

CORE CURRICULUM IN NEPHROLOGY

Pregnancy: Kidney Diseases and Hypertension

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Significant physiologic mechanisms that alter systemic and renal hemodynamics play an important role in the renal response to changes in fluids and electrolytes during normal pregnancy. Unique disorders that may result in hypertension and renal disease can occur in pregnancy, and the impact of pregnancy on patients with underlying renal disease has important implications for maternal and fetal morbidity and mortality. Understanding these mechanisms, disorders, and their management provides the basis for appropriate care of pregnant women with renal disease.

RENAL ANATOMY AND FUNCTIONAL CHANGES OF URINARY TRACT

- Kidney size increases by about 1 cm in length during pregnancy secondary to:
 - Increase in renal vascular volume
 - Hypertrophy of kidney
 - Changes may persist for up to 12 weeks postpartum
 - Increased capacity of dilated urinary collecting system (physiologic hydronephrosis of pregnancy) due to:
 - Estrogen and progesterone influence
 - Inhibition of ureteral peristalsis by prostaglandin E₂
 - Mechanical obstruction of ureters in pregnancy (right > left, may be due to dextrorotation of uterus by sigmoid colon, resolves within 48 hours postpartum in 50% of cases)

- Increased glomerular filtration rate (GFR), urine formation rate, and urine flow

CARDIOVASCULAR AND RENAL PHYSIOLOGY

Blood Pressure Regulation

- Blood pressure (BP) falls shortly after conception and returns to normal at term due to:
 - Peripheral vasodilatation and resistance to angiotensin II secondary to high prostacyclin and prolactin levels; possibly via voltage-dependent calcium channel stimulation
 - Nitric oxide synthesis increases during normal pregnancy and may contribute to systemic and renal vasodilation and fall in BP; it mediates vasodilation via relaxin, produced by placenta and corpus luteum; blockade of nitric oxide production in pregnant rats causes systemic hypertension, increased renal vascular resistance, and reductions in renal plasma flow but unchanged GFR
 - Hemodynamic changes most likely triggered by primary fall in systemic vascular tone early in pregnancy; resulting rapid fall in preload and afterload leads to compensatory increase in heart rate and activation of volume-restoring mechanisms, and subsequently cardiac output increases because of a rise in stroke volume, which develops because vascular filling state normalizes whereas reduced afterload reduction is maintained
- Renin-angiotensin-aldosterone system (RAAS) is stimulated during pregnancy secondary to vasodilatation and vascular resistance to angiotensin II; aldosterone is critical in maintaining sodium balance in setting of dilatation of peripheral vasculature

Volume Regulation

- Circulating blood volume increases by 50% (plasma more than red blood cells, causing physiologic anemia of pregnancy)

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- Red blood cell mass begins to increase in first trimester and steadily rises by 20% to 30% (on iron supplements) above nonpregnant levels by end of pregnancy; among women not on iron supplements, red blood cell mass may only increase by 15% to 20%
- Cumulative sodium retention (500 to 900 mEq [mmol]) stimulated by decreased peripheral vascular resistance leads further to increased extracellular fluid volume, weight gain, and “benign” edema of lower extremities

Renal Hemodynamics

- GFR rises immediately after conception, reaching about 50% above baseline and resulting in significant hyperfiltration in second trimester; GFR then falls by about 20% in last trimester, returning to prepartum levels within 3 months of delivery:
 - Normal plasma creatinine falls to 0.5 mg/dL (44 μ mol/L) and any value above 0.8 mg/dL (71 μ mol/L) should be considered abnormal; there is also a respective fall in blood urea nitrogen
- Renal blood flow increases by as much as 85% in second trimester secondary to:
 - Increased cardiac output, which can reach maximum of 30% to 40% above nonpregnant level by midgestation
 - Increased renal vasodilatation of both afferent and efferent arterioles
 - Filtration fraction (GFR:renal plasma flow) falls towards midtrimester, returns to normal at birth

Prostaglandins and RAAS in Pregnancy

- Increase in prostaglandin synthesis by placental tissue via unknown stimuli results in resistance to hypertensive action of angiotensin II (important factor for arterial BP maintenance), norepinephrine, and arginine vasopressin (AVP)
- Renin and aldosterone levels rise significantly in pregnancy but respond to usual stimuli; however, kaliuresis is blunted by progesterone

Water Metabolism

- Pregnant women have downward resetting of osmotic threshold for both AVP secretion and thirst (probably secondary to chorionic

gonadotropin), which begins early in first trimester with a new steady-state plasma osmolality maintained until term

- Osmotic thresholds for thirst and antidiuretic hormone release each decrease about 10 mOsm/kg during initial weeks of human gestation leading to hypo-osmolality and lower serum sodium values
- Water balance is maintained by ability to dilute or concentrate urine maximally, despite increased renal blood flow and high prostaglandin E₂, an AVP antagonist
- Transient diabetes insipidus secondary to high placental vasopressinase activity usually occurs at term and is short lived but, if necessary, can be treated with the synthetic AVP analog desmopressin (DDAVP), which is not metabolized by vasopressinase

Mineral Metabolism

- Sodium balance is maintained, despite 50% increase in GFR and respective increased filtered Na⁺, by increasing Na⁺ reabsorption both in proximal tubule (under influence of capillary hydraulic pressure and oncotic pressure in renal interstitial space) and in distal portions (under influence of hormonal factors)
- Potassium metabolism remains unchanged, despite cumulative retention of about 350 mEq of K⁺ (necessary for fetal-placental development and expansion of maternal red blood cell mass) and increased aldosterone levels
 - Progesterone, produced by placenta, is increased throughout pregnancy and competes with aldosterone for binding to mineralocorticoid receptor causing natriuresis
 - Progesterone may play role in preventing kaliuresis that normally occurs when aldosterone levels are elevated and substantial quantities of sodium are presented to distal nephron sites; there is also a relative activation of RAAS because increased estrogen production raises angiotensinogen
- Calcium absorption from gastrointestinal tract increases secondary to high 1,25(OH)₂

vitamin D₃ levels produced by both kidney and placenta leading to hypercalciuria (exceeding 300 mg/d)

Uricosuria and Glucosuria

- Increased GFR increases urate clearance, resulting in decrease in serum uric acid; increased filtered load of glucose and less efficient tubule reabsorption may result in renal glucosuria

Acid-Base Regulation

- Pregnancy stimulates ventilation resulting in mild chronic respiratory alkalosis (ie, hypocapnia with lower serum bicarbonate) due to central nervous system stimulation by progesterone
- Early morning urine is more alkaline than in nonpregnant women, but acid excretion ability is unchanged

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RENAL DISEASE COMPLICATING PREGNANCY

Urinary Abnormalities

Proteinuria and hematuria

- Increase in GFR and glomerular capillary permeability to albumin results in about 80% increase in fractional albumin excretion with values lower than microalbuminuria range

- Up to 300 mg proteinuria/day can be normal
- Significant proteinuria may indicate unmasked kidney disease, worsening of preexisting renal disease, de novo development of renal disease, or development of preeclampsia
- Hematuria is almost always result of intrinsic process

Bacteriuria and urinary tract infections

- Asymptomatic bacteriuria is risk factor for urinary tract infection (UTI) in pregnancy
- Bacteriuria warrants prompt diagnosis and treatment even when asymptomatic, because of increased risk of bacteremia, septic shock, renal failure, or midtrimester abortions
- UTI frequency is same as in nonpregnant women
- Risk factors are diabetes, sickle cell trait or disease, as well as lower socioeconomic status
- Contributing factors are dilated urinary collecting system combined with slowed emptying, urine stasis, and vesicoureteral reflux
- Glucosuria and aminoaciduria also help bacterial growth
- UTI can evolve into pyelonephritis in about one third of cases
- Asymptomatic bacteriuria can be treated with 3-day course of amoxicillin, a cephalosporin, or nitrofurantoin
- Pyelonephritis can be treated with intravenous cefazolin or ceftriaxone, although ampicillin in combination with gentamicin can be used
- Trimethoprim-sulfamethoxazole, tetracyclines, and fluoroquinolones should be avoided

Acute Renal Failure in Early Pregnancy

Prerenal azotemia

- Secondary to hyperemesis gravidarum or hemorrhage of spontaneous abortion

Acute tubular necrosis

- May be due to: volume depletion secondary to hyperemesis gravidarum or hemorrhage of spontaneous abortion

- Septic abortion with associated shock in first trimester
- Gram-negative sepsis, most commonly *Escherichia coli*, with resultant hypotension
- Myoglobulinuria secondary to Clostridium-induced myonecrosis of uterus
- Diagnosis:
 - Clinical setting
 - Urinalysis with coarse granular casts, increased fractional excretion of sodium
- Treatment:
 - Supportive therapy with intravenous fluids, antibiotics, and dialysis as indicated

Renal cortical necrosis

- More likely to occur in pregnancy than other conditions that cause acute tubular necrosis due to early recruitment of cortical blood flow during normal gestation
- More frequently seen in older women, multigravidas, and multiple gestations, and is caused by obstetric catastrophes (abruptio placentae, septic abortion, severe preeclampsia, amniotic fluid embolism, and retained fetus)
- Primary disseminated intravascular coagulation and severe renal ischemia may be initiating event in this disorder
- Presents with gross hematuria, flank pain, and severe oliguria or anuria in appropriate clinical setting
- Diagnosis:
 - Noninvasively by computed tomography demonstrating a radiolucent rim in the cortex parallel to capsule, or
 - Invasively by renal biopsy or angiogram with patchy blood flow or absent nephrogram
- Renal functional recovery typically requires months and is incomplete, and may lead to end-stage renal disease

Pyelonephritis

- Unlike nongravid state, pyelonephritis may result in reduced GFR and even acute renal failure that recovers with appropriate antibiotic therapy

Acute Renal Failure in Late Pregnancy

Preeclampsia, eclampsia, and HELLP syndrome (See Hypertensive Disorders of Pregnancy)

Acute tubular necrosis

- Secondary to preeclampsia, HELLP (hemolysis, elevated liver enzymes, and low platelet) syndrome, or uterine bleeding in abruptio placentae

Acute fatty liver of pregnancy

- Presents after week 34 with jaundice and abdominal pain and possible fulminant hepatic failure in severe cases
- Laboratory:
 - Hyperbilirubinemia with mild to severe elevation of aspartate aminotransferase and alanine aminotransferase
 - Hypoglycemia, hypofibrinogenemia, and coagulation abnormalities may occur in severe cases
- Commonly associated with acute renal failure
- Characterized by microvesicular fatty infiltration of hepatocytes without inflammation or necrosis; pathogenesis may be related to defects in mitochondrial beta-oxidation of fatty acid
- Diagnosis:
 - Clinical presentation
 - Compatible laboratory results
- Current imaging modalities may be of limited use in detection of fat in liver of these patients, and diagnosis should be suspected in all women with above clinical features in absence of abruptio placentae
- Treatment:
 - Immediate delivery and supportive care
- Outcome:
 - Most recover completely
 - Severe cases may require liver transplantation

Postpartum acute renal failure and thrombotic thrombocytopenic purpura–hemolytic uremic syndrome

- Typically presents with severe hypertension, microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure days to weeks after normal pregnancy

- Patients can have severe deficiency of ADAMTS-13 activity in thrombotic thrombocytopenic purpura
- Retained placental fragments may play a role and require dilatation and curettage
- May be systemic disease of diffuse vascular endothelial cell injury
- Major clinical issue is to differentiate from preeclampsia and HELLP syndrome
- Renal biopsy shows glomerular thrombi and fibrin deposition as well as fibrinoid necrosis within arterioles
- Prognosis and treatment:
 - Reduced mortality and morbidity have been attributed to plasma exchange or plasmapheresis
 - Although there are no controlled studies in pregnancy, chronic kidney disease (CKD) frequently occurs

Other Causes of Acute Renal Failure in Pregnancy

Obstructive uropathy

- Oliguria or anuria in setting of moderate or severe dilatation of urinary collecting system, particularly on left, is suggestive of obstructive uropathy
- Etiologies:
 - Gravid uterus
 - Polyhydramnios
 - Kidney stones
 - Enlarged uterine fibroids
- If not at term, can be successfully treated with ureteral stenting

Nephrolithiasis

- Occurrence of urinary calculi is same as in nonpregnant women, despite increased urinary Ca^{2+} excretion in pregnancy secondary to increased intake and gastrointestinal Ca^{2+} absorption
- Women present with flank or abdominal pain plus microscopic or gross hematuria
- Ultrasonography is recommended procedure to avoid radiation risk
- Increased risk of UTI
- Ureteral stents can be placed safely in women unable to pass ureteral calculus spontaneously
- Extracorporeal shock wave lithotripsy, although not recommended, has been used

Antiphospholipid antibody disease

- Patients with anticardiolipin antibodies and lupus anticoagulant are at increased risk of fetal loss and worsening of renal function
- All pregnant women with lupus should be screened for anticardiolipin antibodies and lupus anticoagulant activity
- Treatment options include low-dose aspirin and heparin depending on levels and previous obstetric history, including early fetal loss and/or thrombosis

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PREGNANCY IN WOMEN WITH UNDERLYING RENAL DISEASE

Background

- Fertility is diminished in women with CKD
- Although rare (about 1.5%), women on long-term dialysis may become pregnant
- Most patients experience increased BP (25%), increased proteinuria (50%), and also may have decrease in GFR that can be either reversible or irreversible
- Pregnancy in women with CKD is associated with increased fetal loss, intrauterine growth retardation, and prematurity compared with that in women with normal renal function
 - Risk factors include hypertension, nephrotic syndrome, acute onset of renal disease, or history of previous renal disease
 - High maternal blood urea nitrogen levels can act as osmotic diuretic within fetal renal system beginning at about weeks

19 to 21 of gestation and can result in early labor and fetal loss

Progression of Underlying Renal Disease in Pregnancy

- Likelihood of progression depends more on severity of underlying disease rather than type
- Fetal outcome depends on level of renal function at beginning of pregnancy
- Underlying hypertension, proteinuria, and advanced CKD are risk factors for renal functional deterioration
- One third of women with moderate renal insufficiency are at risk of rapid decline in renal function after pregnancy compared to those with mild renal dysfunction (GFR > 70 mL/min [1.17 mL/s] or creatinine < 1.4 mg/dL [124 μmol/L])
- Hypertension during pregnancy with characteristic dilated afferent arteriole of glomerulus may play detrimental role in underlying disease due to high intraglomerular capillary pressure induced by transmission of systemic BP into glomerulus
- In some series membranoproliferative glomerulonephritis, focal glomerulosclerosis, and reflux nephropathy have been associated with poorer renal outcomes
- Autosomal dominant polycystic kidney disease (ADPKD): Women with renal insufficiency and hypertension are at increased risk for preeclampsia:
 - Screening for cerebral aneurysm should be considered before natural labor
 - Normotensive women with ADPKD usually have successful, uncomplicated pregnancies but hypertensive women with ADPKD are at high risk for fetal and maternal complications
- Systemic lupus erythematosus: Stable, inactive systemic lupus erythematosus for 6 months or more prior to conception is major determining factor of reduced risk of lupus flare during pregnancy:
 - Renal lupus flare during pregnancy presents with proteinuria, hypertension, and decrease in GFR mimicking preeclampsia making distinction difficult after twentieth gestational week; flare may be par-

ticularly severe if lupus presents during pregnancy

- Hypocomplementemia is more characteristic of lupus flare, but because complement levels rise in pregnancy this may be difficult to determine
- Lupus patients should be screened for anti-SSA because of its association with congenital heart block
- Cyclophosphamide in early pregnancy and mycophenolate mofetil are potentially teratogenic, but steroids and azathioprine can be used for treatment
- Diabetes: May cause pregnancy-induced exacerbations in proteinuria and hypertension without significant rate of decline in GFR; proteinuria usually decreases postpartum
- Women with sudden unexplained deterioration in renal function or symptomatic nephrotic syndrome can undergo renal biopsy if BP is well controlled and coagulation factors are normal
 - Biopsy after week 32 is not recommended

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MANAGEMENT OF RENAL FAILURE IN PREGNANCY

Dialysis

- Dialysis should be initiated in pregnancy when serum creatinine range is 3.5 to 5.0 mg/dL (309 to 442 μmol/L) or GFR below 20 mL/min (0.33 mL/s)

- Fetal outcome is improved with longer more frequent hemodialysis sessions; target is 20 h/wk
- These women typically have worsening hypertension, develop premature labor, and have small-for-gestational-age fetuses
- Anemia can be treated with erythropoietin, although higher doses are required
- Nutritional considerations and proper weight gain are essential for successful pregnancy with recommended weight gain of 0.3 to 0.5 kg/wk in second and third trimesters
- Avoid hypotension to lessen chance of fetal hypoperfusion
- Continuous ambulatory peritoneal dialysis or continuous cycling peritoneal dialysis with small volume and frequent exchanges also can be used successfully
- Peritoneal dialysis can avoid intermittent hypotension and anticoagulation but may increase risk of hypokalemia and peritonitis
- Spontaneous abortion rate is about 50% in women on dialysis, but in pregnancies that continue overall fetal survival has been reported as high as 71%
- Infant survival is higher when pregnancies are conceived before dialysis is initiated
- Hemodialysis should be performed almost daily to improve outcomes and prevent hypotension or significant metabolic shifts

PREGNANCY IN WOMEN AFTER RENAL TRANSPLANTATION

Background

- Restores fertility in women with end-stage renal disease
- Pregnancies typically are successful, especially in living-related donor transplant recipients
- Risks include miscarriages, therapeutic terminations, stillbirths, ectopic pregnancies, preterm births, low-birth-weight babies, and neonatal deaths

Guidelines for Considering Pregnancy in Renal Transplant Recipients

- Good general health for about 2 years after transplantation
- Stable allograft function (serum creatinine <2 mg/dL [177 μ mol/L], preferably <1.5 mg/dL [133 μ mol/L])

- No recent episodes of acute rejection or evidence of ongoing rejection
- Normal BP or minimal antihypertensive regimen (only 1 drug)
- Absence of or minimal proteinuria (<0.5 g/d)
- Normal allograft ultrasound (absence of pelvicalyceal distension)

Recommended Immunosuppression

- Prednisone <15 mg/d; steroids put women at risk for impaired glucose tolerance, hypertension, increased infection, ectopic pregnancy, or uterine rupture
- Azathioprine \leq 2 mg/kg/d
- Cyclosporine or tacrolimus at therapeutic levels; use of calcineurin inhibitor-based regimens can induce or exacerbate hypertension; breastfeeding while on cyclosporine is not recommended
- Mycophenolate mofetil and sirolimus are contraindicated and should be stopped 6 weeks before conception is attempted
- Methylprednisolone is drug of choice for acute rejection episodes during gestation

Risk of Pregnancy Complications in Transplant Recipients

- Hypertension increases with use of immunosuppressive medications, such as calcineurin inhibitors
- Rejection is not common but can be treated with steroids or antibodies
- Preeclampsia develops in about one third of pregnant women receiving kidney or pancreas-kidney transplants
- About half of all pregnancies end in preterm delivery due to hypertension
- Because of changing volumes of distribution and alterations in extracellular volume that accompany gestation, blood levels of immunosuppressive medications require more frequent monitoring
- Transplant recipients are at risk for infections that are dangerous for fetus (cytomegalovirus, toxoplasmosis, herpes)

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HYPERTENSIVE DISORDERS OF PREGNANCY

Background

- Hypertension in pregnancy defined as systolic BP > 140 mm Hg and diastolic BP > 90 mm Hg
- Most common medical complication of pregnancy (10% of pregnancies) with bimodal frequency: young primiparous (3 to 8 times more susceptible) as are older multiparous women
- Associated with significant increase in maternal as well as fetal mortality and morbidity
- Leading cause of premature birth
- Classification of hypertensive disorders of pregnancy:
 - Chronic hypertension
 - Preeclampsia–eclampsia
 - Preeclampsia superimposed on chronic hypertension
 - Gestational hypertension

Chronic Hypertension

- Hypertension (defined as ≥ 140 systolic, ≥ 90 diastolic) present before pregnancy or diagnosed before twentieth week of gestation
- May include hypertension diagnosed during pregnancy that does not resolve after delivery
- May be associated with nephrosclerosis with minimal proteinuria
- Increases risk of preeclampsia, abruptio placentae, intrauterine growth retardation, and second-trimester fetal death
- In stage 1 and 2 hypertension, women may require less or even no antihypertensives if BP is controlled

- Methyldopa is preferred agent for treatment of hypertension in pregnancy; in women who enter pregnancy with well-controlled BP, same regimen can be continued
- Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are contraindicated

Preeclampsia–Eclampsia

Background

- Systemic syndrome, unique to pregnancy, characterized by hypertension and proteinuria in primigravid, previously normotensive women, typically occurring after twentieth week of gestation and resolving with delivery
- Frequency of preeclampsia development in late pregnancy correlates linearly with increase in systolic pressure during first trimester
- Eclampsia is defined as occurrence of seizures, with no other etiology, in woman with preeclampsia

Pathophysiology

- Major features are uteroplacental hypoperfusion and fetal ischemia caused by inadequate vascularization of placenta essential for fetal–maternal circulation; there is inadequate embryonal trophoblastic cell invasion of uterine wall and spiral arteries secondary to failure of cytotrophoblast epithelial-to-endothelial transformation and subsequent lack of adhesion molecules, integrins, and cadherins
- Circulating antiangiogenic factors (increased levels of soluble fms-like tyrosine kinase-1 [sFlt1]) antagonize angiogenic and vasodilatory effects of vascular endothelial and placental growth factors; this may impair placentation by preventing angiogenesis and stimulate endothelial dysfunction, manifested as systemic vasoconstriction and coagulopathy
- Rising circulating levels of both soluble endoglin and ratios of sFlt1:placental growth factor recently have been reported as markers that may predict development of preeclampsia
- Increased RAAS activity coupled with lower density of angiotensin II receptors seen in

normal pregnancy is reversed, resulting in abnormally increased sensitivity to vasoconstrictor effects of angiotensin II

- Also characterized by increased synthesis of the vasoconstrictors endothelin and thromboxane (predisposes to platelet aggregation and intravascular clotting) and decreased synthesis of the vasodilators prostacyclin and nitric oxide (secondary to decreased plasma L-arginine from enhanced renal excretion)

Clinical features and epidemiology of preeclampsia

- Risk factors are presence of underlying essential hypertension, diabetes mellitus, family history of preeclampsia, renal disease, twin pregnancies, antiphospholipid syndrome, factor V Leiden deficiency, fetal hydrops, insulin resistance, and hydatidiform mole (first trimester occurrence)
- Usual sequence is weight gain with edema, particularly of hands and face, with increased BP and proteinuria of variable degree
- Renal blood flow and GFR fall with a decreased urate clearance and increased calcium reabsorption leading to hyperuricemia and hypocalciuria; GFR can decrease by 30% to 40% compared with normotensive controls, resulting in serum creatinine levels that may be 1.0 to 1.5 mg/dL (88 to 133 $\mu\text{mol/L}$); hyperuricemia may correlate with clinical severity of preeclampsia, with values commonly >4.0 mg/dL (354 $\mu\text{mol/L}$), which may be helpful in clinical monitoring
- Usually begins after the thirty-second week of pregnancy but may begin earlier in women with preexisting renal disease or hypertension (rarely before twentieth week of gestation); disease may be seen postpartum, with hypertension and seizures occurring within 24 to 48 hours after delivery
- When hypertension and proteinuria occur before 20 weeks, etiologies other than preeclampsia should be sought
- Usually resolves within 10 days after delivery
- Diastolic hypertension is prominent, with systolic pressure usually <160 mm Hg

- Systolic BP >200 mm Hg suggests preeclampsia superimposed on underlying chronic hypertension
- Pulmonary edema can occur in preeclampsia due to changes in pulmonary capillary permeability
- Hyperreflexia secondary to central nervous system excitability reflects severity of neurologic involvement
- When preeclampsia is more severe and occurs with hemolysis, elevated liver function tests, and low platelets, it is referred to as HELLP syndrome, which commonly is associated with severe hypertension and variable degrees of renal failure; HELLP syndrome also may be associated with pulmonary edema, ascites, and acute renal failure, usually occurring in the setting of disseminated intravascular coagulation

Pathology of preeclampsia

- Kidney biopsy shows swelling of glomerular endothelial cells with deposition of fibrinogen or fibrinogen derivatives within and under the endothelial cells, plus proliferation of lipid-containing mesangial cells called glomerular endotheliosis
- Lesions resolve as early as 4 weeks after delivery

Treatment of preeclampsia

- Recent trials have failed to demonstrate significant reduction in incidence of preeclampsia or improved outcomes with prophylactic administration of low-dose aspirin or calcium supplements in women at risk
- Bed rest is therapy of choice for mild disease (BP $<140/90$ mm Hg, proteinuria <500 mg/24 h, normal renal function, serum urate level <4.5 mg/100 mL, normal platelet count, and no evidence of hemolysis or hepatic involvement) until adequate fetal size and maturation
- Optimum level at which to treat hypertension has not been defined; first-line drugs are methyl dopa and labetalol; hydralazine can be used for more severe cases; diuretics should be avoided; do not use ACE inhibitors and ARBs

- Magnesium sulfate, a mild vasodilator, is drug of choice for treatment of preeclampsia in preventing seizures, especially postpartum; at serum levels of 4 to 6 mEq/L, magnesium increases prostacyclin synthesis, but increases risk of suppression of myoneuronal transmission and respiratory paralysis leading to maternal death
- Delivery is definitive treatment with any sign of worsening of disease (hyperreflexia, uncontrolled BP, or headaches) especially after thirty-second gestational week
- Presence of seizures (eclampsia) or HELLP syndrome is always indication for delivery

Preeclampsia With Superimposed Chronic Hypertension

- Difficult to distinguish from worsening hypertension in pregnancy
- Suspect in women with hypertension before 20 weeks of gestation who develop proteinuria or sudden increases in BP and/or proteinuria, thrombocytopenia, or liver-function test abnormalities
- More likely to occur in older patients; hypertension persists after delivery
- Risk of developing superimposed preeclampsia is between 20% and 40% in women with some form of underlying renal disease
- Hyperuricemia, proteinuria, or rise in serum creatinine during second half of pregnancy suggests preeclampsia

Gestational Hypertension

- Hypertension (defined as ≥ 140 systolic, ≥ 90 diastolic) that appears after midterm and is not associated with proteinuria
- Resolves after delivery; women are at risk for chronic hypertension
- Risk factors are multiparity, obesity, and positive family history of hypertension

Drug Therapy of Hypertension in Pregnancy

- Goal of therapy is to reduce fetal morbidity and mortality by preventing severe hypertension and/or preeclampsia
- Central alpha agonist, methyldopa, is first-line drug of choice for mild hypertension, although labetalol is effective alternative

- Hydralazine is second-line drug of choice, more commonly used in combination with methyldopa or beta-blocker, because of side effects; it also can be used for parenteral therapy
- Dihydropyridine calcium channel blockers can be used successfully and safely, but they and other calcium channel blockers may increase risk of hypotension if used with magnesium sulfate in preeclampsia
- Beta-blockers, particularly atenolol, may cause fetal bradycardia if used in first trimester but have been used safely later in pregnancy in several series
- Use of diuretics is controversial, although the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy does not recommend discontinuing if it is effectively controlling hypertension before pregnancy; diuretics should always be discontinued if patient develops superimposed preeclampsia, to prevent further volume depletion
- ACE inhibitors and ARBs are contraindicated in pregnancy and have been associated with increased fetal loss in animals and with fetal renal tubular dysplasia, oligohydramnios, perinatal acute renal failure, and other congenital anomalies; there is an increased risk of major congenital malformations to fetus in first-trimester exposure to ACE inhibitors

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