Glomerular Disease and Pregnancy

By Jonathan J. Hogan and Melissa Rosenstein

What changes in proteinuria occur during normal pregnancies?

Proteinuria increases over the course of normal pregnancies, in most patients to levels that are still too low to be detectable by urine dipstick alone. Highy et al. (1) analyzed the 24-hour urine collections of 270 healthy pregnant women (<35 years old with no history of preeclampsia, hypertension, pylonephritis, diabetes, or renal or connective tissue disease) at an average gestation of 26 weeks, finding the mean proteinuria to be 117 mg per day with values at the upper 95% confidence limit to be 260 mg per day. Proteinuria also increased in twin versus singleton pregnancies, and there is a higher likelihood of developing overt proteinuria (>300 mg/dL or urine protein/creatinine [UProt:Cr] ratio of 300 mg/g) in twin pregnancies (2, 3).

How does pregnancy affect patients with preexisting proteinuria?

A few studies have been published describing a significant increase in proteinuria during pregnancy in patients with preexisting proteinuria with diabetes (4) or biopsy-proven, nondiabetic glomerular diseases (5). In one study in patients with diabetes, the mean increase in proteinuria during pregnancy was 248%. This increase in proteinuria may improve or resolve in the months after delivery.

How can one distinguish preeclampsia from other glomerular diseases?

Although performed infrequently, the kidney biopsy remains the gold standard in diagnosing the cause of proteinuria or kidney injury during pregnancy (6). Hypertension is required to make the diagnosis of preeclampsia, but for patients who have underlying hypertensive disease, diagnosing superimposed preeclampsia can be a clinical challenge. Clinical tests (including serum uric acid levels) have not been shown to distinguish preeclampsia from other glomerular diseases in the second and third trimesters. Serum and urine levels of biomarkers, such as soluble fms-like tyrosine kinase 1, soluble endoglin, placentation growth factor, and vascular endothelial growth factor, are considered investigational for the prediction and diagnosis of preeclampsia.

Of note, updated recommendations from the American College of Obstetricians and Gynecologists no longer require a 24-hour urine protein collection to make the diagnosis of preeclampsia; a UProt:Cr ratio of 0.3 g/g is sufficient. Also, for the first time, preeclampsia with severe features can be diagnosed in the absence of proteinuria, whereas a serum creatinine of greater than 1.1 mg/dL or doubling of the baseline serum creatinine is now part of the diagnostic criteria (7).

Is it safe to perform kidney biopsies in pregnant patients?

There are limited published data on percutaneous kidney biopsies (PKBs) in pregnant patients. A systematic review of 197 PKBs performed during pregnancy at a median time of 25-week gestation found four patients with major complications (2%), all of which occurred during weeks 23 to 28 (8). All patients developed large peritubular hematomas requiring transfusions. The authors reported one twin pregnancy with an association between kidney biopsy, placental abruption, and preterm delivery, and a second pregnancy where the association between kidney biopsy, preterm labor, and fetal death could not be excluded. Minor complications (hematomas not requiring transfusion and microscopic hematuria with flank pain) occurred in 5% of patients. This study found that a PKB performed for GN or preeclampsia led to changes in management in 66% of patients. Another small study compared PKB complication rates in women with hypertension during pregnancy with those of healthy pregnant controls, with only one major complication observed in a patient with severe preeclampsia (9). A gravid uterus may also necessitate alternatives to the prone position for the biopsy.

Significant renal dysfunction is a contraindication for expectant management of preeclampsia with severe features, and delivery (even at very preterm gestational age) is recommended. A kidney biopsy is most useful in the early third trimester, because if a nonpreeclampsia diagnosis is made, treatment can be initiated with the goal of prolonging the pregnancy and avoiding the many neonatal complications of prematurity (Table 1). Comparing the risks and benefits of kidney biopsy with delivery should always take into account the gestational age of the fetus and be done in consultation with the obstetrician and neonatologist (10).

What is the effect of preeclampsia on long-term kidney health?

There seems to be a link between the development of hypertensive disorders during pregnancy and kidney disease later in life. One Taiwanese study found an association between hypertensive disorders during pregnancy (including preeclampsia) and eventual chronic kidney disease (adjusted hazard ratio [HR] = 9.38) and ESRD (adjusted HR = 12.4) (11). A second study in Norway showed a low rate of ESRD after pregnancy (3.7 per 100,000 women per year) but that women with preeclampsia had an increased relative risk of ESRD (12). This group also found that women whose pregnancies were complicated by preeclampsia, preterm delivery, and/or intrauterine growth restriction had an increased incidence of requiring kidney biopsies later in life, with a variety of kidney histologies observed. This observation suggests that, in addition to causing direct kidney damage, preeclampsia may exacerbate or unmask other underlying renal diseases.

It is important to note that the effects of preeclampsia may persist after pregnancy. One prospective cohort study found that it can take as long as 2 years for hypertension and proteinuria to resolve after delivery, with longer time to resolution for patients with more severe hypertension and proteinuria (13).

How does glomerular disease affect pregnancy outcomes and vice versa?

The association between kidney disease and maternal–fetal complications is well-described (14–16), even for patients with preserved GFR (17). Moreover, patients with moderate and severe renal insufficiency at baseline (generally defined as a serum creatinine <1.4 to 1.5 mg/dL or estimated GFR <40 mL/min) are at risk for developing irreversible worsening of their kidney function during pregnancy, particularly for patients with >1 g per day proteinuria at baseline (18).

Most data on glomerular diseases and pregnancy are descriptive case series from the 1970s to 1990s. However, it is important to recognize these studies’ limitations: older or flawed classifications of patients’ kidney diseases, conclusions drawn about patients with glomerular disease as a whole rather than by individual disease, and subsequent advances in the understanding and management of these disorders and premature infants. Notwithstanding these limitations, the mere presence of kidney disease has been shown to be associated with adverse maternal and fetal outcomes in multiple studies.

Patients with lupus have significantly higher rates of preeclampsia and other maternal/fetal complications during pregnancy, such as intrauterine growth restriction. A prior history of lupus nephritis is the strongest predictor of these complications as well as development of a lupus flare during pregnancy.

Multiple case series have explored IgA nephropathy and pregnancy, the largest of which are from Japan, China, and Italy. The largest such series (223 women in Italy with IgA nephropathy with serum creatinine <1.2 mg/dL at the time of biopsy) found no difference in the rate of GFR decline in patients who became pregnant versus those who did not become pregnant during the follow-up period (median of 10 years) (19). Other smaller studies have suggested that lower levels of pre-pregnancy proteinuria are associated with improved long-term kidney function and that lower pre-pregnancy GFRs may be associated with higher rates of preeclampsia.

The published literature for patients with minimal
change disease, FSGS, and membranous nephropathy who become pregnant or develop these disorders during pregnancy is limited to case reports and case series.

**What medications are safe to use for glomerular disease in pregnancy?**

The use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) is contraindicated in the second and third trimesters. There is some controversy about the association between use of ACEIs and ARBs in the first trimester and congenital malformations, but it is currently recommended that they be avoided altogether in pregnancy.

Data quality for the use of immunosuppression during pregnancy is heterogeneous and drawn mostly from the transplant, rheumatology, and oncology literature. Agents used commonly during pregnancy include hydroxychloroquine, glucocorticoids, calcineurin inhibitors, and azathioprine, whereas cyclophosphamide and mycophenolate mofetil are teratogenic and are not recommended. Women using these agents should be asked about their reproductive intentions, and if they desire pregnancy, they should be switched to other agents in the preconception period. Rituximab use during pregnancy has not been found to have an association with congenital abnormalities or miscarriages, although transient depletion of neonatal B cells has been reported (20). It is unfortunate that the letter characterization of the Food and Drug Administration for medication use in pregnancy (categories A, B, C, D, and X) often does not reflect the current clinical practice in using these agents (Table 2). When considering initiating or discontinuing medications for kidney disease, consultation with maternal–fetal medicine specialists is recommended.

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### References


| Table 1. Common complications of premature birth |
|----------------|----------------|
| Complication       | Treatment(s)                             |
| Respiratory distress syndrome | Surfactant, antenatal corticosteroids, respiratory support (CPAP, mechanical ventilation) |
| Necrotizing enterocolitis           | Bowel rest and gastric decompression, antibiotics, surgical intervention if necessary |
| Intraventricular hemorrhage              | Supportive care, neurological intervention if necessary |
| Hypothyroidia                      | Temperature control strategies             |
| Patent ductus arteriosus            | Supportive care, closure for severe cases  |
| Hyperglycemia/hypoglycemia          | Adjustment of glucose content in feeds, insulin/dextrose infusions as needed |
| Sepsis                           | Supportive care, antibiotics               |
| Retinopathy of prematurity          | Retinal ablation, anti-VEGF therapy       |

**Abbreviations:** CPAP = continuous positive airway pressure ventilation; VEGF = vascular endothelial growth factor

| Table 2. Food and Drug Administration pregnancy risk categories for agents commonly used in glomerular disease |
|----------------|----------------|
| Agent           | FDA pregnancy risk factor category | Comment                   |
| ACEIs, ARBs     | D                        | Contraindicated            |
| Prednisone      | C/D                      | Use permitted during pregnancy, limit dosing |
| Azathioprine    | D                        | Use permitted during pregnancy |
| Cyclophosphamide| D                        | Avoided during pregnancy   |
| Rituximab       | C                        | Limited experience during pregnancy |
| Cyclosporin, tacrolimus | C                  | Use permitted during pregnancy |
| Mycophenolate mofetil | D                  | Contraindicated; black box warning |

**Category C:** animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. **Category D:** there is positive evidence of human fetal risk on the basis of adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

**Abbreviations:** ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; FDA = Food and Drug Administration.