for the management of reproductive health in rheumatic and musculoskeletal diseases [51, 56], EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with SLE and/or APS [50], systematic review and meta-analysis of pregnancy outcomes in patients with systemic lupus erythematosus and lupus nephritis [7] as well as recently published clinical practice guideline on pregnancy and renal disease [57].

The Delphi technique has shown to be a reliable tool for discovering new ideas and determining the direction of future-oriented research. The technique enlists the help of a group of experts to determine the degree of agreement and resolve disagreements on a topic [58]. There was wide consensus on all the domains included in this work. When agreement or disagreement varies from 50 to 80% [59], Delphi approach produces consensus. The agreement in our study varied from 88.5 to 100%, demonstrating a strong trend among Egyptian health care experts about the management of LN women during pregnancy.

According to published statistics, pregnant SLE women are more likely to have a caesarean section (>33%, OR 1.7). This has been related to a range of factors and gestations [29]. Caesarean section, on the other hand, is an additional risk factor for VTE (OR 2–6.7 vs. vaginal birth) [18], comes with risks of bleeding and infection, and has ramifications for future pregnancies. As a result, we believe Caesarean sections should only be used for obstetric reasons (maternal and/or foetal issues) [1].

The study's key strengths are related to the participants' variety as well as their knowledge, the high levels of consensus reached, and agreement with the most recently published recommendations. In addition, the PICO methodological approach was adopted as the work's fundamental pillar.

Limitations of the guideline: Though the recommendation is based on the most up-to-date information at the time of publication, one of its flaws is the lack of comparable evidence to guide therapy selection. This includes the major evidence on comparative benefit/efficacy and harms. Because there were no head-to-head comparative studies found in the literature analysis, this study relied on indirect comparisons between trials/therapies. Interpreting the findings should be done with caution; the results of future studies may need changes to the conclusions or recommendations in this report. In the interests of unique patients and special circumstances, it may be necessary or even advantageous to deviate from the standards. Deviation from rules, like conformity to guidelines, may not be a defence against a claim of negligence. Also, we did not contain obstetricians in the group of expertise.

Conclusion

Lupus nephritis (LN) is a severe and prevalent symptom of SLE that is associated with increased mortality and morbidity. Pregnancies in women with LN are also more likely to result in maternal and/or foetal-neonatal problems. This was especially noticeable in people who had previously or currently had LN. For these reasons, the treating healthcare professional has often to face several challenges of pregnancy in this cohort of patients. This guideline endorsed a management strategy tailored to the individual patient's condition with a mix of treatment modalities as well as non-/pharmacological modalities. Patient education plays an important role in securing success in the patients' management.

Abbreviations

ACR: American College of Rheumatology; ACE: Angiotensin-converting enzyme; aPL: Anti-phospholipid antibodies; APS: Anti-phospholipid syndrome; BMI: Body mass index; CEBM: Centre for Evidence-Based Medicine; CHB: Congenital heart block; CEG: Consensus, Evidence-based, Guidelines; DVT: Deep venous thrombosis; GFR: Glomerular filtration rate; HCQ: Hydroxychloroquine; IUGR: Intra-uterine growth retardation; LMWH: Low molecular weight heparin; LN: Lupus nephritis; NLS: Neonatal lupus syndromes; NSAIDs: Non-steroidal anti-inflammatory drugs; PICOT: Patient/Population, Intervention, Comparison, Outcomes and Time; PCR: Protein creatinine ratio; PE: Pulmonary embolism; RCTs: Randomised-controlled trials; SLE: Systemic lupus erythematosus; T-APS: Thrombotic anti-phospholipid syndrome; T2T: Treat-to-target; VTE: Venous thromboembolism.

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Authors' contributions
Conceptualization and design, Yasser El Miedany, Mohammed Hassan Abu-Zaid, Sally Saber; Acquisition of data, Yasser El Miedany, Mohammed Hassan Abu-Zaid; Formal analysis, Maha El Gaafary; Investigation, Ahmed Ezzat and Abeer Mokbel; Methodology, all authors; Writing – original draft, Yasser El Miedany, Mohammed Hassan Abu-Zaid and Samar Tabra; Final approval of the version to be submitted, all authors.

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Availability of data and materials
The data will be available upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was performed in accordance with the Helsinki Declaration. This was a multistep process which followed the "Clinical, Evidence-based, Guidelines" (CEG) initiative protocol (ethical approval code: 34842/8/21, ethical board Tanta University) aiming at setting up an actionable clinical gold standard for treat-to-target management of rheumatic and bone diseases. All the participants were kept anonymous, in compliance with data protection regulations.

Consent for publication
Not applicable.

Competing interests
The authors declare that the corresponding author and Rehab Ali are associate editors in the Egyptian Rheumatology and Rehabilitation; Mohammed Mortada and Yasser El Miedany are from the editorial board of the journal. The other authors declare that they have no competing interests.

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