Published in final edited form as:

Adv Chronic Kidney Dis. 2013 September ; 20(5): 402–410. doi:10.1053/j.ackd.2013.06.004.

Women, renal disease and pregnancy

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Abstract

A number of glomerular diseases may occur in women of childbearing age. Pregnancy in such patients should be planned when the disease has been in remission for a minimum of six months in order to minimize maternal and fetal complications. Immunosuppressive agents should be optimized prior to conception to include those that are safe for pregnancy. The complexity of medical management when caring for these patients calls for a multidisciplinary team approach, consisting of a nephrologist, rheumatologist, obstetrician and a pharmacist. This review will address the physiological changes of pregnancy that may affect glomerular disease presentation, activity, and diagnosis; specific glomerular diseases, both primary and secondary to systemic diseases, in the context of pregnancy; fetal and maternal complications, and long-term effects; diagnosis and differential diagnosis; and treatment strategies that are considered relatively safe with respect to fetal intrauterine exposure.

Keywords

renal disease; proteinuria; preeclampsia; pregnancy; glomerular disease

Introduction

Chronic kidney disease is seen in approximately 4% of women of childbearing age,¹ and includes a number of primary renal diseases and renal diseases secondary to systemic illness. Fertility may be preserved in those without advanced renal insufficiency (serum creatinine >3 mg/dL) and in those without previous treatment with cytotoxic alkylating agents. The relationship between glomerular disease and pregnancy is complex, as pregnancy may affect maternal disease activity and progression to end-stage renal disease (ESRD), and the effects of the renal disease and its treatment may affect the pregnancy, including the developing fetus. Renal disease may be present before conception (and be active or quiescent), may flare during pregnancy, or it may occur *de novo* during pregnancy.

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Financial disclosures – Dr. Garovic is the inventor of technology referenced in this article. That technology has been patented by Mayo Clinic, but is currently not licensed. All other authors report no conflict of interest.

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Adverse pregnancy outcomes are more common in patients with active renal disease (Figure 1) and in those with advanced renal insufficiency. Complications include spontaneous abortion, prematurity, intrauterine growth retardation, preeclampsia and renal disease flare. As such, for all types of renal disease, remission of disease for a minimum of six months prior to conception is recommended.² The optimal therapeutic approaches for glomerular disease in the non-pregnant population may not be appropriate for use during pregnancy. Preconception counseling and planning of pregnancy is a key component, with the goal of therapy being to control disease activity (both renal and systemic) with agents that are relatively safe for the growing fetus. This care should involve a multidisciplinary team. The physiological changes that occur during normal pregnancy should be taken into account when assessing glomerular disease presentation, activity, and diagnosis in pregnant patients.

Physiological Changes of Pregnancy

Pregnancy is associated with important changes in renal physiology.³ The glomerular filtration rate (GFR) increases by up to 50% above baseline levels, primarily due to elevations in cardiac output and renal blood flow.⁴ Consequently, normal pregnancy is associated with a decrease in the serum creatinine concentration by an average of 0.4 mg/dL. Therefore, serum creatinine levels that are considered normal for non-pregnant women (e.g. serum creatinine 0.9 mg/dL) may indicate underlying renal disease during pregnancy. In addition, the combination of progesterone-induced ureteral smooth muscle relaxation and ureteral compression secondary to the enlarging fetus results in dilatation of the urinary collecting system, creating a physiological hydronephrosis, which is more prominent on the right side.

Pregnancy also results in a physiological increase in protein excretion due to a combination of increased GFR and increased permeability of the glomerular basement membrane,⁵ with an acceptable upper limit of normal of 300 mg/day.⁶ This physiological increase in protein excretion during pregnancy is further exaggerated in patients with proteinuric renal disease, particularly toward the end of pregnancy.⁷ This worsening proteinuria coupled with either *de novo* or worsening of preexisting hypertension control may represent either a flare of underlying glomerular disease or preeclampsia, a pregnancy-specific condition clinically characterized by hypertension and proteinuria. Although several clinical and laboratory features may facilitate diagnosis, renal biopsy should be considered when a non-invasive evaluation is non-diagnostic.

Another major adaptation that occurs during normal pregnancy is the modulation of both innate and adaptive immunity, with the goal of establishing maternal tolerance to the semi-allogeneic fetus that expresses both maternal and paternal antigens. A shift from a Th1 cell-mediated to a Th2 antibody-mediated immune response, also referred to as Th2 polarization, leads to the relative suppression of Th1-mediated immunity, which may contribute to maternal tolerance of the fetus.^{8,9} However, this shift towards a Th2 response may increase the risk of flare of Th2-mediated diseases, such as systemic lupus erythematosus (SLE), during pregnancy.¹⁰

These physiological changes of normal pregnancy also should be considered when evaluating renal function and renal disease during pregnancy.

Specific Renal Diseases

1. Lupus Nephritis

Systemic lupus erythematosus (SLE) is a multi-system, autoimmune, connective tissue disease seen frequently in women of childbearing age. Although previously reported to be

associated with poor pregnancy outcomes, recent reports indicate an improvement in pregnancy outcomes, with optimal management including planning of pregnancy during periods of disease quiescence.¹¹ Up to 75% of patients with SLE have clinically evident renal disease.¹² Lupus nephritis (LN) has been associated with an increased risk of maternal mortality (OR 20.0), Caesarean section (OR 1.7), preterm labor (OR 2.4) and preeclampsia (OR 3.0).¹³ Maternal mortality is most frequently seen in patients with active disease and, when it occurs, is most frequently due to opportunistic infection.¹⁴ The rate of fetal loss may be >50% in patients with active renal disease,¹⁵ which is further elevated in those with a previous pregnancy affected by complications due to LN.¹⁶ Reported lupus flare rates during pregnancy vary, but a meta-analysis reported that renal flares affect one in four pregnancies complicated by LN.¹⁷ Patients with proliferative disease on renal biopsy (class III or IV LN) have a higher incidence of hypertension and preeclampsia (37.1%) compared to those with non-proliferative disease (class II or V LN) (11.1%).¹⁸

The management of established lupus for the purposes of pregnancy involves modification of immunosuppressive and antihypertensive medications to those that are most appropriate for pregnancy, by balancing the need for therapy to maintain disease remission with the risk of flare. For new disease or a flare of existing disease during pregnancy, induction and maintenance regimens are based on corticosteroids, azathioprine, hydroxychloroquine and calcineurin inhibitors.¹⁹

2. Antiphospholipid Antibodies/Syndrome

Antiphospholipid antibodies (APL), including lupus anticoagulant and anticardiolipin antibodies, bind to cardiolipin and/or β_2 glycoprotein-I bound to phospholipids. Antiphospholipid syndrome (APS) occurs when these antibodies are present in association with pregnancy complications and/or venous or arterial thromboses. Both APL and APS frequently are associated with SLE and further increase the risk of fetal loss and preeclampsia.²⁰ A meta-analysis reported that APL are positive in 1/4 of lupus pregnancies.¹⁷ Patients with APS and a history of arterial thromboses should be advised against pregnancy due to an additional increased risk for stroke, maternal morbidity and maternal mortality.²¹ Anticoagulation is the mainstay of management to improve pregnancy outcomes. Immunosuppression is usually only indicated in those with active SLE.

3. Diabetic Nephropathy

Diabetic nephropathy affects approximately 6% of women with type 1 diabetes.²² Although nephropathy is less frequently encountered in women of childbearing age with type 2 diabetes mellitus, the increasing obesity epidemic in younger people may change this pattern in the future. The degree of pre-pregnancy renal disease is correlated with the risk of pregnancy complications,²³ including preeclampsia, independent of the severity of proteinuria in early pregnancy.²⁴ Similarly, the risk of deterioration in renal function (including progression to ESRD) is increased with serum creatinines of ≥ 1.4 mg/dL.²² The mainstay of management is strict glycemic control, which has increased perinatal survival to 95%.²⁵ Many of these patients will also be treated with ACE-I or ARB prior to pregnancy, which should be changed to other antihypertensive agents prior to conception. The use of ACE-I for 3–6 months prior to conception may confer a renal protective effect during pregnancy even after their discontinuation.²⁶

4. Focal Segmental Glomerulosclerosis

Focal segmental glomerulosclerosis (FSGS) is the most common glomerular disorder that causes ESRD in the USA²⁷ and commonly presents with nephrotic syndrome,²⁸ which increases the risk of pregnancy complications. Primary FSGS presents with the acute or subacute onset of nephrotic syndrome, often in the absence of renal insufficiency, and

accounts for 80% of cases.²⁹ Secondary FSGS may be seen in association with IgA nephropathy, vasculitis, lupus, infection (HIV, parvovirus, CMV, EBV) or drugs/toxins (interferon, heroin, lithium or pamidronate). The presentation of FSGS may be very similar to preeclampsia and, therefore, making the correct diagnosis is crucial as the management of these conditions differ.

The management of FSGS includes blood pressure control with agents safe for use during pregnancy, volume management, fluid restriction, and a low-salt diet, as well as ruling out secondary causes of FSGS that require specific therapy. The use of ACE-I or ARB is contraindicated. Although there were concerns that diuretics may reduce plasma volume³⁰ and increase maternal and fetal complications, they have subsequently been shown to be well tolerated during pregnancy without any adverse perinatal effects.³¹ Corticosteroids are first line therapy, although it may take up to 16 weeks to achieve remission.³² Although prednisone may be more rapidly metabolized during pregnancy,³³ current prednisone dosing is similar in both pregnant and non-pregnant patients. This should be taken into consideration when failing to achieve renal disease remission during pregnancy. Calcineurin inhibitors are the second line agents of choice. Therapy should be continued for a minimum of twelve months before tapering, in order to maintain remission. Tacrolimus can be used in pregnancy, but not sirolimus, due to its embryotoxicity, fetotoxicity, risk for impaired fetal growth and fetal loss.

5. Minimal Change Disease

Minimal change disease is responsible for 10–25% of the cases of nephrotic syndrome in adults.³⁴ Similar to FSGS, management focuses on blood pressure control and volume management. Corticosteroid use is the mainstay of treatment and results in the complete remission of proteinuria in the majority of cases. Once remission is achieved, a slow taper is required to maintain remission and minimize the risk of adrenal suppression, which has been associated with an increased risk of relapse.³⁵ Those with frequent relapses of glucocorticoid-dependent disease can be treated with azathioprine or calcineurin inhibitors. In the setting of pregnancy, azathioprine and tacrolimus are advised. (Table 2)

6. Membranous Nephropathy

Membranous nephropathy (MN) also presents with nephrotic syndrome and is characterized by diffuse thickening of the glomerular basement membrane. The majority of cases are idiopathic and the M-type phospholipase A1 receptor (PLA2R) expressed on podocytes has been identified as a major antigen in human idiopathic MN.³⁶ The management of membranous nephropathy during pregnancy can be difficult, as ACE-I/ARB, lipid lowering agents, and warfarin are contraindicated. Instead, alternative anticoagulation and immunosuppressive agents (rarely required) that are safe during pregnancy are used.

7. IgA Nephropathy

Immunoglobulin A (IgA) nephropathy is the most prevalent primary glomerulonephritis, most often diagnosed during the 2nd and 3rd decades, and therefore, affects women of childbearing age. A recent prospective cohort study (n=245) reported that pregnancy does not affect long-term renal outcomes in those with preserved renal function.³⁷ Outcomes appear to be best when proteinuria is reduced pre-pregnancy,³⁸ and the risk of adverse renal outcomes is highest in the presence of a GFR < 70ml/min/1.73m², uncontrolled hypertension, or severe arteriolar and tubulointerstitial disease on renal biopsy.³⁹ The majority of these patients are also treated with ACE-I or ARB outside of pregnancy, and again, these medications should be discontinued prior to conception. If blood pressure control is required, other safer agents should be initiated. For the patients treated with

immunosuppression, these agents should be reviewed prior to conception and modified appropriately.

8. Vasculitides

Takayasu's arteritis most commonly presents in patients aged 10–40 years,⁴⁰ making it the second most common vasculitis encountered during pregnancy, after SLE. Common presenting features include, renal insufficiency, hypertension, stroke, and heart failure, and these pregnancies are at increased risk of preeclampsia.⁴¹ Other vasculitides predominantly affect men or women after childbearing age and, as such, are infrequently encountered during pregnancy. ANCA vasculitides (including granulomatosis with polyangiitis and microscopic polyangiitis) rarely present during pregnancy. A review identified only 36 reported cases since 1970 and suggests that pregnancies with active ANCA disease have poor outcomes, despite aggressive therapy.⁴² The transplacental transfer of MPO-ANCA has been reported, which increases the risk of fetal/neonatal disease, including pulmonary hemorrhage and renal involvement.⁴³ The management of these disorders requires immunosuppression, which, during pregnancy, predominantly consists of corticosteroids and calcineurin inhibitors (tacrolimus). Cyclophosphamide can be considered for those with active disease, but does increase the risk of fetal loss and congenital malformations.

9. Atypical Hemolytic-Uremic Syndrome

Atypical hemolytic-uremic syndrome (aHUS) occurs due to uncontrolled complement activation. A retrospective cohort study (n=100) of patients with aHUS reported that 21 cases occurred in association with pregnancy, with 18/21 having complement abnormalities, suggesting that pregnancy may act as a trigger. These patients were found to have an increased risk of fetal loss and preeclampsia, and 76% had developed ESRD by final follow up.⁴⁴ Similar to the non-pregnant state, management primarily consists of plasma exchange. The safety of targeted anticomplement agents, such as eculizumab, during pregnancy is unknown.

10. Systemic Sclerosis/Scleroderma

Although scleroderma more commonly affects women, the mean age of onset is 40 years and it is not frequently seen during childbearing years.⁴⁵ It is unclear if pregnancy increases the risk of scleroderma renal crisis, which includes abrupt renin-mediated hypertension and renal impairment. This complication is seen in 5% of patients with this disorder, most commonly within 5 years of disease onset.⁴⁶ In the non-pregnant state, optimal management of a scleroderma renal crisis includes, ACE-I or ARB therapy, both of which should be avoided during pregnancy. However, in the setting of life-threatening maternal disease, the use of these agents during pregnancy may be justified.

Diagnosis and treatment of renal disease in pregnancy

For known renal disease prior to pregnancy, the mainstay of management should include preconception counseling, with pregnancy planned to occur when the disease is stable and quiescent, and after a minimum of six months of disease remission. Management should include a multidisciplinary team consisting of a nephrologist, an obstetrician (ideally, a maternal fetal medicine specialist), and other relevant specialists (including a rheumatologist, immunologist, endocrinologist and pharmacist). Before attempting to conceive, teratogenic medications (including immunosuppressive and antihypertensive agents with adverse fetal effects) should be changed to those appropriate for pregnancy.

During the preconception-counseling visit, all relevant clinical and laboratory data should be reviewed in order to inform the patient about the risks associated with pregnancy. An

assessment of disease activity, blood pressure, proteinuria and stability of renal function should be performed, and any available renal biopsies should be reviewed to risk stratify the pregnancy. Depending on the renal disease in question, baseline laboratory tests, including rheumatologic serologies may be indicated.

Once pregnancy is confirmed, monthly prenatal visits are indicated, with the frequency of laboratory testing and fetal ultrasound examinations determined by disease activity/severity. Delivery should be planned in advance, and ideally, high-risk pregnancies should be delivered at a tertiary referral center. For those patients with thrombocytopenia or coagulation abnormalities, a consultation with an anesthesiologist may be indicated to plan intrapartum care, including analgesia.

Renal disease may present *de novo* during pregnancy or a pre-existing renal disease may flare. As many renal diseases present with proteinuria and hypertension, the distinction between renal disease and preeclampsia must be made to guide therapy. The evaluation should include a patient history, physical examination, blood pressure measurement, urinalysis and relevant laboratories (Table 1). For those with known renal disease, results should be compared to those from the preconception-counseling visit.

A definitive diagnosis may require a renal biopsy to confirm the appropriate treatment; delivery for preeclampsia, and immunosuppressive therapy for active renal disease.⁴⁷ In addition, a renal biopsy should be considered to facilitate the initiation of disease-specific therapies when the underlying diagnosis is unclear after this assessment. Renal biopsy can be performed safely in patients with adequate blood pressure control and normal coagulation parameters.⁴⁸ However, renal biopsy is not advisable after 32 weeks of gestation, due to difficulties with patient positioning and tolerability of the procedure. At that gestational age, delivery may be a reasonable option, allowing for postpartum care of the mother that is not restricted by concerns of fetal risk.

Antihypertensive Agents

For many renal diseases, the antihypertensive agents of choice include, ACE-I and ARBs, as they are known to reduce proteinuria and may delay the progression of nephropathy. However, both classes are teratogenic and are associated with an increased risk of congenital malformations of the cardiovascular and central nervous systems. As such, these agents should be changed to safer alternatives, such as methyldopa, labetalol or nifedipine prior to conception.^{49,50} Diuretics are acceptable medications that can be continued in patients with pre-pregnancy hypertension.

Anticoagulation

Anticoagulation may be required for patients with APL, APS, or nephrotic range proteinuria. However, warfarin is contraindicated for use during pregnancy due to its teratogenicity and increased risk of life-threatening hemorrhage in the infant.⁵¹ Patients should be treated with either unfractionated heparin or low molecular weight heparin during pregnancy. For patients without a previous history of thrombotic events, but meeting the obstetric criteria for APS (≥ 3 pregnancy losses or a late pregnancy loss), prophylactic dose anticoagulation with low dose aspirin (81 mg/day) and heparin should be used. For those with APL, but not meeting the above criteria, therapeutic options include, close clinical surveillance, aspirin monotherapy, or heparin monotherapy. Prophylactic heparin dosing should be considered for those with nephrotic syndrome due to the associated hypercoagulability.¹⁹ Although newer agents, such as the direct thrombin inhibitors and factor Xa inhibitors, are useful in other conditions, their use has not been studied in patients with nephrotic syndrome.⁵² In addition, as there is animal evidence suggesting potential risk in pregnancy and no

overwhelming evidence of benefit over other therapies, their use during pregnancy is not currently advised.

Immunosuppression

Immunosuppressive therapy may be indicated for induction therapy for new onset of renal disease, flare, or maintenance therapy for patients in remission. The optimal therapeutic approaches for renal disease in the non-pregnant state may not be appropriate for use during pregnancy due to unacceptable risks to the fetus, in addition to side effects from these agents seen in non-pregnant patients (Table 2).

Preeclampsia

Preeclampsia is a pregnancy-specific disorder clinically characterized by hypertension (blood pressure $\geq 140/90$ mm Hg) and proteinuria (≥ 300 mg in a 24-hour urine).⁵³ It affects approximately 5% of pregnancies and remains a leading cause of both maternal and fetal morbidity and mortality worldwide. The etiology and pathogenesis of this disorder remain elusive, resulting in a failure to develop specific preventive and treatment options.

The pathogenesis of preeclampsia is related to endothelial dysfunction that is, at least in part, mediated by elevated levels of the soluble receptor for vascular endothelial growth factor (VEGF) of placental origin.⁵⁴ This soluble receptor, commonly referred to as sFlt-1 (from fms-like tyrosine kinase receptor-1), may bind and neutralize VEGF, and thus decrease free VEGF levels, which are required for active fetal and placental angiogenesis in pregnancy. A mouse model of podocyte-specific heterozygous VEGF-A expression supports the role of VEGF-A in glomerular development and maintenance: by 2 ½ weeks they develop proteinuria and severe endotheliosis (characterized by glomerular endothelial swelling with occlusion of the capillary lumens, leading to “bloodless” glomeruli), which is considered to be the pathologic hallmark of preeclampsia.⁵⁵ Similarly, a previous human study reported glomerular injury in patients who were treated with anti-VEGF inhibition (with bevacizumab).⁵⁶ In addition, the mechanism of proteinuria in preeclampsia may relate to podocyturia, i.e. the urinary excretion of glomerular epithelial cells.^{57,58} The loss of a critical number of podocytes may impair the filtration barrier and, as such, may predate proteinuria, as demonstrated by a recent study that showed that podocyturia predates the clinical diagnosis of preeclampsia.⁵⁹

Long-Term Cardiovascular and Renal Effects

Women with hypertensive pregnancy disorders, including preeclampsia, are at an increased risk for both cardiovascular and renal disease later in life.^{60,61} With respect to renal disease, a history of preeclampsia has been associated with a higher frequency of microalbuminuria up to 5 years after delivery,⁶¹ is a risk factor for undergoing a kidney biopsy later in life⁶² and, ultimately, developing ESRD,⁶³ even after controlling for traditional risk factors.⁶⁴ At present, women with a history of preeclampsia and proteinuria that persists 3–6 months postpartum need to be seen by a nephrologist for consideration of a renal biopsy. Continued follow up of renal function and proteinuria after preeclamptic pregnancies may facilitate early detection of renal disease and prompt intervention.

Acknowledgments

Grant support

The project described was supported by Award Number K08 HD051714 (Vesna D. Garovic) from the Eunice Kennedy Shriver National Institute of Child Health & Human Development and by Award Number P-50 AG44170 (Vesna D. Garovic) from the National Institute on Aging. The content is solely the responsibility of the authors and

does not necessarily represent the official views of the National Institutes of Health. The writing of the manuscript and the decision to submit it for publication were solely the authors' responsibilities.

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Clinical Summary

- Pregnancy in women with renal disease increases risks for adverse maternal and fetal outcomes.
- The major goal of immunosuppressive therapy in pregnancy is control of disease activity with medications that are relatively safe for a growing fetus.
- To optimize maternal and fetal outcomes, pregnancy should be planned to occur after achieving a stable remission of 6 months before conception.
- A multidisciplinary team approach including a nephrologist, rheumatologist, and obstetrician, who have experience with these pregnancy related complications, as well as a pharmacist, is recommended when caring for these patients.

Figure 1.

Renal biopsy findings of class IV lupus nephritis in a pregnant patient (trichrome stain, 400x) A 31-year pregnant woman with a history of SLE who developed a lupus flare in August 2012, with signs and symptoms of fatigue, generalized malaise, headaches, synovitis, migrating polyarthritis, arthralgias, and night sweats, when hydroxychloroquine was initiated. In September of 2012, she became pregnant, and was referred to Mayo Clinic at 17 weeks of gestation with hypertension (blood pressure of 178/108 mm Hg), nephrotic range proteinuria (4.6 grams/24 hour urine), and with active urinary sediment (>25% dysmorphic red blood cells). After adequate blood pressure control with nifedipine and labetalol, a renal biopsy was performed. The biopsy was uneventful and showed evidence of diffuse proliferative, class IV, lupus nephritis with subendothelial deposits (arrows). Treatment with prednisone, azathioprine, and tacrolimus was initiated, which resulted in improvement of the proteinuria (decreased to 2.5 grams/24 hour urine). Her pregnancy ended with an intrauterine fetal demise at 21 weeks of gestation. Three months later, her blood pressure was adequately controlled on nifedipine, and the proteinuria decreased to 256 mg/24 hour urine. This case demonstrates the poor pregnancy outcomes in patients with active lupus nephritis at the time of conception, despite subsequent adequate blood pressure control and reduction in disease activity.

Table 1

Distinction between Preeclampsia & Renal Disease

	Preeclampsia	Renal Disease
Timing in Pregnancy	After 20 weeks gestation	Any gestational age
Leucopenia or Thrombocytopenia	Absent	May be present
Active urine sediment	Absent	May be present
Other organ involvement	Absent	May be present
Autoantibodies	Absent	May be present
Hypertension	Present	Often present
Elevated serum creatinine	Typically absent	Commonly present

Table 2

Use of Immunosuppressive Medications during Pregnancy

Agent	FDA Category*	Pros	Pregnancy-Specific Cons
Corticosteroids	C	Well established efficacy Low-dose prednisone (5–10mg/day) safe, as low risk of adrenal insufficiency & thymic hyperplasia in infants ⁶⁵	Risk of orofacial clefts (3/1,000 births), ^{66,67} but not confirmed in a more recent study ⁶⁸ Glucose intolerance, premature labor
Hydroxychloroquine	None	Safe (200–400 mg/day) and efficacious in patients with LN. Discontinuation in gravid patients may increase the risk of flare ^{69–73}	Minimal
Azathioprine	D	Recommended for treatment of SLE to minimize risk of flare ⁷⁴ Safer than MMF, despite similar FDA category	Increased risk of ASD, VSD and preterm birth ⁷⁵ At doses > 1.5–2mg/day, there is an increased risk of suppressed neonatal hematopoiesis
Mycophenolate mofetil (MMF)	D	None	Teratogenicity ^{76,77} Avoid during pregnancy Discontinue > 6 weeks prior to conception ⁷⁷
Cyclosporine	C	Used more commonly than tacrolimus, as there is a longer experience with cyclosporine ⁷⁸	Renal dysfunction
Tacrolimus	C	May achieve comparable lupus nephritis remission rates to cyclophosphamide ⁷⁹	Higher risk of preeclampsia, hyperkalemia and renal dysfunction than cyclosporine ⁸⁰
Cyclophosphamide	D	Patients with breast cancer treated with cyclophosphamide during pregnancy had no significant fetal complications ⁸¹	Teratogenic Use is restricted in women who have not completed childbearing ^{74,78}
Methotrexate	X	None	Teratogenic Contraindicated in pregnancy Discontinue > 3months prior to conception ⁸²
Intravenous Immunoglobulin	C	Use for flares of LN refractory to other therapies	Minimal safety data available
Rituximab	C	None	Unknown safety & efficacy ¹⁹ May alter fetal & neonatal B cell development ⁸³

ASD=atrial septal defect; VSD=ventricular septal defect

* US FDA Pregnancy Ratings: Class C=Either studies in animals have revealed adverse effects on the fetus (teratogenic/embryocidal/other), and there are no controlled studies in women, or studies in women and animals are not available. Drugs should only be given if the potential benefit justifies the potential risk to the fetus. Class D=Positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable (e.g. if the drug is needed in a life-threatening situation, or for serious disease where safer drugs cannot be used or are ineffective). Class X=Studies in animals or humans have demonstrated fetal abnormalities, or there is evidence of fetal risk based on human experience, or both. The risk of use of the drug in pregnant women clearly outweighs any possible benefit. Therefore, the drug is contraindicated in women who are or may become pregnant.