

PREGNANCY AND THE KIDNEY

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Disclosures

- None

Objectives

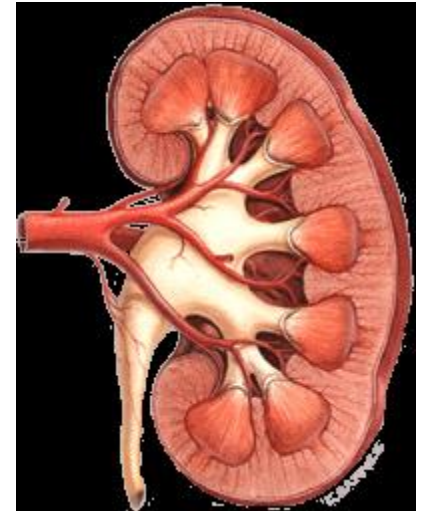
- Review renal physiology in normal pregnancy
- Identify the hypertensive disorders of pregnancy
- Review the new diagnosis and management strategies for preeclampsia
- Identify and review causes of Acute Kidney Injury in pregnancy
- Review chronic kidney disease in the pregnant patient

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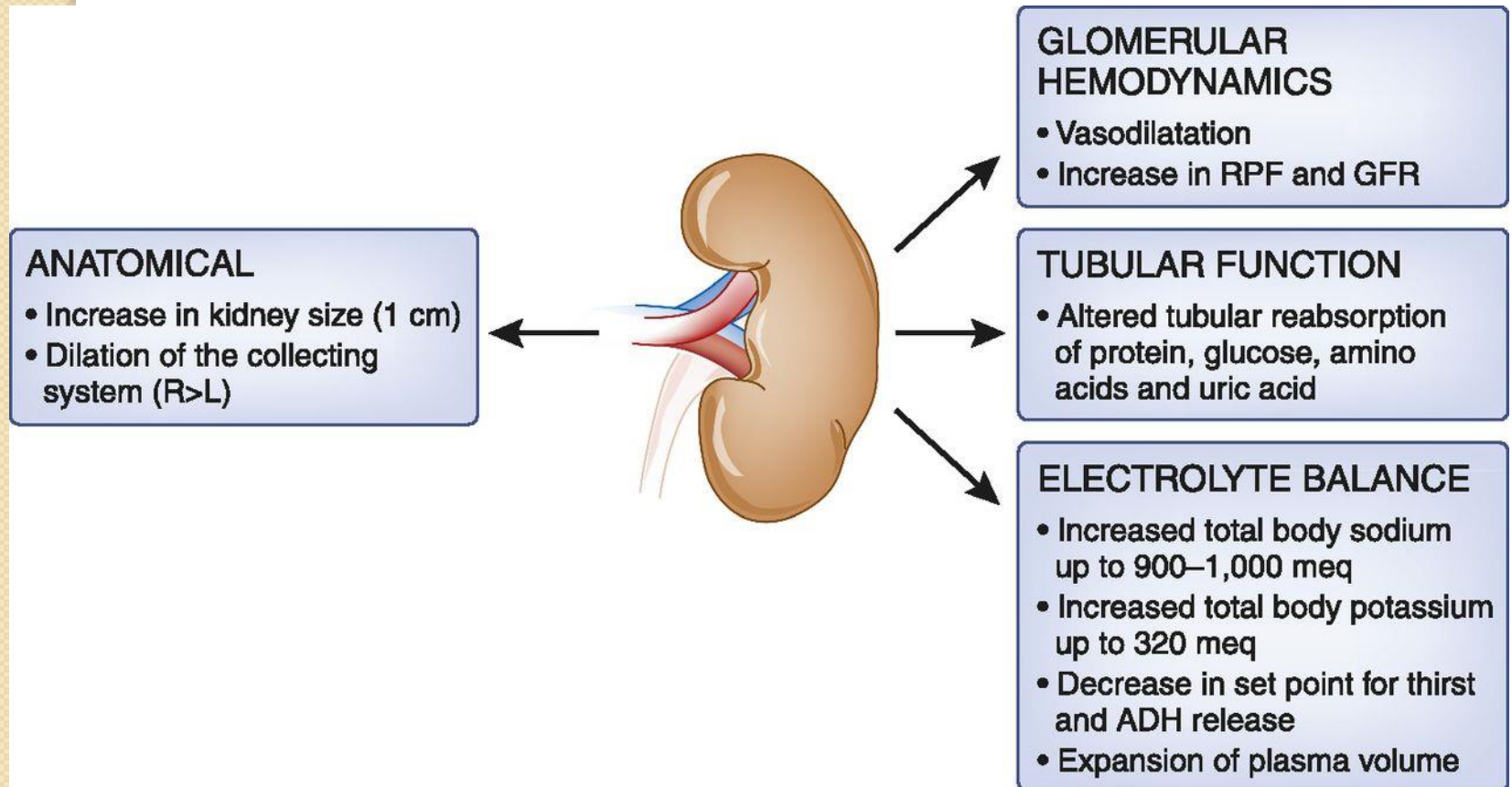
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Renal and urinary tract physiology in normal pregnancy

- Anatomic changes
- Renal hemodynamics
- Electrolytes and Acid-base changes
- Polyuria and Diabetes Insipidus



Summary of renal hemodynamic and metabolic adaptations to normal human pregnancy.



Ayodele Odutayo, and Michelle Hladunewich CJASN
2012;7:2073-2080

Anatomic changes

- Increased **renal size** — Both kidneys increase in size by 1 to 1.5 cm during pregnancy. Kidney volume increases by up to 30 percent, primarily due to an increase in renal vascular and interstitial volume.
 - There are no histological changes or changes in number of nephrons
- The **renal pelvises** and caliceal systems may be dilated as a result of progesterone effects and mechanical compression of the ureters

Renal and urinary tract physiology in normal pregnancy- **Anatomic changes**

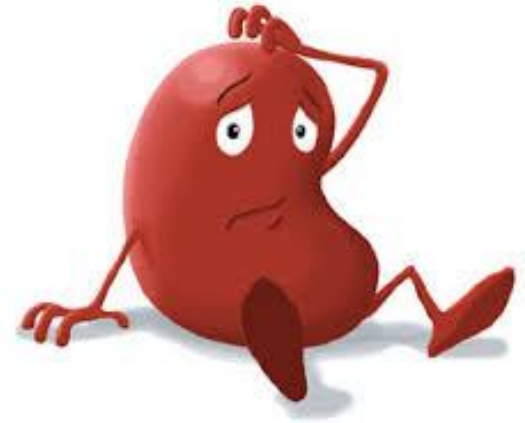
- **Ureters** — Dilatation of the ureters and renal pelvis (hydroureter and hydronephrosis) is more prominent on the right than the left and is seen in up to 80 percent of pregnant women.
- These changes can be visualized on ultrasound examination by the second trimester, and may not resolve until 6 to 12 weeks postpartum.

Anatomic changes

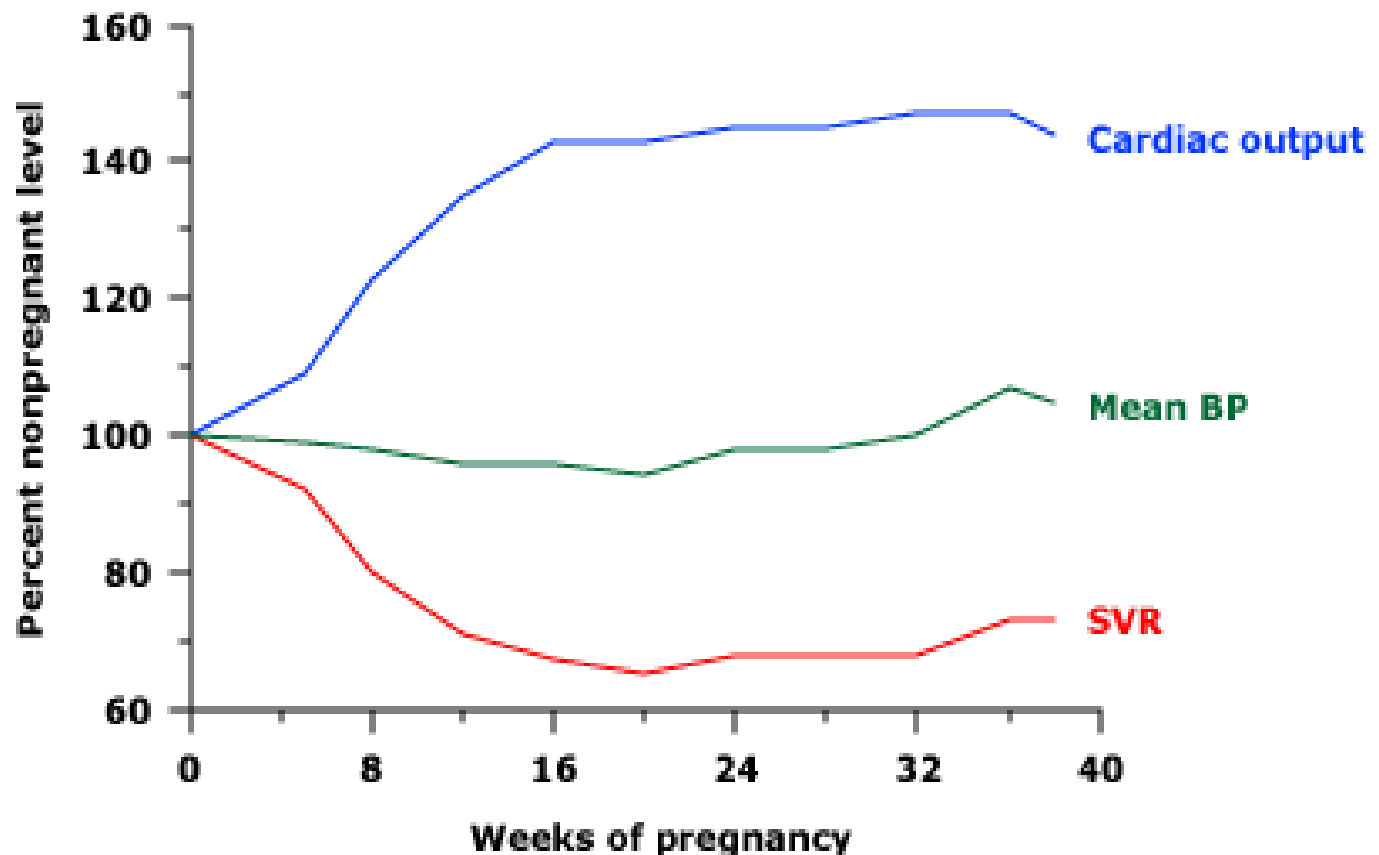
- **Bladder** — The bladder mucosa is edematous and hyperemic in pregnancy. Although progesterone-induced bladder wall relaxation may lead to increased capacity, the enlarging uterus displaces the bladder superiorly and anteriorly, and flattens it, which can decrease capacity. Studies of bladder capacity during pregnancy have yielded conflicting results.
- **Vesicoureteral reflux** — Bladder flaccidity may cause incompetence of the vesicoureteral valve. Combined with increased intravesical and decreased intraureteral pressure, results in intermittent vesicoureteral reflux

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Hemodynamic changes in normal pregnancy



Normal pregnancy is characterized by an increase in cardiac output, a reduction in systemic vascular resistance, and minimal change in mean blood pressure. These changes are associated with a 10 to 15 beat/min increase in heart rate.

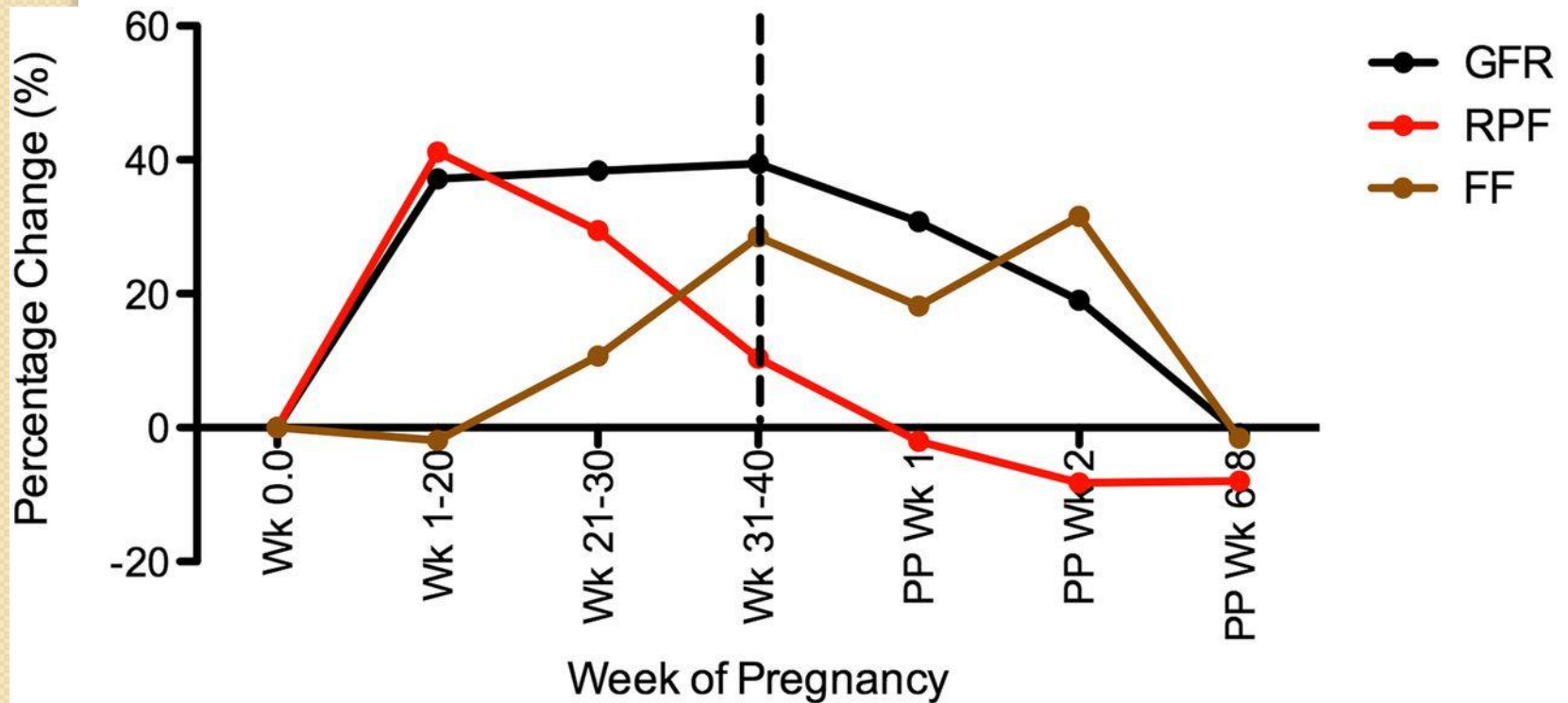
Renal Hemodynamics

- **Increase in GFR** — Glomerular filtration rate (GFR) rises markedly during pregnancy, primarily due to elevations in cardiac output and renal blood flow.
- The physiologic increase in GFR during pregnancy results in a decrease in serum creatinine concentration, which falls by an average of 0.4 mg/dL to a normal range of 0.4 to 0.8 mg/dL . Thus, a serum creatinine of 1.0 mg/dL , while normal in a non-pregnant individual, reflects renal impairment in a pregnant woman.

Renal Hemodynamics

- Creatinine may remain within the normal range despite a significantly reduced GFR. A small rise in serum creatinine usually reflects a marked reduction in renal function.
- Small fluctuations in serum creatinine may represent renal injury in pregnancy.

Percentage increment in GFR, RPF, and FF as measured by inulin or iothalamate and p-aminohippurate clearance methodology, respectively, at different time points during gestation.



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Renal and urinary tract physiology in normal pregnancy-

Electrolytes and Acid-base changes

- **Mild hyponatremia** — The plasma osmolality in normal pregnancy falls to a new set point of about 270 mosmol/kg, with a proportional decrease in plasma sodium concentration that is 4 to 5 meq/L below nonpregnancy levels
- The reduced set point for plasma osmolality has been attributed to pregnancy-related vasodilation and resultant arterial underfilling, which stimulates ADH release and thirst.

Electrolytes and Acid-base changes

- **Increased protein excretion** — Urinary protein excretion rises in normal pregnancy from the nonpregnant level of about 100 mg/day to about 180 to 200 mg/day in the third trimester.
- **Hypouricemia** — Serum uric acid declines in early pregnancy because of the rise in GFR, reaching a nadir of 2.0 to 3.0 mg/dL

Electrolytes and Acid-base changes

- **Decrease in serum anion gap** — For reasons that are not well understood, there appears to be a small reduction in serum anion gap in pregnant women.
- **Impaired tubular function** —
Pregnancy is associated with reductions in fractional reabsorption of glucose, amino acids, and uric acid.

Variable	Change in pregnancy
Kidney size	The kidney length increases by 1 cm to 1.5 cm, and kidney volume increases by up to 30%
Hydronephrosis	Physiological dilation of the urinary collecting system with hydronephrosis in up to 80% of women (Rt > Lt)
Renal blood flow	Increased by 80% above baseline
GFR	150–200 mL/min (rises 40–50% above baseline)
S. creatinine	Falls to 0.4 to 0.5 mg/dL ($n = 0.8$)*
Uric acid	Falls to 2.0 to 3.0 mg/dL ($n = 4–5$)
BUN	Falls to 8 to 10 mg/dL ($n = 13$)*
Sodium	Mild hyponatremia (Fall of 4–5 mol/L)
Osmolality	Falls to a new osmotic set point of about 270 mosm/kg

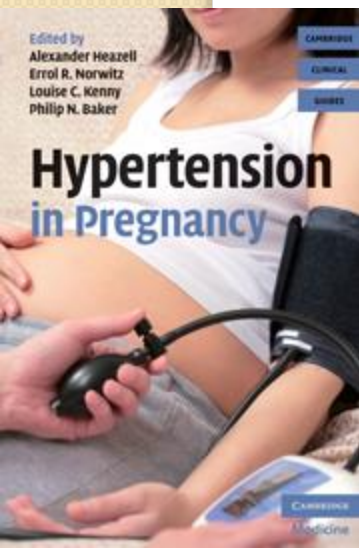
*Considered normal in a non-pregnant individual, reflects renal impairment in a pregnant woman.

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Identify the hypertensive disorders of pregnancy

- **Preeclampsia-eclampsia** – Preeclampsia refers to the syndrome of new onset of hypertension and either proteinuria or end-organ dysfunction most often after 20 weeks of gestation in a previously normotensive woman. Eclampsia is diagnosed when seizures have occurred.
- **Chronic (preexisting) hypertension** – Chronic hypertension is defined as systolic pressure ≥ 140 mmHg and/or diastolic pressure ≥ 90 mmHg that antedates pregnancy, is present before the 20th week of pregnancy, or persists longer than 12 weeks postpartum.
- **Preeclampsia-eclampsia superimposed upon chronic hypertension** – Preeclampsia-eclampsia superimposed upon chronic hypertension is diagnosed when a woman with chronic hypertension develops worsening hypertension with new onset proteinuria or other features of preeclampsia (eg, elevated liver enzymes, low platelet count).
- **Gestational hypertension** – Gestational hypertension refers to elevated blood pressure first detected after 20 weeks of gestation in the absence of proteinuria or other diagnostic features of preeclampsia.



Criteria for the diagnosis of preeclampsia

Systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg on two occasions at least four hours apart after 20 weeks of gestation in a previously normotensive patient
If systolic blood pressure is ≥ 160 mmHg or diastolic blood pressure is ≥ 110 mmHg, confirmation within minutes is sufficient
and
Proteinuria ≥ 0.3 grams in a 24-hour urine specimen or protein (mg/dL)/creatinine (mg/dL) ratio ≥ 0.3
Dipstick 1+ if a quantitative measurement is unavailable
In patients with new-onset hypertension without proteinuria, the new onset of any of the following is diagnostic of preeclampsia:
Platelet count $< 100,000$ /microliter
Serum creatinine > 1.1 mg/dL or doubling of serum creatinine in the absence of other renal disease
Liver transaminases at least twice the normal concentrations
Pulmonary edema
Cerebral or visual symptoms

Adapted from: Hypertension in pregnancy: Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013; 122:1122.

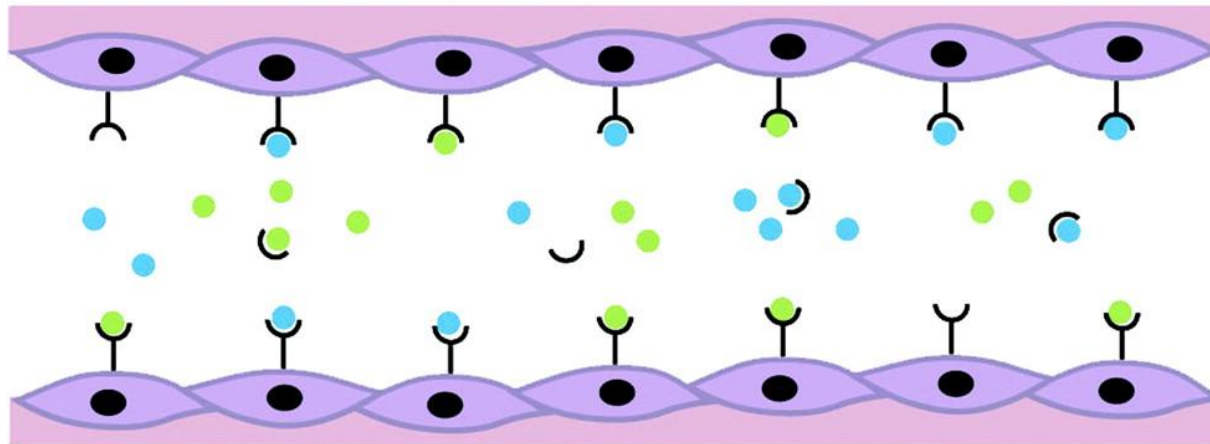
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Brief pathophysiology of preeclampsia

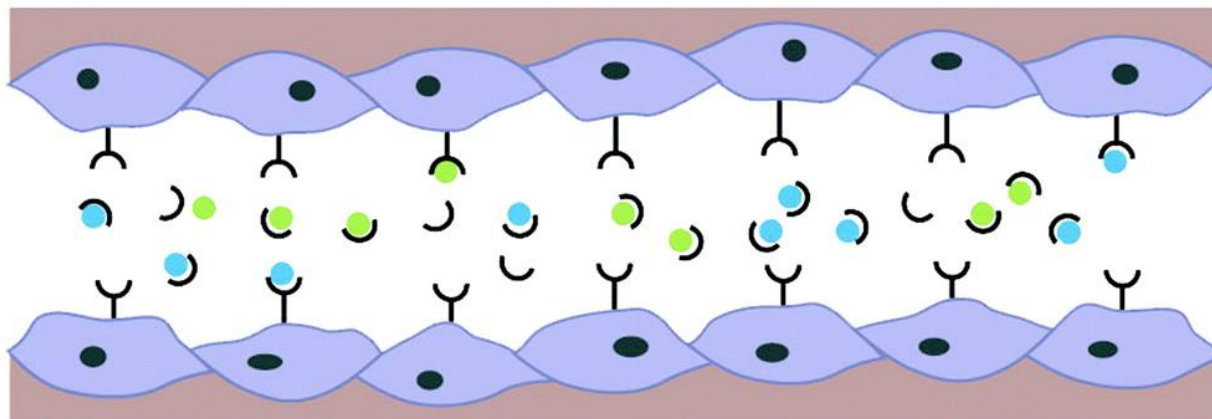
- In preeclampsia, there is pathologic evidence of placental ischemia
- Incomplete spiral artery remodeling and subsequent placental ischemia lead to the release of factors into the maternal circulation that produce endothelial dysfunction. (Htn 2005)
- Excess placental production of soluble FMS like tyrosine kinase I (sFlt-I) contributes to endothelial dysfunction in preeclampsia. (Circulation 2011)
- sFlt-I antagonizes VEGF and PlGF by binding to them in circulation

Normal Pregnancy



Vasodilation

Preeclampsia



Vasoconstriction



FLT-1



VEGF



PIGF



sFLT-1

A brief background

- In 2003, it was shown that preeclampsia is associated with elevated levels of sFlt-1, and that intravenous injection into pregnant mice causes preeclampsia. (J Clin Invest 2003)
- Subsequently in 2004, it was shown that sFlt-1 was elevated and women with preeclampsia, and levels were elevated weeks before clinical disease.
- Studies with biologic agents, and existing drugs including statins and beta blockers are underway to assess efficacy by decreasing sFlt-1 levels

Review the new diagnosis and management strategies for preeclampsia

- March 2016, JASN, Thadhani *et al.*
- Open label pilot study looking at the safety and potential efficacy of therapeutic apheresis to remove circulating soluble FMS-like tyrosine kinase-1 (sFlt-1) in 11 pregnant women.



Potential efficacy of apheresis for preeclampsia

March 2016, JASN, Thadhani *et al.*

- This study aimed to assess if reducing serum concentration of sFlt-1 using apheresis could limit disease progression?
- Apheresis was performed using negatively charged columns to remove positive recharged sFlt-1



Potential efficacy of apheresis for preeclampsia

March 2016, Thadhani *et al.*

- 11 pregnant women with early preeclampsia diagnosed between 23 and 32 weeks gestation were studied.
- Women served their own controls for physiologic changes associated with apheresis
- 22 women with preterm preeclampsia not treated with apheresis; and 22 women who delivered preterm for reasons other than preeclampsia were selected as controls

Potential efficacy of apheresis for preeclampsia

March 2016, Thadhani *et al.*

- Mean reduction in sFlt-1 concentrations was 18%
- Woman treated with apheresis experienced a 44% reduction in urinary protein to creatinine ratio.
- Delivery was delayed in women treated with apheresis from 8 to 15 days; compared with a delay in the untreated group of 3 days.
- In the neonates, oxygen therapy was reduced from 11 +/- 5 days in the control group, to 2 +/- 2 days in the apheresis group

Accompanying Editorial

- ‘This study reports a much-needed novel intervention in the management of preterm preeclampsia’
- ‘Apheresis may be an important component of a broader intervention of synergistic agents, and does not seem to be associated with significant complications’
- ‘Randomized trial with a control group is clearly indicated’

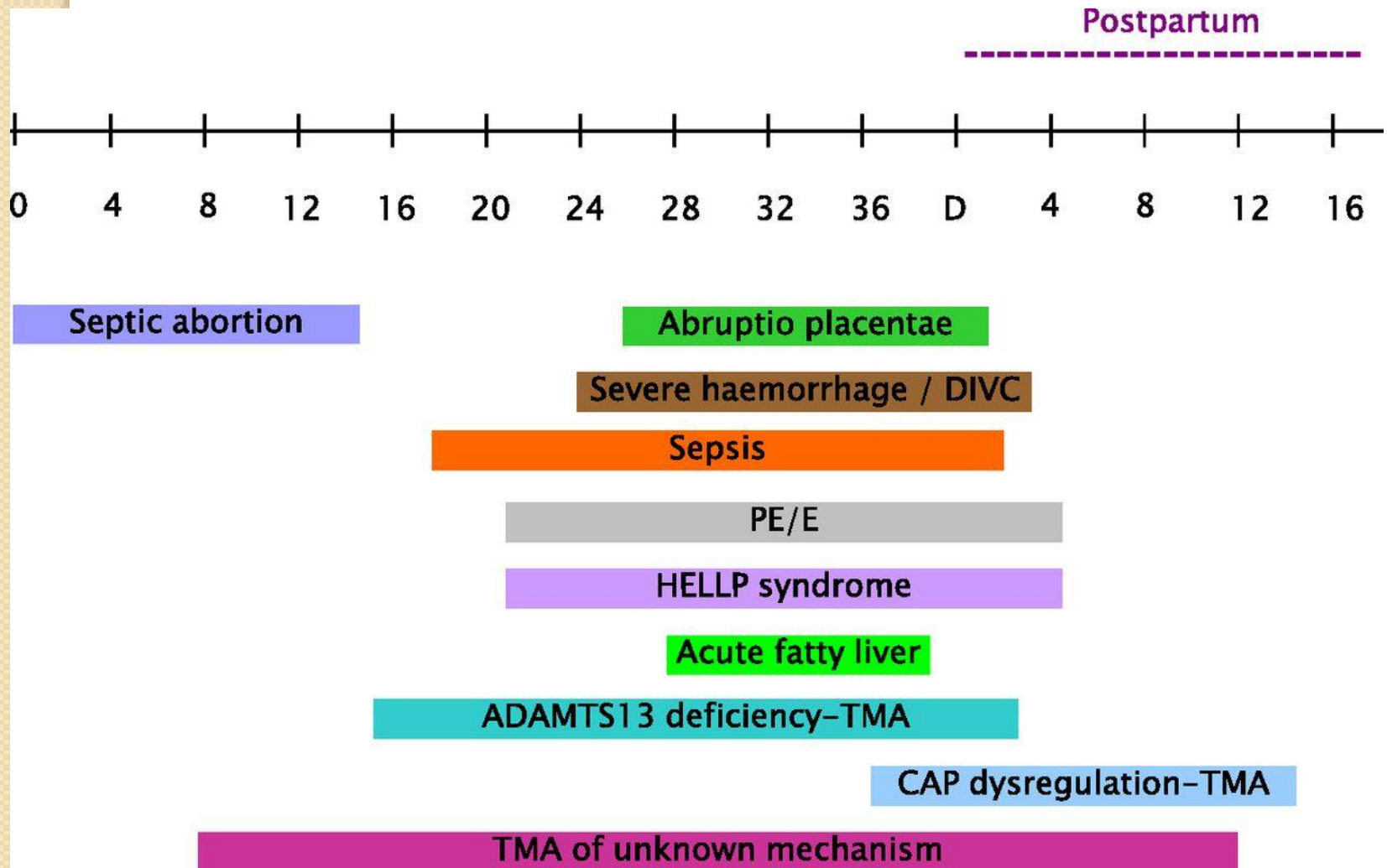
Biomarkers for prediction of Preeclampsia

- Low sFlt-1/PlGF ratio of <38 – very high negative predictive value for preeclampsia- 99.3% (Am J OBGN, 2012)
- Although not considered robust predictors of preeclampsia when measured in early pregnancy, sFlt1 and PlGF are promising markers for diagnosis and risk stratification and woman presenting later in gestation with suspected preeclampsia. Studies are currently underway.

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Main causes of pregnancy-related AKI depending on their predominant timing of occurrence during pregnancy.



Fadi Fakhouri et al. CJASN 2012;7:2100-2106

Identify and review causes of Acute Kidney Injury in pregnancy

- First 20 weeks:
- **Prerenal** disease due to hyperemesis gravidarum
- Acute tubular necrosis (**ATN**) resulting from a septic abortion
- AKI associated infection and/or sepsis
- After 20 weeks:
- Severe **preeclampsia**, with or without HELLP syndrome
- Thrombotic thrombocytopenic purpura (**TTP**, acquired or hereditary) or complement-mediated hemolytic uremic syndrome (HUS)
- Acute fatty liver of pregnancy (**AFLP**)
- **ATN** or acute cortical necrosis associated with hemorrhage (placenta previa, placenta abruption)

Causes of Acute Kidney Injury in pregnancy- TMA

- Pregnancy may trigger either TTP or HUS
- **TTP** is caused by an acquired or constitutional deficiency of activity of ADAMTS13, a Von Willebrand factor- cleaving protease. Pregnancy has been shown to induce the onset or relapse of ADAMTS13 deficiency-related TTP.
- a**HUS** is caused by mutations in genes that encode complement-regulatory proteins, which result in uncontrolled complement activation. Pregnancy is a well-recognized trigger for episodes of HUS in patients with these mutations.

Causes of Acute Kidney Injury in pregnancy - AFLP

- **Acute fatty liver of pregnancy** — Acute fatty liver (fatty infiltration of hepatocytes without inflammation or necrosis) is a rare complication of pregnancy that is associated with AKI in up to 60 percent of cases
- Patients present in the third trimester with clinical signs consistent with preeclampsia (hypertension, thrombocytopenia) but also have hypoglycemia, hypofibrinogenemia, liver function test abnormalities with hyperbilirubinemia, and a prolonged partial thromboplastin time (PTT)

Causes of Acute Kidney Injury in pregnancy

- **Renal cortical necrosis** — Renal cortical necrosis used to be an important cause of AKI associated with catastrophic obstetric emergencies such as placental abruption with massive hemorrhage or amniotic fluid embolism

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Review chronic kidney disease in the pregnant patient

- Effect of pregnancy on CKD
- Effect of CKD on pregnancy

Estimating GFR in pregnancy

- GFR equations (like MDRD) underestimate GFR by 20-25% in pregnant women
- 24 urine collections could be more accurate- cumbersome and there is risk of urinary retention in pregnant women
- Cystatin C- may be released by the placenta – making it less accurate
- Serum Creatinine – most practical for now.

Effect of pregnancy on CKD

- Pregnancy associated loss of renal function increases with worsening baseline CKD
- An elevated plasma creatinine concentration (above 1.5 mg/dL), proteinuria and hypertension are the major risk factors for permanent exacerbation of underlying renal disease.
- It has been proposed that the type of disease also may be important as accelerated progression may be more likely in membranoproliferative glomerulonephritis, focal segmental glomerulosclerosis, and reflux nephropathy.
- Women with vesicoureteral reflux may be at increased risk for urinary tract infection.

Effect of CKD on pregnancy

- Maternal Outcomes
- Fetal Outcomes

Effect of CKD on pregnancy

- Pregnancy complications – Preterm delivery (<37 weeks gestation), SGA, cesarean section, and need for neonatal intensive care - are more common in CKD than the general population
- Rates increase with each CKD stage

CKD and Pregnancy

- Pregnancy in mild to moderate CKD
- **Pregnancy in a dialysis patient**
- Pregnancy in a transplant patient

Pregnancy in dialysis patients

- Infertility is common in women with end-stage renal disease secondary to dysfunction of the hypothalamic-pituitary-gonadal axis.
- Pregnancy is rare among women with ESRD. More intensive hemodialysis may improve the likelihood of conception in these women.
- Women on dialysis have a 10-fold lower probability of delivering a liveborn baby than those with renal transplantation, who in turn, have a tenfold lower probability of delivering a liveborn baby compared to the general population. (NDT 2014)

Pregnancy in dialysis patients

- Live birth rates range from about 50% to 80% in various studies
- Of all live births, about 85% of the babies are premature; and there are higher rates of maternal complications including preeclampsia, polyhydramnios, and cesarean section.

Pregnancy in dialysis patients

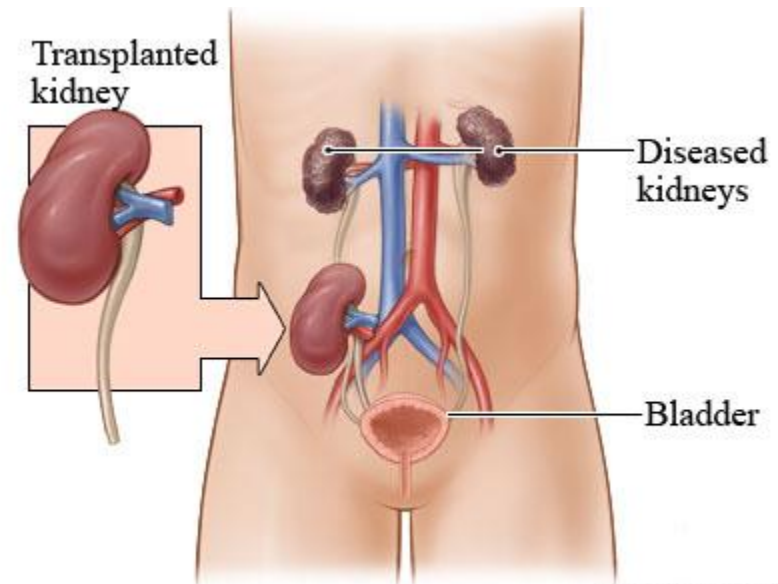
- Intensive dialysis of more than 36 hours per week is associated with higher rates of live birth and lower risk of severe prematurity compared with less intense dialysis in pregnant women (JASN 2014)
 - Av weekly dialysis – 43 vs 17 hrs
 - Live Births - 82% vs 53%
 - Av duration of pregnancy – 36 vs 27 weeks

Management of the pregnant dialysis patient

Intensification of dialysis
Blood urea nitrogen should be maintained below 50 mg/dL (17 mmol/L) to avoid polyhydramnios.
If hemodialysis is used, intensification of the regimen should be considered; five to seven sessions per week is likely to provide more optimal control of uremia and better fecal outcomes. The prescription should include bicarbonate buffer, minimal heparinization and slow-rate ultrafiltration, in order to avoid dialysis hypotension and volume contraction.
If peritoneal dialysis is used, the exchange volumes should be decreased (eg, to 1.5 liters) and the frequency should be increased.
Adequate supply of calories and protein
Protein intake should be 1 g/kg per day plus an additional 20 g/day for fetal growth.
Diet should be supplemented with water soluble vitamins and zinc.
Antihypertensive regimen
Diuretics, ACE inhibitors, angiotensin receptor blockers (ARBs) are avoided. Acceptable antihypertensives include labetalol, Nifedipine XL, methyldopa, and metoprolol.
The diastolic blood pressure should range between 80 and 90 mmHg.
Correction of anemia
Erythropoietin should be given to maintain a hemoglobin level of at least 10 to 11 g/dL.
Iron and folic acid should be supplemented.
Avoidance of metabolic acidosis
Prevention of hypocalcemia
Oral calcium carbonate should be administered.
Hypercalcemia should be avoided at the end of hemodialysis treatment.
Treatment of premature labor
The use of beta agonists as first-line drug treatment is preferred.
Nonsteroidal anti-inflammatory drugs are used with great caution and only for a limited duration.
Reinforced fetal monitoring as soon as viability is reached

CKD and Pregnancy

- Pregnancy in mild to moderate CKD
- Pregnancy in a dialysis patient
- **Pregnancy in a transplant patient**



Pregnancy in a transplant patient

- Fertility generally returns after renal transplantation.
- However, the rates of both pregnancy and successful pregnancy (ie, resulting in a live birth) remain far lower than in the general population.
- The best data come from a longitudinal cohort of 30,078 female transplant recipients aged 15 to 45 years (2009):
- During the first three posttransplant years, the unadjusted pregnancy rate was 33 per 1000 women, compared with more than 100 per 1000 women in the general population.

Pregnancy in a transplant patient

- Women are usually advised to wait at least one year after living, related-donor transplantation and two years after deceased transplantation to avoid complications arising from immunotherapy and rejection (AST- AJTrans, 2005)
- In addition, the renal allograft should be functioning well, with a stable serum creatinine level <1.5 mg/dL and urinary protein excretion <500 mg/day

Pregnancy in a transplant patient

Immunosuppressive medications:

- Cyclosporin – safety not established, usually continued
- Tacrolimus- safety not established, usually continued
- **Mycophenolate** – contraindicated
 - Birth defects rate 23%, NTPR - Clini Trans 2010
- Azathioprine- safety not established, usually continued
- Sirolimus - contraindicated



Allograft Rejection during Pregnancy

- Uncommon
- Timing and nature of rejection episodes unknown
- Allograft biopsies during pregnancy have been done with no complications
- Optimal management unknown; high dose steroids usually used.

- Thank you!





Pregnancy in mild to moderate CKD

- **Fetal outcomes** are also worse in women with CKD.
- In one meta-analysis, the frequency of preterm birth (<37 weeks) was significantly higher among women with renal impairment (13 versus 6 percent)
- In a second meta-analysis, compared with women without CKD, the risks of pregnancy failure, premature birth, cesarean section, and small for gestational age/low birth weight were higher in CKD patients, with ORs of 1.8, 5.72, 2.67, and 4.85, respectively.

Pregnancy in mild to moderate CKD

- CKD is associated with higher rates of adverse **maternal outcomes**.
- In a meta-analysis of 13 cohort studies, pregnant women with preexisting renal impairment were significantly more likely to develop gestational hypertension, preeclampsia, eclampsia, or to die (12 versus 2 percent).
- Maternal mortality was more frequent in those with CKD (4 versus 1 percent), although this was not statistically significant.
- In a second meta-analysis of nine studies, the preeclampsia odds ratio (OR) was 10.36 in women with CKD compared with women without CKD.

Renal and urinary tract physiology in normal pregnancy-

Electrolytes and Acid-base changes

- **Transient DI of pregnancy** — Between the eighth week and mid pregnancy, the metabolic clearance of ADH increases four- to six-fold because of an increase in vasopressinase (also known as oxytocinase), which is produced by the placenta. In most pregnant women, plasma concentrations of ADH remain in the normal range, despite increased metabolic clearance, because of a compensatory increase in ADH production by the pituitary gland.
- A small number of pregnant women, however, develop transient DI, which is underdiagnosed because polyuria is often considered normal during pregnancy. The possibility of this disorder should be considered in women with intense polydipsia and polyuria in the third trimester.
- Hyponatremia can occur if water intake is restricted, as in the peripartum period. If unrecognized and untreated, hyponatremia can result in serious neurologic consequences in both the mother and fetus.

Findings which increase the certainty of the diagnosis of preeclampsia

Systolic blood pressure of 160 mm Hg or more
Diastolic blood pressure of 110 mm Hg or more
Proteinuria occurring for the first time during pregnancy, especially if 2.0 g or more in 24 hours. A qualitative result of 2+ or 3+ is also suggestive.
Serum creatinine greater than 1.2 mg/dL (106 mmol/L)
Platelet count less than 100,000 cells per cubic millimeter
Evidence of microangiopathic hemolytic anemia (eg, elevated lactic acid dehydrogenase)
Elevated liver enzymes (eg, alanine aminotransferase or aspartate aminotransferase)
Persistent headache or other cerebral or visual disturbances
Persistent epigastric pain

Working group report on high blood pressure in pregnancy. National Institutes of Health, Washington, DC 2000.