Pregnancy and Glomerular Disease
A Systematic Review of the Literature with Management Guidelines

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Abstract
During pregnancy, CKD increases both maternal and fetal risk. Adverse maternal outcomes include progression of underlying renal dysfunction, worsening of urine protein, and hypertension, whereas adverse fetal outcomes include fetal loss, intrauterine growth restriction, and preterm delivery. As such, pregnancy in young women with CKD is anxiety provoking for both the patient and the clinician providing care, and because the heterogeneous group of glomerular diseases often affects young women, this is an area of heightened concern. In this invited review, we discuss pregnancy outcomes in young women with glomerular diseases. We have performed a systematic review in attempt to better understand these outcomes among young women with primary GN, we review the studies of pregnancy outcomes in lupus nephritis, and finally, we provide a potential construct for management. Although it is safe to say that the vast majority of young women with glomerular disease will have a live birth, the counseling that we can provide with respect to individualized risk remains imprecise in primary GN because the existing literature is extremely dated, and all management principles are extrapolated primarily from studies in lupus nephritis and diabetes. As such, the study of pregnancy outcomes and management strategies in these rare diseases requires a renewed interest and a dedicated collaborative effort.

Introduction
Pregnancy is a physiologic stress, wherein failure to adapt can result in adverse pregnancy outcomes. Systemic and renal vasodilation results in a drop in BP along with a decrease in renal vascular resistance leading to increased renal plasma flow, and consequently, nearly a 50% increase in glomerular filtration. Inadequate adaptation occurs in women with underlying hypertension and CKD, and is a poor prognostic indicator. In general, more resistant hypertension and advanced CKD are associated with greater risks of renal disease progression, prematurity, and growth restriction. Data from Italy estimate the risks for deterioration of kidney function are 7.6%, 12.6%, 16.2%, and 20% at stages 1–4, respectively (1). Furthermore, fetal outcomes deteriorate along this same continuum with preterm delivery before 37 weeks gestation increasing from 24% in stage 1 CKD to 89% in stages 4 and 5 CKD and neonatal birth weight dropping by approximately 1300 g between the two groups (mean birth weight 2966 ± 659 and 1639 ± 870 g in stage 1 and stages 4 and 5 CKD, respectively) (1). It is important to note that only 16% of the patients in this study had glomerular disease, and of those with advanced CKD (stages 3–5), only 11 of 45 had in excess of 1 g urine protein.

As such, pregnancy in young women with CKD is anxiety provoking for both the patient and the clinician providing care, and because the heterogeneous group of glomerular diseases often affects young women, this is an area of heightened concern. In this invited review, we discuss pregnancy outcomes in young women with glomerular diseases. We have performed a systematic review in attempt to better understand these outcomes among young women with primary GN, we review the studies of pregnancy outcomes in lupus nephritis, and finally, we discuss a potential construct for management.

Systematic Review of Primary Glomerular Diseases
A comprehensive review of pregnancy outcomes has been conducted in lupus nephritis (2), but there are limited data assessing pregnancy risk associated with other forms of primary GN. Accordingly, we conducted a systematic review of the literature on pregnancy outcomes in women with biopsy-proven primary glomerular-based diseases. The outcome of interest was the frequency of live births according to primary GN etiology and the influence of baseline characteristics on pregnancy outcomes. Full study methods are in Supplemental Material. In summary, results from 18 studies, including 887 women and 1414 pregnancies, were abstracted from studies published after 1980 (Supplemental Figure 1, Supplemental Table 1). Study heterogeneity was significant, precluding any pooling of data, and baseline characteristics were often not reported or inadequately described, precluding determination of the potential influence of hypertension, renal insufficiency, or proteinuria on pregnancy outcomes (Supplemental Table 2). Over time, the pathologic descriptions of some glomerular diseases have also evolved, and the definitions of


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important pregnancy complications, such as preeclampsia, have changed. As such, the review is narrative, and urgent contemporary data are required. Table 1 below summarizes pregnancy outcomes.

The most commonly reported GN was IgA nephropathy, with 12 studies including 10–136 patients (one study included two IgA cohorts) (3–13). The proportion of women with hypertension at baseline was reported in eight studies and ranged from 9% to 40%. The proportion of women with increased creatinine at study entry was rarely reported, and definitions of renal insufficiency varied. Across all 12 studies, live birth rate ranged from 70% to 100%. Live birth rates seemed to be lower before 2000 (6,7), but were variable, likely reflecting small study sizes and reporting biases in addition to improvements in neonatal care over the decades. Only five studies reported the mean birth weight, which ranged from 2911 to 3200 g, and few studies (n=5) reported the rate of superimposed preeclampsia, which ranged from 0% to 25%. A minority of studies provided long-term follow-up data. One study reported both sclerosis and vascular disease to be associated with adverse events, but no others attempted to assess the relationship between histologic features and outcome (14).

As expected, general themes that emerged included the association of adverse pregnancy outcomes, including perinatal death, preterm delivery, and small birth weight, with hypertension and renal insufficiency (3–5). In the second largest study of 118 pregnant women (9), women with hypertension at baseline (BP≥140/90 mmHg) or impaired renal function (eGFR<70 ml/min per 1.73 m²) were more likely to have an unsuccessful pregnancy. Perinatal mortality was 33% in women with hypertension compared with 1% in normotensive women and 14% in women with renal dysfunction compared with 3% in women with normal renal function. The largest study to date, published in 2010, reported outcomes for 229 pregnancies and compared renal outcomes of 136 pregnant women with 87 nonpregnant women, all with serum creatinine levels ≤1.2 mg/dl at diagnosis (10). Although pregnancy did not affect renal disease progression in this study, a second much smaller group studied with impaired renal function (n=10 with baseline serum creatinine levels >1.2 mg/dl, averaging 1.65±0.39 mg/dl) showed hastened progression, suggesting an imminent need for more data in women with IgA at more advanced stages of CKD. Finally, the most recently published study noted an association between proteinuria and adverse pregnancy outcomes (13).

Time-averaged proteinuria, the arithmetic average of proteinuria during pregnancy and follow-up, was inversely associated with infant birth weight (correlation coefficient = -0.61; P<0.001) and also associated with adverse pregnancy outcomes, including severe preeclampsia and intrauterine death (13). The strategy for managing worsening proteinuria during pregnancy in women with IgA is presently unclear.

Data to support prepregnancy counseling for the other forms of primary glomerular disease are very sparse. Only four studies reported outcomes for women with FSGS (3,4,6,15), all were published before 1990, and all were small (17–31 pregnancies), with limited reporting of disease severity or hypertension. The proportion of live births ranged from 55% to 94% with high rates of complications (e.g., spontaneous abortion, 8%; preterm delivery, 24%; small for gestational age, 4%; perinatal death, 16% [3]), with hypertension, impaired renal function, and nephrotic-range proteinuria identified to be associated with the greatest risk (3,4). Only two studies included women with minimal change disease (5,16) or membranous nephropathy (5,17), and similarly, nephrotic-range proteinuria and hypertension in the early stages of pregnancy were associated with worse pregnancy outcomes. In 33 pregnancies in 24 women with membranous nephropathy (17), only 20% (two of 10) of women with >5 g/24 h proteinuria had a live infant born after 32 weeks gestation compared with 91% (21 of 23) with ≤5 g/24 h (P<0.001), suggesting management of nephrotic syndrome with pregnancy-safe immunosuppression is likely critical and highlighting the urgent need for contemporary, collaborative studies to provide informed prepregnancy counseling.

Overview of Pregnancy Outcomes in Lupus Nephritis

The onset of lupus most frequently occurs in women of child-bearing age (18), and therefore, it is imperative that nephrologists are comfortable with reproductive counseling in this subpopulation. Unlike the other primary glomerular diseases, there are now robust data to inform pregnancy outcomes and guide a management approach, including a systematic review (2) and two large multicenter prospective studies (19,20) as well as numerous smaller retrospective analyses. The take-home message from all of these studies is that women with active disease should be strongly discouraged from conceiving until their lupus is controlled.

Evidence from meta-analysis data, 37 studies of 2751 pregnancies in 1842 women, showed a higher risk of adverse outcomes, including fetal loss, preeclampsia, preterm delivery, and small for gestational age infants, in those with active disease in early pregnancy (2). Furthermore, any maternal disease flare and renal flare were estimated to occur in 26% and 16% of pregnancies, respectively. A recent prospective multicenter cohort study of 71 pregnancies in 61 women with lupus nephritis reported an increased odds for preterm delivery by 15% for each increase of proteinuria by 1 g/d every trimester (20). Even low C3 and C4, without systemic manifestations, have been reported to be associated with increased risk in a prospective cohort (21). Other factors that adversely affect pregnancy outcomes, including fetal or neonatal death, birth before 36 weeks due to placental insufficiency, hypertension or preeclampsia, small for gestational age neonate (below the fifth percentile), and maternal renal flares in women with lupus nephritis, include severity of preexisting disease, nonwhite ethnicity, presence of antiphospholipid antibody or lupus anticoagulant, and hypertension (19,21,22). One cohort study suggested that women with classes 3 and 4 lupus nephritis are more likely to have pregnancies complicated by preeclampsia and lower-birth weight babies than those with class 2 or 5 lupus nephritis (23), but histologic class was not associated with different outcomes in the aforementioned meta-analysis (2). As such, women with normal renal function and quiescent disease can expect to have excellent pregnancy outcomes. A recent large prospective cohort study of 385 women with inactive
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Studies are arranged in order of date of publication and then alphabetically by first author. BW, birth weight; GA, gestational age; NA, not available; MCD, minimal change disease; MN, membranous nephropathy.

*Postpartum defined as maternal outcomes—exact postpartum timeframe unclear.

Data collected from 85 subjects who remained in follow-up for at least 3 years.

Number of subjects with hypertension (rather than number of pregnancies).
lupus, excluding those with creatinine concentration >1.2 mg/dl and/or a urinary protein-to-creatinine ratio >1000 mg/g, reported that 81% did not experience any adverse events (19). Severe maternal flares were rare, occurring in the second trimester in only 2.5% and third trimester in 3.0% of women (19). However, those with previous lupus nephritis, despite preserved GFR, have been reported to have higher rates of preterm delivery and earlier-onset preeclampsia than women with lupus without renal involvement (24). Estimates of pregnancy outcomes in women with more severe renal impairment and controlled lupus require extrapolation from literature that includes different etiologies of renal disease, and the risk of renal progression is related to severity of renal impairment and the potential for reactivation or flare of the disease.

Women with anti-Ro/Anti-Sjögren’s-syndrome–related antigen A (SSA) antibody should be informed of the potential risk of development of fetal heart block due to placental transfer of Ig leading to endocardial fibroelastosis. In a retrospective cohort study of 186 pregnancies, 5% of offspring were affected; however, this was only in women with titters ≥50 U/ml (25). Similarly, neonatal cutaneous lupus was reported to be more common in women with high-titer anti-La/Anti-Sjögren’s-syndrome–related antigen B (SSB) (≥100 U/ml), occurring in 57% of infants (25). The European League against Rheumatism guidelines recommend that all women with suspected fetal dysrhythmia or myocarditis, especially those with anti-Ro/SSA and/or anti-La/SSB antibody, should have fetal echocardiography (26).

In addition to pregnancy-safe immunosuppression (in Immunosuppression below), hydroxychloroquine is now recognized as a critical component of disease management in women with lupus nephritis. Hydroxychloroquine is recommended to be commenced or continued for all women with lupus nephritis because prospective cohort studies have shown maternal and fetal benefits (20,21). Those who discontinue hydroxychloroquine have been reported to have higher incidence of lupus flares, leading to greater use of antenatal steroids (27). No increased risk of congenital abnormalities is confirmed from a recent meta-analysis (28), although a higher rate of spontaneous abortion in exposed pregnancies than controls was noted with disease activity as a potential confounder. As such, there are no reported adverse effects on the fetus or neonate. Furthermore, there are limited data to suggest up to an 85% reduction in the risk of fetal growth restriction (20) and recurrence of fetal heart block (29).

Management Recommendations

Despite lack of data in the primary glomerular diseases, recent evidence from the Predictors of Fertility Outcomes in Systemic Lupus Erythematosus and Antiphospholipid Syndrome (PROMISSE) Study (19) and other smaller studies in systemic lupus (20) and even vasculitis (30) that show much better outcomes in women with adequately controlled disease before pregnancy have indirectly informed care in other glomerular diseases (Figure 1). Prepregnancy optimization is defined as stabilization of rapid progression where possible, minimization of urine protein with pregnancy-compatible immunosuppression, and control of hypertension with pregnancy-safe antihypertensive agents, while actively delaying pregnancy when these conditions cannot be met. During pregnancy, careful surveillance to detect the first signs of maternal or fetal compromise is critical, whereas postpartum care must include ongoing vigilant care of the underlying GN along with emotional support to assist young mothers to cope with a chronic disease while raising a child. Table 2 includes acceptable therapeutic agents that can be used in pregnancy.

Prepregnancy Care

Contraception. Given the risks associated with pregnancy in women with CKD, an unplanned pregnancy should be vigorously avoided to ensure that conception does not occur before disease quiescence or while confirmation of disease stability after adjustment to pregnancy-safe medications. As such, questions about sexual activity and contraception should be part of routine nephrology care in young women, but are often overlooked. Estrogen-containing contraception is contraindicated in all women with vascular disease, and should be used with caution in young women with hypertension and CKD due to the increased risk of thrombosis and exacerbation of hypertension (31). Furthermore, there is limited evidence from studies in women with diabetic nephropathy that estrogen may exacerbate preexisting proteinuria (32), possibly secondary to stimulation of the renin angiotensin system (RAS) (33,34). As such, progesterone-only preparations are generally recommended and include the progesterone-only pill, which is now available with a wider dosing window in some countries, intramuscular depot injections, and the intrauterine coil (preferably in multiparous women due to difficulties with insertion in nulliparous women). Barrier contraception is less reliable, and therefore, is not recommended as a sole method of birth control.

Fertility. The desire to have a child is innate; therefore, many women will want to conceive at some time during their journey with CKD, but both their underlying disease as well as treatment choices can affect fertility. Along with advancing renal dysfunction are increased rates of infertility due to hormonal aberrations and progressive sexual dysfunction due to medication side effects, fatigue, symptoms of depression, and altered body image, which can be significant due to the cosmetic side effects of commonly used immunosuppressive agents in patients with glomerular diseases (35). Assisted conception is, therefore, likely to be used more widely in women with various forms of GN due to increased availability; however, to date, there are no data to guide this practice.

It is recognized that there is a reduction in the number of pregnancies reported with advancing severity of renal disease, and many women with advanced CKD report amenorrhea or erratic cycles. A small cohort study of 17 women with CKD reported an increase in luteinizing hormone in women with CKD and reduced cyclic changes in hypothalamic-pituitary-ovarian hormones (36), whereas others have confirmed an increase in both prolactin production and clearance with reducing GFR (37). Self-reporting of menopause suggests that it occurs early in women with CKD (38), but these data are confounded by the
lack of biochemical evidence of menopause and may reflect misreporting of anovulatory cycles secondary to renal disease. The choice to use cyclophosphamide must also be made with care because there is a direct association between ovarian damage and the prescribed dose, duration, and route of administration of this medication, with oral cyclophosphamide inducing a more sustained amenorrhea than intravenous administration as noted in a Chinese study of 212 women (39). Furthermore, advancing age significantly increases the risk for irreversible ovarian damage in young women. A controlled retrospective cohort study of 39 women age 40 years old reported sustained amenorrhea after cyclophosphamide therapy in 12% of women 25 years of age, 27% of women 26–31 years of age, and 62% of women 30 years old (40). The use of leuprolide acetate, a synthetic gonadotropin-releasing hormone analog, to limit ovarian damage has not been studied in women with GN, and its use is not routine in this patient population. Of three recent meta-analyses conducted in women with malignancies and rheumatologic diseases, two found a significant benefit with regard to resumption of menses and ovulation (41,42), whereas another found no benefit of gonadotropin-releasing hormone analog cotreatment (43). It is, therefore, best to attempt to avoid cyclophosphamide in women of child-bearing age and use other agents where possible and appropriate (e.g., mycophenolate mofetil for lupus nephritis and rituximab for vasculitis).

**Disease Optimization.** As mentioned, a sustained clinical remission before conception has been noted to significantly improve maternal and fetal outcomes in women with both lupus nephritis (19,20) and vasculitis (30), and active nephritis is associated with higher rates of preeclampsia, increased premature delivery, small for gestational age births, and accelerated loss of renal function (2,44). From this, we deduce that any active GN will potentially contribute to adverse pregnancy outcomes, and control of the glomerular disease with pregnancy-safe immunosuppression is desirable, whereas all potentially teratogenic medications must be discontinued. A reasonable approach includes treatment with pregnancy-safe immunosuppression (Immunosuppression below) to retain remission for at least 3–6 months before a pregnancy attempt (45). In patients without immunologic treatment options, control of urine protein with agents that block the RAS is the mainstay of therapy. Although clearly teratogenic in the second and third trimesters of pregnancy (BP Therapy below), data for teratogenicity with only early pregnancy exposure are no longer supported (46). Unfortunately, the potential use of these agents in pregnancy planning is not derived from data published in the management of GN, but comes from small, uncontrolled studies in patients with diabetic nephropathy, wherein intensive treatment with angiotensin-converting enzyme inhibition in addition to optimization of glucose control before conception have been shown to stabilize proteinuria during pregnancy (47,48), and compared with older preexisting literature, prolong gestation and improve birth weights (49). Data in other primary glomerular diseases are urgently required, especially IgA nephropathy, which is a common entity with management outside of pregnancy that is debated.

**Antenatal Care**

**Immunosuppression.** Women with GN often receive conflicting information from health care professionals regarding medication safety during pregnancy. Reassurance regarding balance of risk versus benefit is frequently needed, while cautioning women that the recommendation from pharmaceutical companies and information that they glean from online sources may conflict with current expert opinion.
Safety data for immunosuppressive agents come from large registry and population studies of women with transplants, but can be used to inform treatment for women with GN.

Prednisone is considered to be relatively safe in pregnancy, and benefits of continuation usually considerably outweigh any risk. Early case-control studies suggested an increased incidence of cleft lip and palate with first trimester exposure (50), but subsequent well conducted population studies did not confirm an association (51). Prednisone is metabolized by placental 11β-hydroxysteroid dehydrogenase type 2 to inactive cortisone; therefore, the fetal dose is minimal. However, dexamethasone, administered for fetal lung maturation, is not inactivated, and the fetus is exposed to approximately 30% of the maternal dose. High doses of prednisone have been associated with premature rupture of membranes (52); however, the simultaneous influence of preexisting disease activity contributing to preterm delivery is unknown. Other reported complications are similar to those in nonpregnant patients, including high rates of gestational diabetes, weight gain, hypertension, osteoporosis, cataracts, infection, and mood changes. Stress doses of glucocorticoids (typically hydrocortisone) are recommended during labor for women taking the equivalent of prednisone 20 mg or more for >3 weeks (53).

Azathioprine is frequently the drug of choice to maintain disease quiescence during pregnancy. A Danish population study compared the outcomes of 11 infants exposed in utero to azathioprine with those of 19,418 pregnancies without exposure and reported an increase in malformations, prematurity, and perinatal mortality (54). However, several hundreds of pregnancy outcomes in transplant recipients prescribed azathioprine during pregnancy have been reported with rates of congenital malformations comparable with those in the general population (55). Azathioprine requires activation by inosinate pyrophosphorylase to metabolite 6-mercaptopurine, which is absent in the fetal liver.

Studies of transplant recipients also support safety of calcineurin inhibitors, with no evidence of increased risk of teratogenicity with cyclosporin or tacrolimus (55–57). Frequently, calcineurin inhibitor concentrations fall during pregnancy, assumed due to increased hepatic metabolism, and may require an increase in dose up to 20%–25% compared with prepregnancy doses (58). A small study of ten women suggested that tacrolimus concentrations may be greater in pregnancy relative to postpartum (59); hence, low therapeutic ranges should be targeted because high concentrations may cause nephrotoxicity and hypertension. Some experts do not monitor concentrations during pregnancy given the uncertainty of the relevance of recommended targets in pregnancy, and instead, titrate doses as dictated by changes in the clinical condition.

Cyclophosphamide and mycophenolate mofetil are teratogenic and should be avoided during pregnancy. Cyclophosphamide is associated with calvaria, ear and craniofacial structure, limb and visceral organ abnormalities, and developmental delay with first trimester exposure. Calcium and vitamin D supplementation (in women who may be deficient) is required during labor for women taking the equivalent of prednisone 20 mg or more for >3 weeks (53). Azathioprine requires activation by inosinate pyrophosphorylase to metabolite 6-mercaptopurine, which is absent in the fetal liver.

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treatment is preferable. In our practice, we currently consider rituximab only as a last resort in early pregnancy pending further data. Neonatal monitoring is recommended before routine vaccination, with delay if necessary. There are no long-term follow-up studies of infants with in utero exposure to rituximab, and therefore, its potential deleterious effects on the developing immune system remain unknown.

**BP Therapy.** To date, there have been no studies conducted to establish BP treatment goals in young women with any form of CKD, but it is well accepted that poorly controlled hypertension during pregnancy significantly worsens both maternal and fetal outcomes, and experts agree that maintaining BP<140/90 mmHg is prudent in this patient population (63); the safety of which has been recently confirmed in an unblinded, multicenter, randomized, controlled study in pregnant women with either chronic or gestational nonproteinuric hypertension (64). The Control of Hypertension in Pregnancy Study (CHIPS) randomized 987 women to either less tight (target diastolic BP =100 mmHg) or tight (target diastolic BP =85 mmHg) BP control. The achieved BP difference was 85.3 compared with 89.9 mmHg in the tight versus less tight group, respectively. No significant difference between the groups was noted in the primary outcome, a composite of pregnancy loss or high-level neonatal care for >48 hours, which was 31.4% in the less tight versus 30.7% in the tight control group. Of note, there was also no difference in low birth babies or perinatal mortality. The most significant trial finding was that women receiving less tight (versus tight) control more commonly developed severe hypertension (>160/110 mmHg) at 40.6% versus 27.5% (P<0.001), which would be a particularly concerning deterioration in a woman with underlying kidney disease.

There are a number of drug options for the management of hypertension in pregnancy, including methyldopa, labetalol, hydralazine, and long-acting nifedipine. Although labetalol is frequently considered the first-line agent, a secondary analysis of the CHIPS cohort noted that women treated with methyldopa (versus labetalol) had fewer adverse perinatal and maternal outcomes, including fewer babies who were small for gestational age, fewer deliveries <34 and <37 weeks, less severe hypertension, and preeclampsia (65). The use of methyldopa seemed to be especially beneficial for women with preexisting hypertension. Another study showed higher rates of respiratory distress syndrome, sepsis, and seizures in infants of mothers with chronic hypertension dispensed only labetalol compared with those dispensed only methyldopa (adjusted odds ratio, 1.51; 95% confidence interval [95% CI], 1.02 to 2.22) (66), suggesting that this is an area that requires further research in women with CKD. Although diuretics are often avoided due to the theoretical concern of intravascular contraction, they can be used in select women. Similarly, other β-blockers (e.g., metoprolol) and calcium channel blockers (e.g., amlodipine and diltiazem) have been used, but again, only in women in whom the aforementioned safer alternatives are not tolerated pending further studies. Inhibitors of the RAS are strictly contraindicated beyond the first trimester due to their potential to cause cardiac and renal defects, including atrial septal defects, ventricular septal defects, pulmonary stenosis, patent ductus arteriosus, renal dysgenesis, and the associated complications of oligohydramnios (limb contractures, pulmonary hypoplasia, and hypocalvaria) (67).

**Management of Worsening Proteinuria.** Worsening proteinuria in pregnancy poses a significant diagnostic and therapeutic challenge to the practicing clinician. Although lupus nephritis and vasculitis may flare during pregnancy, the effect of pregnancy on the other primary glomerular diseases is unclear. Certainly, GN can present or flare during pregnancy, and at least early on in pregnancy, the diagnostic approach is similar to the nonpregnant state, including a careful urinalysis and the relevant serologic assessment. With the exception of serology and complement levels, there are presently no other established biomarkers for use in pregnancy. Although M-type phospholipase A2 receptor in membranous nephropathy (68) and soluble urokinase plasminogen activator receptor in FSGS (69) have been described in case reports, their use in pregnancy requires further study. Of note, pregnancy is essentially a state of acute-phase response, and therefore, complement levels should be normal or high. Falling complement, even within the normal range, suggests that lupus is becoming more active.

Kidney biopsy is not contraindicated in pregnancy, but should be considered only when the information garnered is likely to affect the treatment approach. In lupus and vasculitis, serology can often assist with diagnosis, rendering biopsy less necessary. However, the presentation of de novo significant proteinuria or nephrotic syndrome early in pregnancy (during the first or second trimester) typically does necessitate a renal biopsy to establish a diagnosis and guide immunosuppressive therapy, and it is considered safe as long as BP is adequately controlled. A recent meta-analysis of 39 studies that compared the associated complications of 243 antepartum with 1236 postpartum kidney biopsies showed a significantly higher complication rate with antepartum compared with postpartum biopsies (7% versus 1%; P=0.001), but fortunately, most complications were minor, such as loin pain and macroscopic hematuria early in gestation, with all significant complications occurring between 23 and 26 weeks (70). Of note, the aim of 23 of the studies was to study the morphology of preeclampsia, the potential presence of which should be considered a contraindication to biopsy given the associated hypertension and the potential to develop coagulopathies (hemolysis, elevated liver enzymes and low platelets). Furthermore, biopsy becomes more technically difficult as the gravid uterus grows, often precluding prone positioning. As such, the risks often outweigh the benefits of establishing a diagnosis after approximately 30 weeks of gestation, but each patient requires careful individualized consideration. In patients in whom renal biopsy has been delayed to the postpartum period, it is ideal to wait approximately 4–6 weeks for complete resolution of potential coexisting endotheliosis (71), but again, the clinical condition will dictate the most appropriate timing.

After a diagnosis is established, immunosuppressive treatment should begin promptly, because the symptoms of nephrotic syndrome can be severe in pregnant women. In addition to the already reviewed immunosuppressive options (Immunosuppression above), pulse methylprednisolone and plasmapheresis are options that can be applied for a more rapid effect where appropriate. However, supportive therapy is often required while awaiting a response to definitive treatment or when definitive diagnosis or treatment is delayed. Peripheral edema is common in healthy pregnancies and can be severe in
pregnant women with the nephrotic syndrome. Serum albumin levels also decrease in normal pregnancy (72), and therefore, hypoalbuminemia can also be severe. Conservative treatments include compression stockings and avoidance of prolonged standing. Loop diuretics are appropriate for severe edema, and supportive albumin infusions have been reported in case reports of women with severe nephrosis (73,74). Severe hypoalbuminemia (albumin <25 g/L) is also associated with an increased risk of venous thromboembolic events (75), and pregnancy itself is a prothrombotic state. Unfortunately, there are no available data to guide the use of anticoagulation in this patient population, and practice varies significantly. Expert opinion suggests that women with severe proteinuria and serum albumin <20 g/L should receive thromboprophylaxis throughout pregnancy, but anticoagulation should also be considered in those with less severe nephrotic syndrome with additional risk factors for, for example, obesity, immobility, membranous nephropathy, or vasculitis. Subcutaneous low molecular weight heparin is the anticoagulant of choice. Although thromboprophylaxis is typically held before anticipated delivery, it should be resumed as soon as possible and continued for at least 6 weeks, because the postpartum period carries a particularly high risk of thrombosis (76).

**Preeclampsia Prevention, Diagnosis, and Management.** Women with CKD are at a substantially increased risk for the development of placental disease, and hence, preeclampsia. A recent systematic review and meta-analysis reported a tenfold increased risk of preeclampsia among women with CKD compared with the general population, with effect modifiers including prepregnancy proteinuria and the type of underlying disease (77). Rates of preeclampsia were higher in women with nondiabetic nephropathy, suggesting that glomerular disease might be particularly hazardous (77). As such, all women with GN are candidates for preventative strategies. Low-dose aspirin is now considered part of standard care. In a meta-analysis of 34 randomized, controlled trials, low-dose aspirin started at or before 16 weeks of gestation was associated with a significant reduction in preeclampsia (relative risk [RR], 0.47; 95% CI, 0.34 to 0.65) and intrauterine growth restriction (RR, 0.44; 95% CI, 0.30 to 0.65) (78). Early administration of low-dose aspirin also resulted in a significant reduction of severe preeclampsia and preterm delivery. Similarly, calcium supplementation has been shown to reduce the incidence of preeclampsia. In a Cochrane review of 12 randomized, controlled trials of over 15,000 women, wherein at least 1 g calcium supplementation was compared with placebo, there was a significant reduction in the risk of preeclampsia (RR, 0.48; 95% CI, 0.33 to 0.69) that was even more pronounced in high-risk women and those with a low calcium intake (79). As such, calcium intake should be assessed and supplemented as needed.

An understanding of the pathophysiology facilitates the diagnosis of preeclampsia. The cascade that results in preeclampsia begins with insufficient placentation characterized by inadequate trophoblast invasion and impaired spiral artery remodeling, which ultimately results in placental ischemia and the release of antiangiogenic factors, soluble fms-like tyrosine kinase-1 (sFlt1) and endoglin, that induce widespread maternal vascular endothelial dysfunction by binding to proangiogenic factors, including vascular endothelial factor and placental growth factor (PIGF), neutralizing their effects (80,81). Both sFlt1 and endoglin have been shown to increase before onset of preeclampsia and correlate with disease severity, whereas circulating levels of vascular endothelial factor and PIGF have been noted to significantly decrease. As such, circulating levels of sFlt1 and PIGF are promising potential biomarkers that can predict risk as well as assist diagnosis in women with GN, in whom the diagnosis is especially complex. In women with CKD and chronic hypertension, low maternal PIGF concentrations had high diagnostic accuracy for superimposed preeclampsia requiring delivery within 14 days (82). Unfortunately, these biomarkers are not as yet widely available, and presently, the diagnosis must be made clinically (Table 3). In women with GN and worsening BP or proteinuria, a careful assessment of the placenta along with fetal growth can substantially aid in the diagnosis of preeclampsia because poor or decreasing fetal growth in conjunction with abnormal placental examinations have been showed to be diagnostically useful in patients with CKD (83). The need to assess the mother in conjunction with placental and fetal parameters speaks to the importance of collaborative care between nephrology and obstetrics.

To date, the cornerstone of safe management is expedited delivery, but in a small, open label study, removal of sFlt1 by dextran apheresis seemed safe and prolonged pregnancy

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**Table 3. Diagnosing preeclampsia: Placental and fetal clues**

<table>
<thead>
<tr>
<th>First trimester screen—11–13 wk gestation</th>
<th>Maternal serum screen—15–20 wk gestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼ Pregnancy-associated plasma protein A</td>
<td>▼ Human chorionic gonadotropin</td>
</tr>
<tr>
<td>▼ Active insulin-like growth factors that facilitate placental growth</td>
<td>Excessive secretion by an abnormal syncytiotrophoblast (beware as cleared by kidneys; therefore, less use in more advanced CKD)</td>
</tr>
<tr>
<td>▼ Human chorionic gonadotropin</td>
<td>▼ Dimeric inhibin assay</td>
</tr>
<tr>
<td>Source is fetal liver; therefore, presence suggests breach in the placental villi</td>
<td></td>
</tr>
<tr>
<td>Excessive secretion by an abnormal syncytiotrophoblast (beware as cleared by kidneys; therefore, less use in more advanced CKD)</td>
<td></td>
</tr>
<tr>
<td>▼ Dimeric inhibin assay</td>
<td></td>
</tr>
<tr>
<td>Excessive secretion by an abnormal trophoblast</td>
<td></td>
</tr>
</tbody>
</table>

**Abnormal placental appearance**

- Length <10 cm, thickness >4 cm, heterogeneous appearance, echogenic cystic areas
- Abnormal at 1.45

**Abnormal uterine artery Doppler examination**

- Presence of bilateral notching or pulsatility index >1.45

**Abnormal umbilical artery Doppler**

- Absent or reverse end diastolic flow

**Poor fetal growth**

- Decreasing growth percentile
- Intrauterine growth restriction or growth below the tenth percentile for gestational age
- Abdominal circumference below the 2.5th percentile

Modified from data presented at http://www.mountsinai.on.ca/care/placenta-clinic, with permission.
in women with early-onset preeclampsia (84). Controlled studies are needed to further investigate dextran apheresis as a therapeutic option. Magnesium sulfate will be prescribed to prevent escalation to eclampsia and must be used with caution in women with renal dysfunction. Close collaboration between high-risk obstetrics and nephrology is essential to establish the diagnosis and safely manage these vulnerable women and babies because the false diagnosis of preeclampsia will result in unnecessary urgent delivery and iatrogenic prematurity, whereas the failure to detect superimposed preeclampsia may have severe maternal and fetal consequences. Mode of delivery should be dictated by standard obstetric practice and should not be influenced by the presence or severity of GN.

**Postpartum Care**

Both immunosuppressive medications and antihypertensive treatments deemed safe during pregnancy are also typically of acceptable risk during breastfeeding, and breastfeeding should be encouraged in women with all forms of CKD due to the established fetal and maternal benefits, despite manufacturer recommendations, which invariably suggest that lactation be avoided. Minimal prednisone and azathioprine are excreted in breast milk (85). Levels of both the calcineurin inhibitors have been assayed in breast milk and assessed in neonates, with most frequently undetectable levels for cyclosporin (86) and at most, 0.23% of the maternal weight-adjusted dose for tacrolimus (87). However, the change in maternal physiology mandates early reassessment of trough levels and readjustment of dose to avoid nephrotoxicity in both the mother and potentially, the baby. At times, significant disease activity necessitates the use of either mycophenolate mofetil or cyclophosphamide, precluding breastfeeding. The large monoclonal antibodies do not pass into breast milk, and rituximab may provide a viable alternative for some forms of active nephritis in the postpartum. With respect to antihypertensive agents, methyldopa, labetalol, and long-acting nifedipine are most used. Diuretics again may theoretically hamper milk supply due to dehydration and are typically avoided. A number of inhibitors of the RAS have been assessed in breast milk and have been deemed absent, including enalapril, captopril (88), and quinapril (89). As such, targeting of proteinuria with RAS inhibition can be initiated early in the postpartum period. Because these pregnancies are high risk, the emotional toll that they can have on a young woman cannot be understated. Careful screening for postpartum depression and lack of coping is mandatory, and ongoing multidisciplinary support is critical for maternal wellbeing.

**Summary**

Although it is safe to say that the vast majority of young women with glomerular disease will have a live birth, the counseling that we can provide with respect to individualized risk remains imprecise. In the primary glomerular diseases, the existing literature is extremely dated, and all management principles are extrapolated primarily from studies in lupus nephritis. As such, the study of pregnancy outcomes and management strategies in these rare diseases requires a renewed interest and a dedicated collaborative effort to answer the many unanswered questions.

Fortunately, such studies are underway within existing GN collaborative groups, including Cure Glomerulonephropathy, which will hopefully provide important data to help guide young women making this life-altering decision.

**Disclosures**

None.

**References**


95. K. B. and A.O. contributed equally to this work.

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