Kidney Disease in Special Populations: Genetics, Infection, Obesity, and Pregnancy

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Level: PA/Medical Student **Duration:** 75–100 minutes **Version:** 2026-02-12

Learning Objectives

By the end of this module, students will be able to:

1. **Explain genetic basis** of APOL1-associated kidney disease and screening implications
2. **Recognize** HIV-associated kidney disease phenotypes (HIVAN vs. FSGS)
3. **Manage** sickle cell nephropathy complications (polyuria, hematuria, renal failure)
4. **Assess cardiovascular and renal changes** in pregnancy; distinguish preeclampsia from preexisting CKD
5. **Prevent and manage** acute kidney injury in pregnancy
6. **Recognize APOL1-positive glomerulosclerosis** and collapsing FSGS in HIV/AIDS
7. **Understand obesity-related glomerulosclerosis** and weight loss interventions
8. **Identify COVID-19–associated kidney injury** and post-COVID CKD trajectory

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APOL1-ASSOCIATED KIDNEY DISEASE

APOL1 Gene and Polymorphism

Genetic Background APOL1 (Apolipoprotein L1): - **Location:** Chromosome 22q13 - **Function:** Encodes protein with trypanolytic (antitrypanosomal) activity - **Evolution:** G1 and G2 variants arose in West African populations (selective advantage: resistance to African sleeping sickness—*Trypanosoma brucei*) - **Alleles:** - **G0 (ancestral/reference):** No risk - **G1 and G2 (risk alleles):** Associated with kidney disease; ☐ GFR filtration per nephron but risk of CKD

APOL1-Risk Variants: G1 and G2 G1 allele: - Encodes 6 amino acid changes in APOL1 protein - Associated with sickle cell trait, resistant to trypanosomiasis

G2 allele: - Encodes 2 amino acid changes - Overlapping risk phenotype; slightly different functional consequences

Allele frequency (African descent populations): - **Two APOL1-risk alleles (G1G1, G1G2, G2G2):** 13–15% in US Black population - **Significantly lower in European ancestry:** <1%

Renal Risk Stratification

Genotype	# Risk Alleles	Risk Category	Estimated 10-yr ESRD Risk
G0/G0	0	Low	<2%
G0/G1, G0/G2	1	Intermediate	3–5%
G1/G1, G1/G2, G2/G2	2	High	20–40% (if other risk factors present)

Pathophysiology

APOL1 protein toxicity mechanism: 1. **Increased intraglomerular pressure:** APOL1 risk variants ☐ altered podocyte function ☐ ☐ glomerular hyperfiltration 2. **Oxidative stress:** Mitochondrial dysfunction; ☐ ROS generation 3. **Autophagy dysregulation:** Impaired cellular waste removal 4. **Inflammatory cascade:** Pro-inflammatory cytokine activation 5. **Podocyte injury:** Cell death, foot process effacement, proteinuria 6. **Glomerular sclerosis:** Progressive fibrosis

APOL1-Associated Glomerular Disease Phenotypes

Focal Segmental Glomerulosclerosis (FSGS) **Classic presentation:** - **Proteinuria:** Often nephrotic range (3–10 g/day) - **Hematuria:** Microscopic common, gross rare - **Renal function:** Highly variable; some preserved initially, rapid decline in others - **Response to therapy:** Often steroid-resistant

Collapsing Glomerulopathy **More aggressive variant:** - **Proteinuria:** Nephrotic (often >10 g/day) - **AKI:** Common (Cr rise 1–2 mg/dL over weeks) - **Rapid progression:** ESRD in 6–12 months if untreated - **Histology:** Podocyte hyperplasia with capillary collapse - **Associated with:** HIV/AIDS, medications (pamidronate, anabolic steroids, heroin), TMA

Hypertension-Attributed Nephropathy (MicroA) **Subtle early disease:** - **Proteinuria:** Mild–moderate (0.5–2 g/day initially) - **Hypertension:** Often prominent feature - **Renal function decline:** Gradual; can lead to CKD if untreated

Screening and Risk Assessment

APOL1 Testing Indications: 1. **Black/African American patients with:** - FSGS or collapsing glomerulopathy - CKD of unclear etiology - Proteinuric kidney disease (to refine diagnosis) - Family history of ESRD

2. **Clinical utility:**

- **Two risk alleles:** Heightened surveillance; aggressive BP/proteinuria management
- **One risk allele:** Baseline risk similar to general population; lifestyle modifications
- **G0/G0 genotype:** Reassuring (low genetic risk)

Testing limitations: - APOL1 presence does NOT diagnose disease (many carriers remain healthy) - Environmental/behavioral factors (HTN, proteinuria, smoking, diet) modulate expression - Test results should inform but NOT replace clinical judgment

Management of APOL1-Associated CKD

1. Blood Pressure Control: - **Target:** <120 systolic per SPRINT-CKD (intensive control beneficial) - **Agents:** ACEi/ARB preferred (☐ proteinuria + BP control) - **Monitoring:** Monthly BP; adjust medications for target

2. Proteinuria Reduction: - **Goal:** <0.3 g/day (complete remission) or ☐ >50% from baseline - **First-line:** ACEi or ARB (if not contraindicated) - **Addition:** SGLT2 inhibitor (dapagliflozin, empagliflozin) for synergistic effect - **Consider:** Finerenone (non-steroidal MRA) if eGFR >25 and K☐ <5.5

3. Immunosuppression (FSGS/Collapsing): - **Steroid-resistant FSGS:** Often responds poorly to corticosteroids alone - **Consider rituximab** or **calcineurin inhibitor (tacrolimus, cyclosporine)** if biopsy-proven FSGS - **Evidence base:** Limited; outcomes variable - **Referral:** Nephrology for biopsy-proven disease + specialist management

4. Lifestyle modifications: - **Weight loss:** If overweight/obese (☐ proteinuria) - **Sodium restriction:** <3 g/day - **Smoking cessation:** Improves renal outcomes - **DASH diet:** Cardiovascular + renal protection

5. Monitoring: - **Renal function:** Baseline, then every 3–6 months - **Proteinuria:** 24-hr urine or uACR at baseline, then every 3–6 months (target <0.3 g/day) - **BP:** Home monitoring; goal <120 systolic - **Medication adherence:** Critical; pill counts, pharmacy refills

Prognosis

With two APOL1-risk alleles: - **Hypertensive variants:** Progressive but slower (10–20 years to ESRD if managed well) - **FSGS/Collapsing:** More aggressive (2–5 years to ESRD if resistant to therapy) - **Modifiable risk factors:** HTN control, proteinuria reduction, smoking cessation ☐ renal survival

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SICKLE CELL NEPHROPATHY

Pathophysiology

Sickle hemoglobin (HbS) polymerization: 1. **Low O_2 tension** ☐ HbS polymerization ☐ rigid RBC 2. **Hemolysis:** Shortened RBC life span (10–20 days vs. normal 120 days) 3. **Renal vasculature involvement:** - **Medullary hypoxia:** ☐ O_2 in renal medulla (countercurrent multiplier concentrates HbS) - **Vaso-occlusion:** Sickled RBCs lodge in medullary vessels - **Hemolysis in kidney:** Local tissue damage, inflammation

Result: Progressive glomerulonephritis + medullary necrosis + papillary dysfunction

Clinical Manifestations

Early-Phase Nephropathy (Hyperfiltration) **Presentation:** - **Preserved renal function:** eGFR normal to ☐ (hyperfiltration) - **Hematuria:** Gross (common) or microscopic - **Proteinuria:** Absent or minimal (<0.3 g/day) - **Polyuria/nocturia:** Often striking (concentrating defect from medullary damage) - **Hyperuricemia:** From hemolysis; ☐ gout risk

Timeline: Ages 10–30 years

Late-Phase Nephropathy (Progressive CKD) **Progressive glomerulosclerosis:** - **Proteinuria:** ☐ to nephrotic range (often >3 g/day) - **Hypertension:** Develops - **Progressive renal dysfunction:** eGFR ☐ (some to ESRD) - **Timeline:** Ages 30–50 years

Rates of progression: - ~20% develop chronic kidney disease (eGFR 15–60) by age 40 - ~4% reach ESRD by age 40 (higher in sickle cell disease SS; lower in sickle cell trait AS)

Specific Complications

Polyuria and Concentrating Defect **Mechanism:** Medullary damage (vaso-occlusion, papillary necrosis) ☐ impaired countercurrent multiplier ☐ unable to generate osmotic gradient

Clinical manifestations: - **Polyuria:** 4–6 L/day (vs. normal 1–2 L/day) - **Nocturia:** Severe; impacts quality of life - **Dehydration risk:** Easy dehydration with infections, diuretics, NSAIDs - **Hyperuricemia:** Concentration of uric acid in medullary tubules

Management: - **Hydration:** Emphasize adequate oral/IV fluid intake (especially during crises, febrile illness) - **NSAIDs:** Avoid if possible (☐ AKI risk with dehydration + renal disease) - **Monitor K☐, Ca^{2}☐, PO_4:** Electrolyte abnormalities common

Gross Hematuria **Mechanism:** Papillary necrosis or erosion into collecting system

Clinical presentation: - **Painless gross hematuria:** Often recurrent - **Risk of obstructing clot:** Rare but possible (high urine RBC concentration)

Management: - **Reassurance:** Self-limited in most; resolves within days - **Hydration:** Maintain urine flow to prevent clot obstruction - **Avoid aggressive diuresis:** Dehydration worsens hemolysis - **NSAIDs:** Contraindicated (worsen hematuria risk) - **Imaging:** If hematuria persistent or clot obstruction suspected - **Urology referral:** Rarely needed; reserved for massive hemorrhage (transfusion need) or obstruction

Hyperuricemia and Gout **Mechanism:** Hemolysis ☐ ☐ purines ☐ ☐ uric acid; medullary concentration from polyuria ☐ precipitation

Clinical: - **Gout attacks:** 30–40% of sickle cell patients develop gout by age 40 - **Renal manifestations:** Urate crystallization in tubules ☐ AKI possible

Management: - **Hydration:** Maintain high urine output (☐ uric acid concentration) - **Allopurinol:** 300 mg daily (consider prophylactic if recurrent gout or prior urate nephropathy) - **Febuxostat:** Alternative if allopurinol intolerance - **NSAIDs + diuretics:** Avoid (☐ AKI + gout risk) - **Monitoring:** Serum uric acid goal <6 mg/dL

Papillary Necrosis **Mechanism:** Ischemic necrosis of renal papilla from medullary vaso-occlusion

Clinical presentation: - **Hematuria:** Gross (debris/necrotic tissue sloughed) - **Renal colic:** Pain if necrotic papilla causes obstruction - **Fever/flank pain:** Possible; mimics pyelonephritis - **Imaging:** CT shows papillary necrosis (ring sign similar to analgesic nephropathy)

Management: - **Supportive:** Hydration, analgesia (acetaminophen preferred; avoid NSAIDs), fever management - **Monitor:** For obstruction (oliguria, pain); CT imaging if concern - **Urology:** If obstruction develops (stent placement rare but possible)

Renal Failure in Sickle Cell Disease

Incidence: ~3–4% reach ESRD by age 50 (vs. <1% general population)

Mechanisms leading to ESRD: 1. **Progressive FSGS from hyperfiltration** (most common) 2. **Sickle cell glomerulonephritis** (immune complex glomerulonephritis; rare) 3. **Acute tubular necrosis (ATN)** from sickle crises (vaso-occlusion, rhabdomyolysis) 4. **Chronic vascular disease** (atherosclerosis; multifactorial)

Risk factors for progression: - **Male gender** (more aggressive course) - **Sickle cell disease SS** (worse than sickle cell trait AS or SC disease) - **Baseline proteinuria** (nephrotic-range proteinuria = ☐ risk) - **Hypertension** (common complicating factor) - **Frequent sickle crises** (recurrent ischemia)

Management of Sickle Cell Nephropathy

1. Renal-Protective Therapy: - **ACEi/ARB:** Indicated if proteinuria present (☐ proteinuria ~40%) - **Caution:** Some sickle cell patients on ACEi report fewer crises (anecdotal benefit of vasodilation) - **Monitoring:** K☐, Cr (risk hyperkalemia + AKI if dehydrated) - **SGLT2i:** Consider if proteinuric (dapagliflozin, empagliflozin)

2. Blood Pressure Control: - **Target:** <130/80 (KDIGO recommendation; intensive control beneficial) - **Agents:** ACEi/ARB preferred; CCB acceptable

3. Sickle-Specific Management: - **Hydroxyurea:** ☐ HbS polymerization; ☐ hemolysis + RBC sickling - **Effect:** ☐ HbF (fetal hemoglobin; doesn't polymerize), ☐ hemolysis - **Renal benefit:** Indirect benefit via ☐ hemolysis - **Voxelotor:** ☐ RBC oxygen affinity; ☐ polymerization - **Emerging:** Possible renal protection (under investigation) - **Gene therapy, stem cell transplant:** Curative but high risk/availability limited

4. Polyuria Management: - **Hydration:** Emphasize water intake (min 2–3 L/day) - **NSAIDs:** Absolutely contraindicated - **Electrolytes:** Monitor Na☐, K☐, Ca^{2}☐ for imbalance - **Fluid during crises:** IV hydration essential during vaso-occlusive crises

5. Monitoring: - **Renal function:** Baseline, then annually (or more frequent if CKD present) - **Proteinuria:** Baseline, then annually (target <0.3 g/day) - **BP:** Home monitoring; goal <130/80 - **Hemoglobin/reticulocytes:** Monitor for adequacy of RBC production

Prognosis

- **Mild renal disease:** Many remain stable with proteinuria <1 g/day for years

- **Nephrotic proteinuria:** Progressive; many reach ESRD in 5–10 years if untreated
- **Median age to ESRD (untreated):** ~40 years (vs. >80 years in general CKD population)
- **Dialysis outcomes:** Sickle cell ESRD patients have worse survival on dialysis (☐ infections, cardiovascular events)
- **Transplantation:** Improved outcomes; equivalent allograft survival to non-sickle cell ESRD recipients

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HIV-ASSOCIATED KIDNEY DISEASE

Epidemiology

Incidence: 2–10% of HIV-infected patients (varies by region, comorbidities)

Risk factors: - **Low CD4 count** (<200 cells/μL; highest risk) - **Black/African descent** (3–5× higher incidence; APOL1-related) - **Hepatitis C coinfection** - **IV drug use** - **Diabetes, hypertension**

Histologic Classification

HIV-Associated Nephropathy (HIVAN) **Mechanism:** Direct HIV infection of kidney cells (podocytes, parietal cells) ☐ viral genome integration ☐ cell dysfunction/death

Histology (Biopsy-defining): 1. **Collapsing glomerulopathy** (most common; 80% HIVAN) - Podocyte hyperplasia, capillary collapse, sclerosis - Crescent-like lesions possible 2. **Mesangial proliferation:** Immune complex deposition possible (overlapping pattern) 3. **Tubular dilation:** "Microcystic dilation" of proximal tubules (distinctive) 4. **Interstitial inflammation:** Lymphocytes, plasma cells 5. **Immunofluorescence:** Usually negative (distinguishes from immune complex GN)

HIV-Associated FSGS **Mechanism:** Secondary FSGS; may represent different pathophysiology than HIVAN (possible response to glomerular hypertension)

Clinical distinction: - **Often less proteinuria** than HIVAN (1–3 g/day vs. >10 g/day in HIVAN) - **Better outcomes** than HIVAN (slower progression) - **May respond to therapy**

Immune Complex Glomerulonephritis (ICGN) **Mechanism:** HIV-immune complex deposition (IgG, IgM, C3)

Histology: - **Membranoproliferative (MPGN)** pattern common - **Post-infectious GN-like** appearance - **IgA nephropathy:** Also reported

Clinical feature: Hematuria, RBC casts (not typical of HIVAN)

Other Patterns

- **Minimal change disease** (rare; responds to corticosteroids)
- **Thrombotic microangiopathy** (TMA; associated with advanced HIV)

Clinical Presentation

HIVAN (most common; 80% of HIVKAN): - **Nephrotic proteinuria:** >10 g/day (often!) - **Preserved renal function early:** eGFR may be normal initially - **AKI possible:** Rapid Cr rise to ESRD (weeks–months if untreated) - **Hypertension:** Variable; not always prominent - **Urinalysis:** Proteinuria >3+ on dipstick; minimal hematuria/RBC casts

FSGS (less aggressive): - **Proteinuria:** 1–5 g/day (less than HIVAN) - **More gradual decline:** eGFR ☐ over months

Diagnosis

Clinical suspicion: - **HIV+ patient with proteinuria** (often in setting of low CD4) - **Rapid progression to ESRD** (high clinical likelihood of HIVAN) - **Preserved renal function with heavy proteinuria** (distinctive of HIVAN)

Biopsy (definitive): - **Indicated if diagnosis uncertain** (differentiate HIVAN from immune complex GN, secondary causes) - **Light microscopy:** Collapsing GN, tubular dilation - **EM:** HIV particles in podocytes (electron microscopy; research only) - **IF:** Negative to minimal immune complexes (distinguishes from ICGN)

Management

1. Antiretroviral Therapy (ART) — FOUNDATION: - **Most critical intervention:** Immune reconstitution dramatically improves renal outcomes - **Mechanism:** ☐ HIV replication ☐ podocyte recovery from infected state - **Proteinuria response:** Often ☐ proteinuria 50–80% with immune reconstitution - **Timing:** Start ART immediately if low CD4 + proteinuria - **Expected timeline:** Proteinuria may take weeks–months to improve; Cr stabilization possible even if initially rising

2. Immunosuppression (Adjunctive): - **ACEi/ARB:** First-line for proteinuria reduction (synergistic with ART) - **Expected benefit:** ☐ Proteinuria 40–50% (additional to ART benefit) - **Caution:** Monitor K☐, Cr (hyperkalemia, AKI risk) - **Corticosteroids:** Controversial; may be adjunctive in severe HIVAN - **Mechanism:** Anti-inflammatory, ☐ immune activation - **Dose:** Prednisolone 0.5–1 mg/kg/day × 4–6 weeks, then taper (evidence limited) - **Caution:** Infection risk with steroids + severe immunosuppression (CD4 <50) - **Evidence:** Limited RCT data; observational studies suggest possible benefit if CD4 >200 - **Cyclosporine (CNI):** Reports of benefit in HIVAN (rare use); mechanism unclear - **Evidence:** Anecdotal; not standard - **Risk:** Nephrotoxicity (risk despite already reduced renal function)

3. Blood Pressure Control: - **ACEi/ARB preferred** (proteinuria reduction + BP control dual benefit) - **Target:** <120 systolic (per SPRINT-CKD)

4. Renal Replacement Therapy: - **Hemodialysis/peritoneal dialysis:** If ESRD develops - **Outcomes:** Possible; survival on dialysis ☐ vs. non-HIV ESRD (☐ infections, opportunistic infections, poor compliance) - **Transplantation:** Possible with undetectable VL + adequate CD4; outcomes improving

Response to Therapy and Prognosis

Pre-ART era (1980s–1990s): - **Rapid progression:** 50% ESRD within 1–2 years of diagnosis - **Poor dialysis outcomes:** High mortality

With modern ART: - **Dramatic improvement:** CD4 recovery ☐ podocyte repair ☐ proteinuria ☐ - **Renal recovery:** Some achieve normal eGFR despite initial ESRD trajectory - **Prognosis:** If Cr <2 mg/dL and CD4 recovers >200, ~70% achieve complete remission - **Key: Early ART initiation** at time of HIVAN diagnosis critical

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OBESITY-RELATED GLOMERULOPATHY

Mechanism and Pathophysiology

Obesity-induced renal changes: 1. **Glomerular hyperfiltration:** ☐ GFR (initially) - **Hemodynamic driver:** Obesity ☐ ☐ systemic and glomerular hydrostatic pressure - **Adipokine effect:** Leptin ☐ (activates RAAS, ☐ sympathetic tone) 2. **Podocyte stress:** ☐ filtration pressure + metabolic stress (lipotoxicity) 3. **Proteinuria development:** Foot process effacement 4. **Glomerulosclerosis:** Progressive fibrosis ☐ CKD 5. **Tubular dysfunction:** Salt reabsorption abnormalities

Associated metabolic changes: - **Insulin resistance:** ☐ hyperinsulinemia ☐ renal retention of sodium + volume expansion - **Dyslipidemia:** Lipid accumulation in glomerulus ☐ oxidative stress - **Hypertension:** Obesity-related HTN (renin system activation) - **Inflammation:** Adipose tissue produces inflammatory cytokines (TNF-α, IL-6)

Clinical Presentation

Early phase (obesity with preserved GFR): - **Proteinuria:** Mild (0.3–1 g/day) - **Preserved eGFR:** Often normal or even ☐ (hyperfiltration) - **Hypertension:** Common (~50%) - **Metabolic syndrome:** Often present (HTN, dyslipidemia, impaired glucose tolerance)

Progressive phase: - ☐ **Proteinuria:** May reach nephrotic range - **eGFR decline:** Begins slowly; progressive in some - **Hypertension:** Worsens

Histology (if biopsied): - **Light microscopy:** Glomerulomegaly (enlarged glomeruli), FSGS pattern (segmental sclerosis) - **"Obesity-related glomerulopathy"** pattern (not a specific diagnosis; descriptive) - **Podocyte enlargement:** Common finding - **Immune deposition:** Usually absent (distinguishes from primary FSGS)

Diagnosis

Clinical context: - **BMI >30 kg/m²** (obesity; BMI 30–35 = overweight/Class I obesity; >35 = Class II-III) - **Proteinuria:** Often asymptomatic (discovered on screening) - **Preserved renal function early:** Diagnostic clue vs. primary FSGS - **Absence of systemic disease:** (nega serologies, normal complement) - **Kidney biopsy:** Not routinely needed; diagnosis often clinical

Management: Weight Loss as Primary Therapy

1. Weight Loss (Most Important): - **Target:** 5–10% body weight loss (feasible; associated with proteinuria ☐) - **Greater loss:** 15–20% weight loss ☐ profound proteinuria reduction (~50%) - **Mechanisms:** - ☐ Glomerular filtration pressure (hemodynamic) - ☐ Inflammatory cytokines - ☐ Insulin resistance - Restored podocyte function (possible) - **Timeline:** Proteinuria reduction expected over weeks–months

Methods: - **Lifestyle:** Caloric restriction (500–1000 kcal/day deficit), physical activity (150 min/week), dietary counseling - **Pharmacotherapy:** GLP-1 agonists (semaglutide, tirzepatide), phentermine (short-term) - **Emerging data:** Semaglutide + lifestyle ☐ weight loss >10%; renal benefit being studied - **Bariatric surgery:** Gastric bypass, sleeve gastrectomy - **Effect:** 30–50% weight loss; proteinuria often resolves - **Indication:** BMI >40 or BMI 35–39 with comorbidities (diabetes, HTN, CKD)

2. Pharmacologic Renal Protection: - **ACEi/ARB:** First-line for proteinuria reduction (independent of weight loss) - **Effect:** ☐ Proteinuria 20–40% - **Synergistic with weight loss** - **SGLT2 inhibitor:** Emerging role - **Weight loss:** SGLT2i cause 2–3 kg weight loss (glycosuria) - **Proteinuria reduction:** Additional 20–40% beyond ACEi - **GLP-1 agonist:** Semaglutide - **Weight loss:** 5–15% body weight (dose-dependent) - **Renal outcomes:** Improved in SUSTAIN-6 (☐ ESRD, albuminuria)

3. Blood Pressure Control: - **Target:** <120 systolic (SPRINT-CKD) - **Agents:** ACEi/ARB preferred (dual benefit: BP + proteinuria)

4. Metabolic Control: - **Diabetes:** Tight glucose control (HbA1c <7% if tolerable without hypoglycemia) - **Agents:** Metformin, SGLT2i, GLP-1 agonist - **Dyslipidemia:** Statin therapy (even in non-diabetics with CKD + obesity; cardiovascular benefit) - **Hypertension:** Target <120/70

5. Monitoring: - **Proteinuria:** Baseline, then at 3 months (assess response to weight loss), then every 6 months - **Renal function:** Baseline, then annually (or more if CKD present) - **BP:** Home monitoring

Prognosis

- **With weight loss + ACEi/ARB:** Many stabilize; some achieve near-normal eGFR + resolved proteinuria
- **Without intervention:** Progressive CKD (eGFR ☐ ~1–3 mL/min/year)
- **Bariatric surgery outcomes:** 50–70% achieve complete proteinuria remission

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PREGNANCY AND THE KIDNEY

Physiologic Changes in Pregnancy

Renal Hemodynamics **GFR change:** - ☐ **GFR by 40–50%** during pregnancy (peak mid-trimester) - **Mechanism:** Afferent arteriolar vasodilation (prostaglandin-mediated); ☐ renal plasma flow - **Clinical significance: "Normal" Cr ~0.9 mg/dL pre-pregnancy becomes "elevated" 1.2 mg/dL in pregnancy** (reflects ☐ GFR) - **Adjusted Cr threshold:** Creatinine 0.9–1.1 mg/dL in pregnancy may represent mild renal insufficiency

Tubular changes: - ☐ **Reabsorption of glucose, amino acids:** Dipstick can show glycosuria (benign), proteinuria <300 mg/day (normal) - **Increased urinary calcium:** ☐ Hypercalciuria (can worsen stone risk)

Acid-Base Changes

- **Chronic respiratory alkalosis:** ☐ PCO_2 (24–30 mmHg; progesterone ☐ respiration)
- **Compensatory metabolic acidosis:** Serum HCO_3☐ 18–21 (vs. normal 22–26)

Glomerular Filtration Changes

- **Increase by 50%:** Measured GFR, inulin clearance, creatinine clearance
- **Timeline:** Begins week 6 gestation; peaks by week 9; returns to baseline 8–12 weeks postpartum
- **Clinical use:** Estimated GFR (eGFR) formulas underestimate true GFR in pregnancy; consider creatinine clearance if precise assessment needed

Preexisting CKD in Pregnancy

Impact on Pregnancy and Fetus **CKD Stage 1–2 (eGFR >60):** - **Pregnancy outcomes:** Usually favorable (similar to non-CKD) - **Fetal risk:** Low risk of prematurity, low birth weight if well-controlled BP/proteinuria - **Maternal risk:** Low risk of worsening renal function

CKD Stage 3a–3b (eGFR 30–59): - **Pregnancy outcomes:** Moderate risk - **Fetal outcomes:** ☐ Risk prematurity, IUGR (intrauterine growth restriction), low birth weight - **Maternal renal outcomes:** ~20–30% experience Cr rise during pregnancy; some recover, some permanent

CKD Stage 4 (eGFR 15–29): - **Pregnancy rare:** Often subfertile (uremia affects ovulation) - **High-risk pregnancy:** ☐ Fetal loss, prematurity, IUGR - **Maternal renal:** High risk permanent Cr worsening to ESRD - **Counseling:** Often advised against pregnancy (high maternal-fetal risk)

CKD Stage 5 (ESRD on dialysis): - **Fertility:** Restored with dialysis (sometimes surprising) - **Pregnancy possible but uncommon:** Historically considered contraindicated - **Modern experience:** Some successful pregnancies with intensive dialysis (daily hemodialysis, nocturnal HD) - **Outcomes:** Prematurity >90%, fetal loss ~30%, but live births possible - **Counseling:** Possible but high-risk; requires specialized management

Management of Preexisting CKD in Pregnancy **Preconception counseling:** - **eGFR >60 + normal BP + <0.3 g/day proteinuria:** Low-risk pregnancy - **eGFR 30–60:** Discuss risks (☐ prematurity, fetal complications, possible permanent renal decline) - **eGFR <30:** Consider waiting; optimize renal function pre-pregnancy - **Heavy proteinuria (>1 g/day):** ☐ Fetal risk; goal ☐ proteinuria <0.5 g/day pre-conception if possible

Medication adjustments: - **ACEi/ARB:** CONTRAINDICATED in 2nd–3rd trimester (teratogenic; renal dysgenesis) - **Action:** Switch to methyldopa or labetalol pre-conception or early 1st trimester - **1st trimester:** Emerging data suggest possible risk; exercise caution; benefit-risk assessment - **Post-delivery:** Can resume ACEi/ARB after breastfeeding completed (minimal transfer to breast milk) - **Diuretics:** Generally safe but avoid in volume depletion - **NSAID avoidance:** Especially 3rd trimester (☐ oligohydramnios, fetal renal dysfunction)

Monitoring during pregnancy: - **Renal function:** Baseline, then every trimester (or more frequently if CKD) - **Expected:** ☐ GFR; if Cr rises, concerning for CKD progression or preeclampsia - **Proteinuria:** Baseline 24-hr urine, then each trimester - **Expected:** ☐ Proteinuria 10–30% (benign); >1 g/day increase or new nephrotic proteinuria ☐ preeclampsia screen - **BP monitoring:** Home monitoring; target <140/90 (less stringent in pregnancy) - **Intensified monitoring** if baseline eGFR <60

Preeclampsia and AKI in Pregnancy

Preeclampsia Overview **Definition (ACOG):** - **New hypertension** (≥140/90 on 2 occasions ≥4 hours apart) after 20 weeks gestation - **AND one of:** - **Proteinuria:** ≥0.3 g/24 hrs (or ≥1+ on dipstick) - **Maternal organ dysfunction:** Thrombocytopenia, elevated transaminases, pulmonary edema, cerebral symptoms, acute renal dysfunction

Severe preeclampsia: - **BP ≥160/110** (on 2 occasions ≥15 min apart), OR - **Platelet count <100,000**, OR - **Elevated liver enzymes** (AST/ALT >2× ULN), OR - **Pulmonary edema**, OR - **Acute kidney injury** (serum Cr >1.1 mg/dL or ☐ baseline by ≥0.3 mg/dL)

Preeclampsia-Associated AKI **Mechanism:** 1. **Endothelial dysfunction:** Inadequate placental perfusion ☐ systemic inflammation 2. **Vasoconstriction:** ☐ Glomerular filtration + systemic BP ☐ 3. **Podocyte injury:** Possible direct endothelial-derived factors on podocytes 4. **Thrombotic microangiopathy:** Platelet consumption, MAHA (microangiopathic hemolytic anemia) 5. **Hepatorenal syndrome-like:** Severe disease

Clinical presentation: - **AKI in setting of new hypertension + proteinuria** (classic triad) - **Cr rise:** Often rapid (>0.3 mg/dL); oliguria possible - **Proteinuria:** Often rises sharply (1–5+ g/day; higher in preeclampsia than CKD alone) - **Other features:** Headache, visual changes, epigastric pain, edema, hyperreflexia

Diagnosis: - **Clinical (most common):** New HTN + proteinuria after 20 weeks - **Labs:** ☐ Platelets, ☐ transaminases, ☐ LDH (hemolysis), ☐ haptoglobin - **Placental pathology (postpartum):** Shallow placentation, vascular pathology

Management: - **Definitive treatment:** DELIVERY (cure for preeclampsia; remove placenta) - **Timing:** Delivery urgently recommended if ≥34 weeks (neonatal outcomes improve; maternal risk outweighs prematurity risk) - **<34 weeks:** Hospitalization, antihypertensives, corticosteroids for fetal lung maturity, watchful waiting if stable (balance maternal-fetal risk) - **Antihypertensives:** - **Target:** 140–150 systolic (goal <160 to prevent stroke; not <120 as in non-pregnant HTN) - **Agents:** Methyldopa, labetalol (oral/IV), hydralazine IV (reserved for severe HTN or hypertensive emergency) - **Avoid:** ACEi/ARB, NSAIDs (contraindicated 2nd–3rd trimester) - **Magnesium sulfate:** ☐ Seizure risk (eclampsia prophylaxis) - **Dosing:** 4–6 g IV load over 30 min, then 1–2 g/hr until 12–24 hours postpartum - **Fluid management:** Careful; volume depletion common (intravascular volume depletion despite edema) - **Oliguria:** Often responds to modest IV hydration (balanced crystalloids) - **Avoid aggressive diuresis:** Worsens renal function - **Renal replacement therapy:** If oliguria, hyperkalemia, severe fluid overload

Prognosis of preeclampsia-associated AKI: - **Most recover Cr to baseline 3–6 weeks postpartum** (if no pre-existing CKD) - **Permanent renal insufficiency:** Rare (<5%) if primigravida; ☐ if preexisting CKD - **Recurrence in future pregnancies:** ~25–30% risk of recurrent preeclampsia

Distinguishing Preeclampsia from Preexisting CKD

Feature	Preeclampsia	Preexisting CKD
Timing of hypertension	New after 20 weeks	Present pre-pregnancy
Proteinuria onset	Abrupt rise after 20 weeks	Stable or gradual ☐
Platelets/liver enzymes	☐ Platelets, ☐ transaminases typical	Normal (unless other etiology)
Resolution postpartum	BP, proteinuria normalize 6–12 weeks	Persist postpartum
Renal biopsy findings	Endotheliosis (if performed; rare)	Disease-specific (FSGS, lupus, etc.)

Management distinction: - **Suspected preeclampsia:** Deliver (definitive treatment) - **Preexisting CKD only:** Monitor closely; antihypertensive optimization; continue ACEi/ARB alternatives

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COVID-19 AND THE KIDNEY

SARS-CoV-2 Infection: Acute and Chronic Renal Manifestations

Acute Kidney Injury (AKI) in COVID-19 **Incidence:** 3–10% of hospitalized COVID-19 patients; ☐ in severe/critical illness

Mechanisms: 1. **Viral invasion:** ACE2 receptor (viral entry point) expressed in proximal tubule, podocytes - **Direct podocyte infection:** Proposed mechanism; not definitively proven - **Tubular entry:** Proposed; unclear clinical significance 2. **Indirect systemic effects:** - **Cytokine storm:** IL-6, TNF-α, IL-8 ☐ systemic inflammation ☐ endothelial injury - **Coagulopathy:** ☐ Thrombosis ☐ thrombotic microangiopathy (TMA) possible - **Hemolysis:** Possible from viral effects; contributes to AKI 3. **Multifactorial mechanisms:** ATN likely predominates (sepsis-like, hypoxia, volume status)

Clinical presentation: - **Timeline:** AKI develops during hospitalization (days 1–7 typically) - **Oliguria:** Non-oliguric AKI common (70%) - **Cr rise:** Variable (0.5–4 mg/dL increase reported) - **Urinalysis:** Typically bland (muddy casts rare); possible proteinuria/hematuria - **Associated:** Severe respiratory disease (hypoxia), multiorgan failure common

Risk factors for AKI: - **Age >65 years** - **Preexisting CKD** (eGFR <60) - **Diabetes** (☐ severity) - **Hypertension** - **Severe COVID-19** (ventilator requirement, ICU admission)

Management: - **Supportive care:** Fluid management, oxygen, ventilator support - **Monitor Cr, K☐, PO₄ closely:** Daily in hospitalized patients - **Avoid nephrotoxins:** NSAIDs, ACEi/ARB (controversial; trend toward continuing if possible), radiocontrast if not essential - **RRT if indicated:** Standard ICU indications (oliguria, hyperkalemia, fluid overload, uremia)

Prognosis: - **Most recover Cr to baseline:** Within 3–6 weeks (if no pre-existing CKD) - **ESRD rate:** 3–5% of COVID-19 AKI patients require long-term dialysis - **Mortality:** High (30–50%) in COVID-19 patients with AKI (multifactorial; multiorgan failure)

Post-COVID-19 Chronic Kidney Disease (COVAN) **Emerging concern:** Some COVID-19 survivors show persistent CKD despite AKI recovery

Clinical findings: - **eGFR decline:** 10–20% of hospitalized COVID-19 patients show ☐ eGFR at 60–90 days post-discharge (compared to baseline or expected recovery) - **Proteinuria:** Some develop new proteinuria or persistent proteinuria post-infection - **Mechanism:** Unclear; proposed: - Endothelial dysfunction (lasting podocyte injury from viral invasion or inflammatory mediators) - Renal scarring (TMA, ATN aftermath) - Persistent inflammation (microclots, pro-thrombotic state) - Immune dysregulation (long COVID phenomenon)

Risk factors: - **Severe acute COVID-19** (ICU admission, mechanical ventilation) - **Preexisting CKD - Diabetes - Age >65 years**

Follow-up studies: - **3–6 months post-discharge:** Recheck Cr, eGFR, urinalysis - **Persistent eGFR <60 or new proteinuria:** Nephrology referral for workup (rule out other etiologies; assess for post-COVID CKD)

Management: - **ACEi/ARB if proteinuria:** Standard CKD therapy - **BP control:** Target <130/80 - **Lifestyle:** Cardiovascular risk factor reduction - **Monitoring:** Cr every 3–6 months (assess trajectory)

Prognosis of post-COVID CKD: - **Unknown; under investigation:** Limited long-term data (pandemic still evolving) - **Some suggest improvement:** Possible eGFR recovery months post-infection (inflammation resolution) - **Concern:** Subset may have progressive CKD trajectory

Vaccination and Kidney Disease

SARS-CoV-2 vaccines and AKI: - **No direct association** between vaccination and AKI (extensive post-market surveillance) - **Coincidental AKI:** Reported in vaccinated patients but temporal relationship likely coincidental - **Immune-mediated GN:** Rare case reports of post-vaccine nephritis; causal link unproven

Recommendation: COVID-19 vaccination recommended for ALL patients including those with CKD (prevent severe COVID-19 + AKI risk)

Clinical Scenarios

Scenario 1: APOL1 Risk Alleles with Proteinuria

Clinical: 42-year-old Black male with hypertension (BP 158/96 on amlodipine), eGFR 52, uACR 350 mg/g (overt albuminuria). APOL1 testing reveals G1/G2 (two risk alleles).

Plan: 1. **Start ACEi/ARB:** Lisinopril 10 mg daily (renal protection + BP control) - **Goal:** ☐ Proteinuria 30–50%; target uACR <30 mg/g - **Monitor:** Cr 1 week (expect stable or slight ☐ 10–30%), K☐ 1 week, then q3 months 2. **Tighten BP control:** Increase amlodipine to 10 mg daily; target BP <120 systolic - **Goal:** <120/80 (SPRINT-CKD benefit) 3. **Lifestyle:** Weight loss if overweight, sodium <3 g/day, DASH diet, smoking cessation 4. **SGLT2i:** Consider dapagliflozin 10 mg daily (additional proteinuria ☐ + CKD progression ☐) 5. **Monitoring:** - **3 months:** Recheck uACR (goal ☐ >50% from baseline 350) - **6 months:** Assess BP control, Cr, K☐, proteinuria - **Genetic counseling:** Discuss APOL1 risk to family members (siblings, children); screening consideration

6. **Expected outcome:** With RAAS inhibition + lifestyle, many achieve proteinuria ☐ and slow CKD progression

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Scenario 2: Sickle Cell Disease with Proteinuria

Clinical: 36-year-old male with sickle cell disease SS, multiple prior sickle crises, BP 148/92, eGFR 55, urine dipstick 2+ proteinuria (24-hr urine 2.8 g).

Plan: 1. **Start ACEi/ARB:** Losartan 50 mg daily (proteinuria reduction; possible crisis benefit via vasodilation) - **Monitor:** Cr at 1 week (expect stable ±10%), K☐ 1 week then q3 months - **Note:** Some evidence ACEi reduces vaso-occlusive crisis frequency (anecdotal); possible added benefit 2. **Target BP:** <130 systolic (add CCB if needed; amlodipine safe) 3. **Sickle-specific:** - **Hydroxyurea:** If not already on; ☐ HbS polymerization, hemolysis (indirect renal benefit) - **Hydration:** Educate on adequate fluid intake (polyuria from concentrating defect; risk of dehydration) 4. **Avoid NSAIDs:** Acetaminophen for pain (☐ AKI risk) 5. **Hyperuricemia management:** - **Serum uric acid:** Check baseline (expect ☐ from hemolysis) - **If >8 mg/dL and/or prior gout:** Start allopurinol 300 mg daily - **Maintain hydration:** ☐ Uric acid concentration 6. **Monitoring:** - **Renal function:** Baseline, then 3 months, 6 months, then annually - **Proteinuria:** Goal ☐ to <1 g/day (nephrology referral if nephrotic range develops) - **Hematuria:** Monitor; self-limited usually; no intervention unless massive (rare) 7. **Expected:** With ACEi + hydration + pain control, many stabilize; slow CKD progression vs. untreated

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Scenario 3: Preeclampsia at 28 Weeks

Clinical: 32-year-old primigravida at 28 weeks gestation presents with BP 158/102 (baseline 115/70), proteinuria 4+ on dipstick (24-hr urine 2.8 g), headache, visual changes. Labs: platelets 85,000, AST 120, Cr 1.3 (baseline 0.8).

Diagnosis: Severe preeclampsia (HTN ≥160/110 + proteinuria + maternal organ dysfunction: thrombocytopenia, hepatitis, AKI)

Plan (hospitalization required): 1. **Delivery consideration:** At 28 weeks (borderline periviability; neonatology consult) - **If deliver:** Corticosteroids for fetal lung maturity, magnesium sulfate for seizure prophylaxis - **If expectant management:** Hospitalization, antihypertensives, close monitoring (28–34 weeks more favorable) 2. **Magnesium sulfate:** 4 g IV load over 30 min, then 1–2 g/hr (seizure prophylaxis) 3. **Antihypertensives:** - **Goal BP:** 140–150 systolic (not <120; goal prevent stroke without compromising placental perfusion) - **Agent:** Labetalol 20 mg IV, repeat q10 min (max 80 mg in 10 min interval); then consider oral (methyldopa 500 mg TID or labetalol 400–800 mg BID) - **Avoid:** ACEi/ARB (teratogenic 2nd–3rd trimester), NSAIDs (oligohydramnios, fetal renal dysfunction risk) 4. **Fluid management:** IV fluids cautiously (risk oliguria from intravascular depletion despite edema) - **Oliguria:** Monitor UO; modest hydration trial if UO <0.5 mL/kg/hr - **Avoid aggressive diuresis:** Worsens renal function 5. **Monitor closely:** Daily Cr, K☐, Mg²☐, platelets, liver enzymes, urine output; fetal monitoring (NST, biophysical profile) 6. **RRT if:** ☐ K☐ (>6.0), severe acidosis, fluid overload with pulmonary edema 7. **Postpartum:** Expectation = BP, Cr normalize 3–6 weeks; follow-up renal function at 6 weeks (rule out permanent kidney injury)

Practice Questions

Question 1

A 35-year-old Black female with two APOL1-risk alleles presents with nephrotic proteinuria (uACR 420 mg/g), BP 142/88, eGFR 65, and normal serum complement. Kidney biopsy shows collapsing FSGS. Which of the following is MOST appropriate?

A) Steroid therapy alone (1 mg/kg/day prednisone)
B) ACEi/ARB monotherapy without additional immunosuppression
C) ACEi/ARB + weight loss intervention + close proteinuria monitoring
D) Immediately initiate rituximab + cyclophosphamide
E) Genetic counseling only; observe without therapy

Answer: C (ACEi/ARB monotherapy first-line with lifestyle modification; immunosuppression reserved if resistant)

Rationale: - **APOL1-associated FSGS:** Often steroid-resistant; ACEi/ARB ☐ proteinuria (renal hemodynamic effect) in 40–50% - **Weight loss:** If overweight, ☐ proteinuria (☐ glomerular hyperfiltration) - **Monitor response:** 3 months of ACEi/ARB + lifestyle; if proteinuria ☐ >50%, continue - **Reserve immunosuppression:** If ACEi/ARB + lifestyle fails (persistent nephrotic proteinuria), consider rituximab or CNI (evidence limited; specialist decision) - **Steroid monotherapy:** Ineffective in APOL1-related FSGS (steroid-resistant phenotype) - **Genetic counseling:** YES—family screening for APOL1 (siblings, children); risk stratification

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Question 2

A 24-year-old female with sickle cell disease SS presents with gross hematuria (dark red urine), flank pain, polyuria (8 L/day documented), and BP 148/96. Cr 1.2, eGFR 58, uACR 280 mg/g. Urinalysis shows RBCs, possible RBC casts. Which diagnosis is MOST likely?

A) Lupus nephritis (Class IV)
B) IgA nephropathy
C) Sickle cell nephropathy with hematuria from papillary necrosis
D) ANCA-associated vasculitis (GPA)
E) Diabetic nephropathy

Answer: C (sickle cell nephropathy; polyuria + hematuria + preserv renal function)

Rationale: - **Sickle cell disease = definitive diagnosis** — informs pathophysiology - **Polyuria (8 L/day):** Classic for sickle cell medullary damage (concentrating defect) - **Gross hematuria + flank pain:** Suggests papillary necrosis sloughing necrotic tissue into collecting system - **Preserved eGFR (58):** Sickle nephropathy early hyperfiltration phase - **Mild proteinuria (uACR 280):** Consistent with early sickle glomerulosclerosis - **Hypertension:** Common in sickle cell CKD - **Management:** Hydration, pain control (acetaminophen not NSAIDs), monitor for obstruction; ACEi for proteinuria ☐ - Lupus would have ANA+, complement ☐, anti-dsDNA; not in sickle disease - IgA would have biopsy showing IgA deposits; presentation less consistent - ANCA would have systemic symptoms, elevated ANCA serology, systemic vasculitis

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Question 3

A 30-year-old primigravida at 24 weeks gestation with preexisting CKD (eGFR 35, uACR 180 mg/g) on lisinopril + amlodipine, BP controlled 128/82, presents with new BP 156/98, urine dipstick 3+ protein, headache. Labs: platelets 120,000 (baseline unknown), AST 95. Which is MOST important next step?

A) Continue lisinopril; add hydralazine for BP control
B) Admit for delivery (24 weeks contraindicated for continuation)
C) Start magnesium sulfate; admit for observation; assess for preeclampsia vs. CKD progression
D) Increase lisinopril to 20 mg daily
E) Administer betamethasone and plan delivery immediately

Answer: C (admit for magnesium sulfate + monitoring; distinguish preeclampsia from CKD progression)

Rationale: - New hypertension + new proteinuria rise + thrombocytopenia + transaminitis = preeclampsia features - STOP lisinopril immediately (ACEi teratogenic 2nd–3rd trimester; causes renal dysgenesis, oligohydramnios) - **Magnesium sulfate:** Essential (seizure prophylaxis for preeclampsia) - **Admit for monitoring:** 24 weeks borderline viability; need careful assessment - If confirms severe preeclampsia ☐ delivery urgently recommended (maternal-fetal risk balance) - If CKD progression without preeclampsia ☐ can continue pregnancy with close observation - **Distinguish preeclampsia from CKD progression: - Preeclampsia findings:** New HTN post-20 weeks + NEW proteinuria rise + thrombocytopenia + visual/neuro symptoms ☐ DELIVERY - **CKD only:** Known CKD, stable proteinuria (relative to baseline), no systemic symptoms ☐ continue pregnancy with monitoring - **This patient:** Likely preeclampsia (new HTN + rising proteinuria + low platelets + hepatitis) superimposed on CKD - **Delivery timing:** If confirms preeclampsia, deliver urgently (risks outweigh prematurity)

Clinical Pearl Summary

1. **APOL1-risk variants:** G1, G2 alleles; ☐ kidney disease risk in African descent populations. Presence ≠ disease (environmental factors modulate expression). Two risk alleles = ☐ ESRD risk 20–40%.

2. **APOL1 kidney disease phenotypes:** FSGS (most common), collapsing glomerulopathy, hypertension-attributed nephropathy. Often steroid-resistant; ACEi/ARB + weight loss first-line.

3. **Sickle cell nephropathy:** Medullary hypoxia ☐ polyuria (concentrating defect) + hematuria (papillary sloughing) + proteinuria ☐ progressive glomerulosclerosis. 20% CKD by age 40; 4% ESRD.

4. **HIV-associated nephropathy (HIVAN):** Collapsing GN (most common); nephrotic proteinuria >10 g/day; rapid progression without ART. **ART = cornerstone therapy**; proteinuria often ☐ 50–80% with CD4 recovery.

5. **Obesity-related glomerulopathy:** Weight loss = primary therapy; 5–10% loss ☐ proteinuria ☐; 15–20% loss ☐ 50% reduction. ACEi/ARB + SGLT2i + GLP-1 agonist adjunctive.
6. **Pregnancy and kidney:** GFR ☐ 40–50% (Cr appears ☐); "normal" Cr 0.9 in pregnancy may be elevated. ACEi/ARB contraindicated 2nd–3rd trimester (teratogenic).
7. **Preeclampsia vs. preexisting CKD:** Preeclampsia = new HTN + new proteinuria after 20 weeks + maternal organ dysfunction; requires DELIVERY (definitive cure). CKD = stable before pregnancy; persists postpartum.
8. **Preeclampsia management:** Magnesium sulfate (seizure prophylaxis), antihypertensives (target BP 140–150 systolic, NOT <120), delivery if ≥34 weeks or signs of fetal distress/maternal deterioration.
9. **COVID-19 acute kidney injury:** 3–10% hospitalized patients; multifactorial (ATN, systemic inflammation, possible viral invasion of podocytes). Most recover; 3–5% require long-term dialysis.
10. **Post-COVID CKD (COVAN):** Some survivors show persistent eGFR ☐ or new proteinuria; mechanism unclear (endothelial dysfunction, renal scarring, persistent inflammation). Monitor 3–6 months post-discharge.

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