

Renal Complications of Pregnancy

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Case #1

- A 28 year-old female, admitted at 36 weeks gestation for persistent hypertension (BP 190/100 mmHg) and worsening proteinuria
- Emergent c-section with delivery of a baby who weighed 4 lbs 8 oz
- Post-operatively she remained hypertensive (BP 180/100 mmHg) with complaints of headache, blurry vision, nausea, vomiting and abdominal pain
- She was started on a labetalol drip and was loaded with IV Mg and started on a Mg infusion
- She subsequently had 2 generalized seizures and was transferred to the ICU

Case #1

- Laboratory values:
 - Hgb 7.6, platelets 25,000
 - AST 705, ALT 464, LDH 750
 - BUN/Scr 59/4.9 mg/dl
- Imaging studies:
 - CT abdomen: atelectasis with bilateral pleural effusions, ascites and periportal edema in the liver.
 - MRI of the brain: ventriculomegaly, compression of the aqueduct and 4th ventricle with imminent tonsillar herniation, extensive areas of abnormal T2 prolongation and edema noted within the cerebellum and occipital lobes

Case #1

- Treatment:
 - Emergent placement of external ventricular drain by neurosurgery
 - IV corticosteroids and plasma exchange
- Outcome:
 - Pt improved dramatically and was transferred out of the ICU 3 days later with no neurologic deficits.
 - Labs obtained 2 weeks after discharge were all within normal limits.

Renal Anatomic Changes in Pregnancy

- Increased kidney volume
~70%
- Increase renal length 1.0-1.5 cm (by 20th week)
- “Physiologic hydronephrosis of pregnancy”
 - R>L (up to 89 mm)
 - 80% show hydronephrosis by the 3rd trimester
 - 200-300 ml dead space in ureters
- Decreased ureteral peristalsis
→ inc. PGE₂ → urinary stasis



Physiologic Changes of Pregnancy

| Variable | Change | Rate |
|----------------|-----------|------------|
| Plasma volume | Increases | 30-50% |
| RBC mass | Increases | 20-30% |
| Cardiac output | Increases | 30-50% |
| Stroke volume | Increases | 0-30% |
| Heart rate | Increases | 10-20% |
| Systolic BP | Decreases | 0-5 mmHg |
| Diastolic BP | Decreases | 10-20 mmHg |
| SVR | Decreases | 15% |
| CVP/PCWP | Unchanged | ----- |

Renal Hemodynamic Changes of Pregnancy

- GFR increases
 - 25% by 4 weeks, 40-50% by the end of the 1st trimester
 - SCr falls to 0.4-0.5 mg/dL
- RPF increases due to ↑cardiac output (CO), ↓renal vascular resistance
- Renal vasodilation of afferent and efferent arterioles
 - Mediated by hCG → relaxin → increased nitric oxide (NO)

Consequences of Renal Physiologic Changes

- Physiologic hydronephrosis of pregnancy
- Risk of ascending urinary infections
- Increase in GFR with normal S_{Cr} 0.4-0.5 mg/dL
- Hemodilution of pregnancy
- Respiratory alkalosis, compensated
- Hyponatremia, hypo-osmolality
- Edema common
- Lower plasma uric acid (2.5-3.0 mg/dL)
- Glucosuria

Renal Complications of Pregnancy

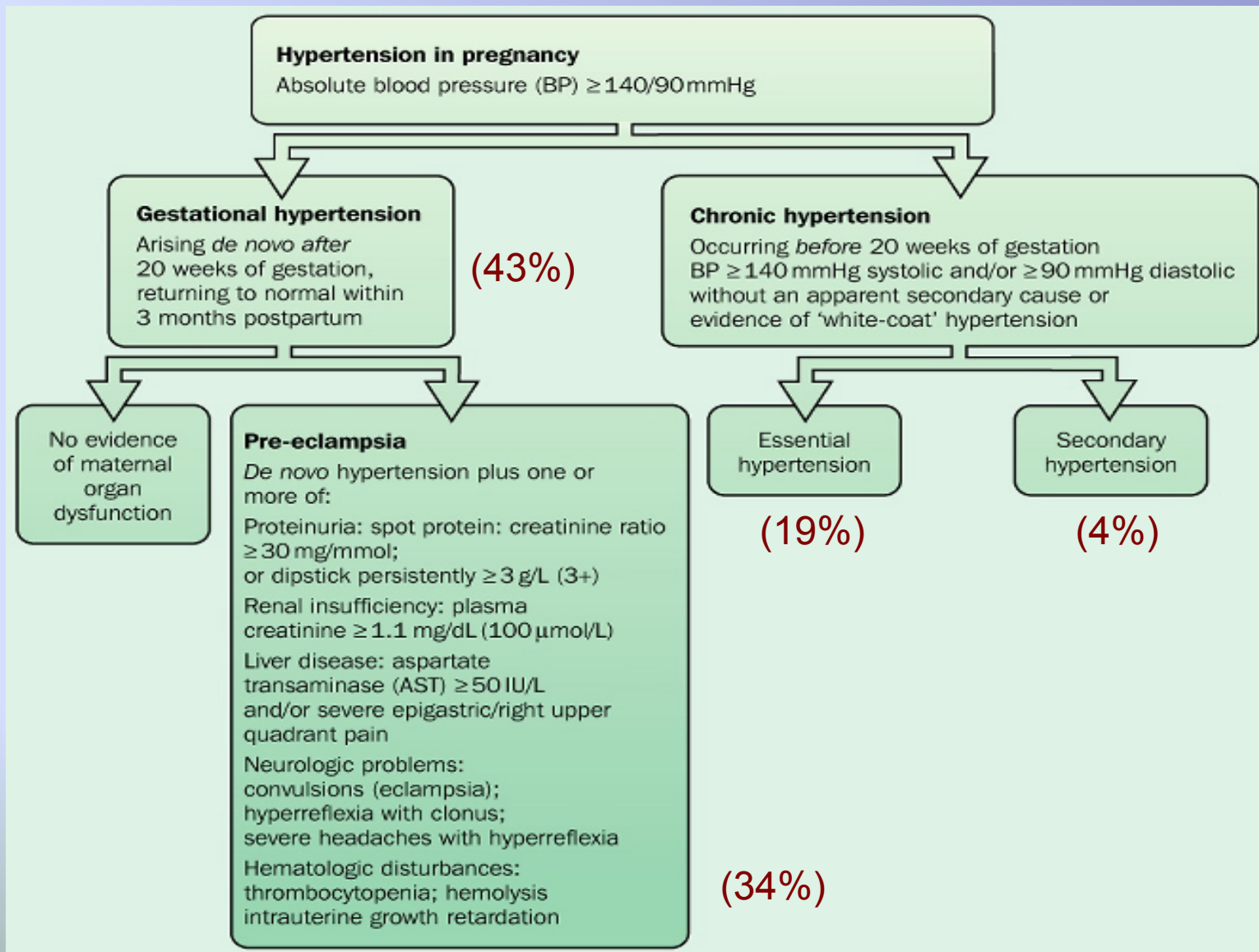
- Hypertension
 - Gestational hypertension
 - Pre-eclampsia/Eclampsia
 - Pre-eclampsia superimposed on chronic hypertension
 - Chronic hypertension
- Urinary tract infections
- Acute renal failure
- Renal disease-pregnancy
- ESRD-pregnancy
- Transplant-pregnancy

Hypertension in Pregnancy

- Definition: $\geq 140/90$ mmHg
- Complicates $\sim 10-12\%$ of all pregnancies
- Bimodal frequency
 - young women + 1st pregnancy, older multiparous women
- Increase in SBP associated with linear increase in pre-eclampsia frequency
- Increased fetal risk: 3-6X stillbirth, 5-15X IUGR, prematurity
- Increased perinatal mortality
 - MAP > 82 mmHg (mid-pregnancy)
 - MAP > 92 mmHg (beginning of 3rd trimester)

MAP = 93 mmHg = 120/80 mmHg

Classification of HTN in Pregnancy



Underlying Chronic Hypertensive Disorders

- Essential familial hypertension
- Renovascular hypertension
- Primary aldosteronism
- Pheochromocytoma
- Thyrotoxicosis
- Glomerulonephritis
- Chronic kidney disease
- Lupus erythematosus

Characteristics of Pre-Eclampsia

- Characterized by **HTN, proteinuria and edema**
- Occurring >20 weeks gestation, usually after 32 weeks
 - Earlier than 32 wks if pre-existing HTN or renal disease
 - Hydatiform mole: 1st trimester
- Post-partum with HTN and seizures within 24-48 hrs (up to 7 days) after delivery
- Resolves within 10 days of delivery

Risk Factors for Pre-eclampsia

- First pregnancy
- Multiple gestations
- Pre-eclampsia in a previous pregnancy
- FHx of pre-eclampsia
- Age > 35 yo
- Thrombophilia: Factor V Leiden, anti-phospholipid antibody
- Chronic renal disease
- Underlying essential HTN
- Vascular or connective tissue disease
- Metabolic syndrome: obesity, insulin resistance, dyslipidemia
- Angiotensinogen gene T235

Multi-Systemic Nature of Pre-Eclampsia

- CNS

- Headache
- Visual disturbances
- Nausea, vomiting
- Hyperreflexia
- Apprehension
- Seizures
- Stroke

- Gastrointestinal

- Epigastric pain (pancreatitis, hepatic ischemia, periportal necrosis, subcapsular hematoma / rupture)
- **HELLP syndrome:** pre-eclampsia, hemolysis, elevated liver enzymes, low platelet count
- Hepatitis: jaundice from hemolysis, elevated liver
- **Acute Fatty Liver of Pregnancy:** extreme manifestation of pre-eclampsia

Multi-Systemic Nature of Pre-Eclampsia

- Pulmonary

- Pulmonary edema due to LV failure

- CV

- Decreased CO
- Increased afterload
- Decreased intravascular volume

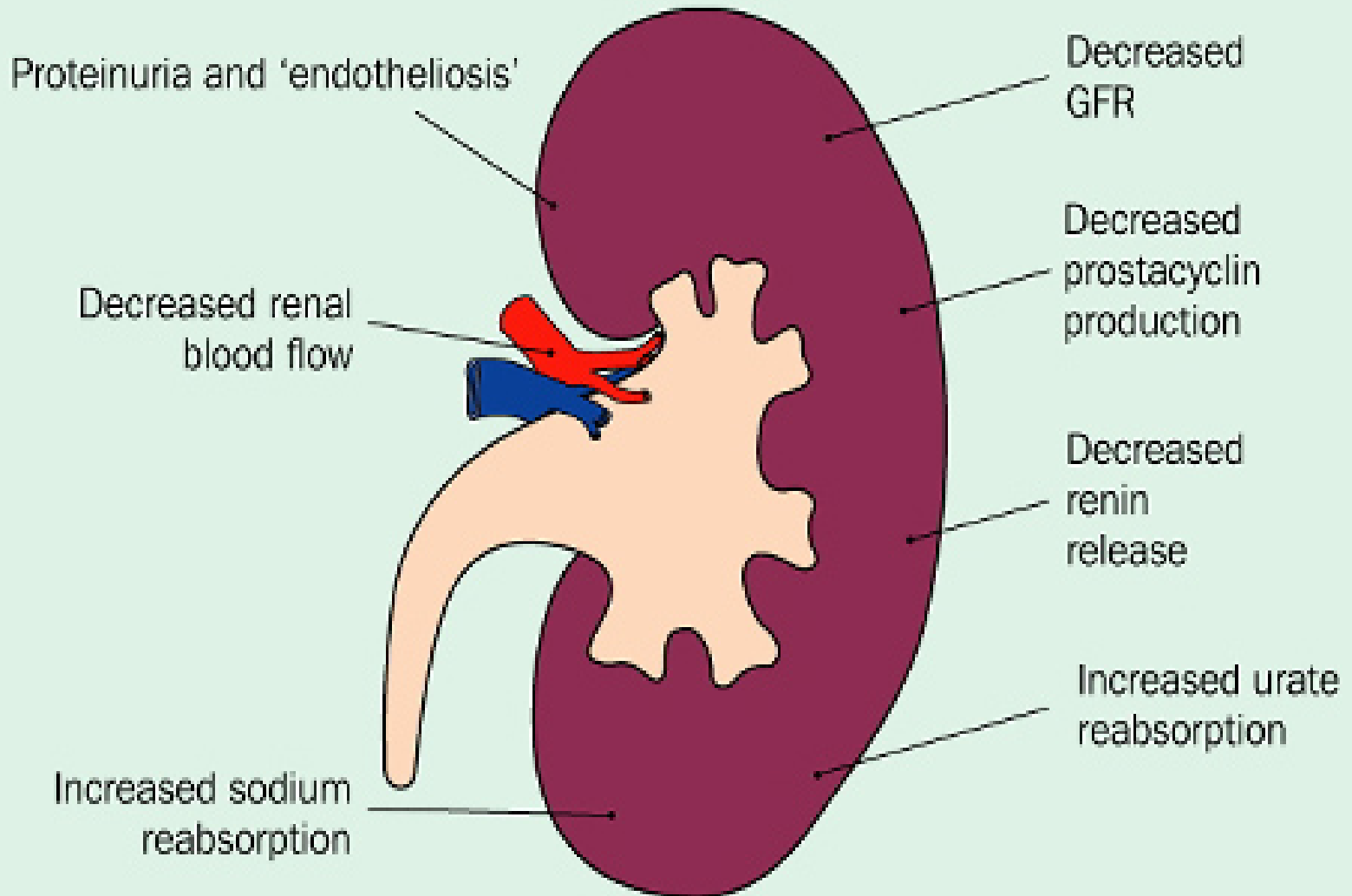
- Heme

- Thrombocytopenia
- Microangiopathic hemolytic anemia
- Bleeding / DIC

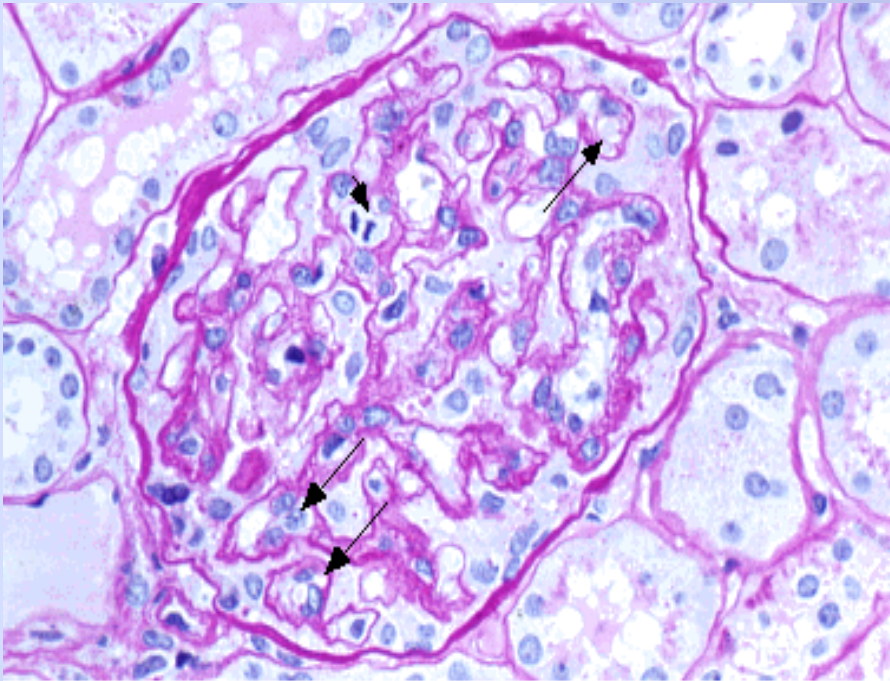
- Renal

- ARF secondary to ATN
- Proteinuria ranging from minimal (>0.5 g/d) to overt nephrotic syndrome
- Hyperuricemia
- Hypocalcemia

Renal Abnormalities in Pre-Eclampsia



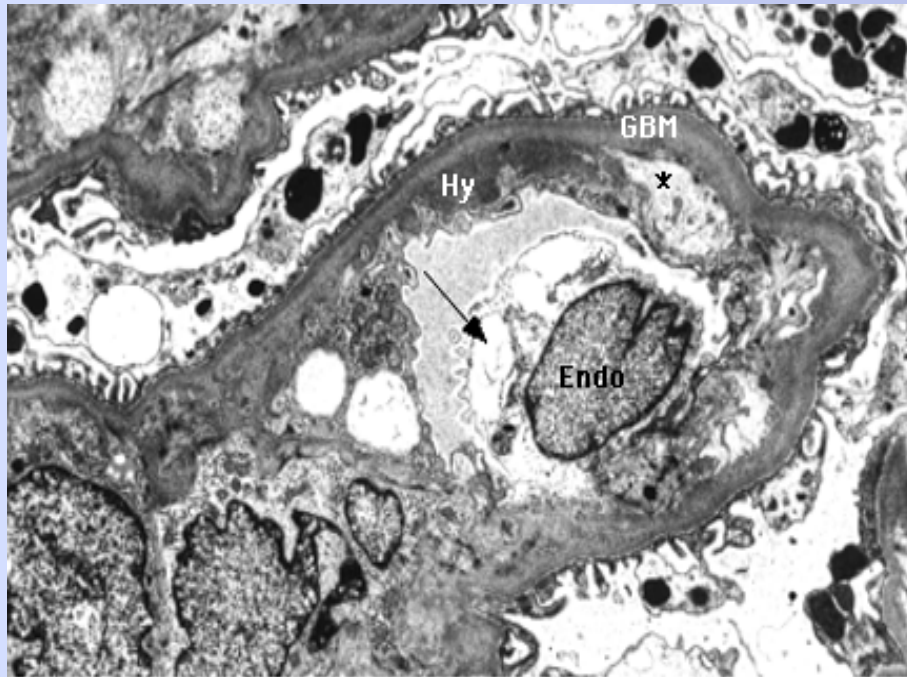
Renal Abnormalities in Pre-Eclampsia



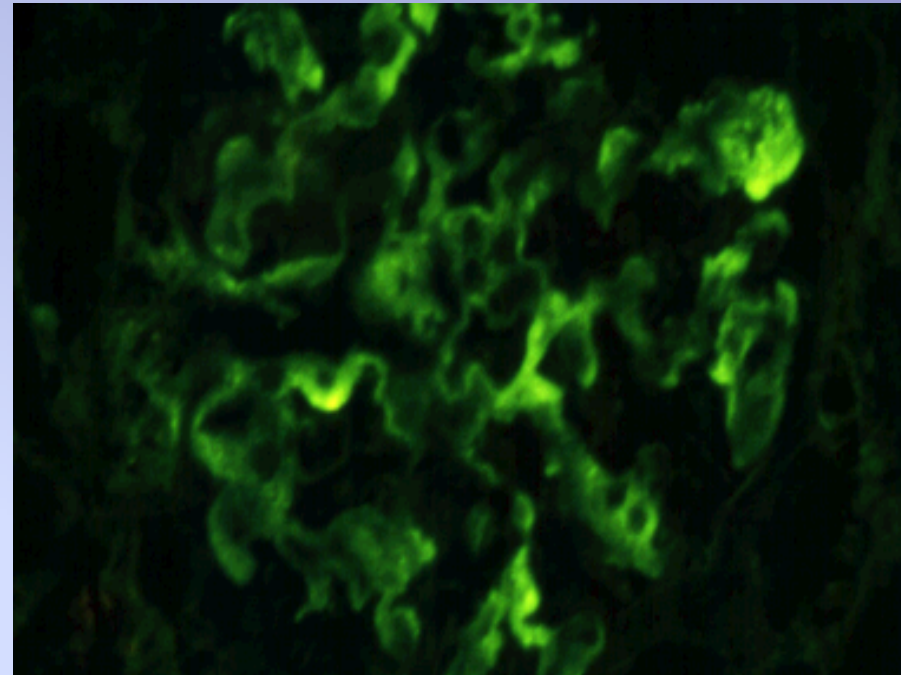
Preeclampsia Light micrograph in preeclampsia showing glomerular endotheliosis. The primary changes are swelling of damaged endothelial cells, leading to partial closure of many of the capillary lumens (large arrows). Mitosis within an endothelial cell (small arrow) is a sign of cellular repair. Courtesy of Helmut Rennke, MD.

- Anatomic changes
 - Glomerular capillary endotheliosis
 - Intracapillary fibrin deposition/thrombi
 - Subendothelial deposits of fibrinogen
 - Renal cortical necrosis can occur which is irreversible but rare

Renal Abnormalities in Pre-Eclampsia



Preeclampsia Electron micrograph in preeclampsia showing narrowing of the capillary lumen due to expansion of the mesangium, swelling of the endothelial (Endo) cell cytoplasm (arrow), and subendothelial deposition of hyaline (Hy) material which represents large macromolecules such as IgM. The damaged endothelial cell has become partially separated (*) from the glomerular basement membrane (GBM). Courtesy of Helmut Rennke, MD.



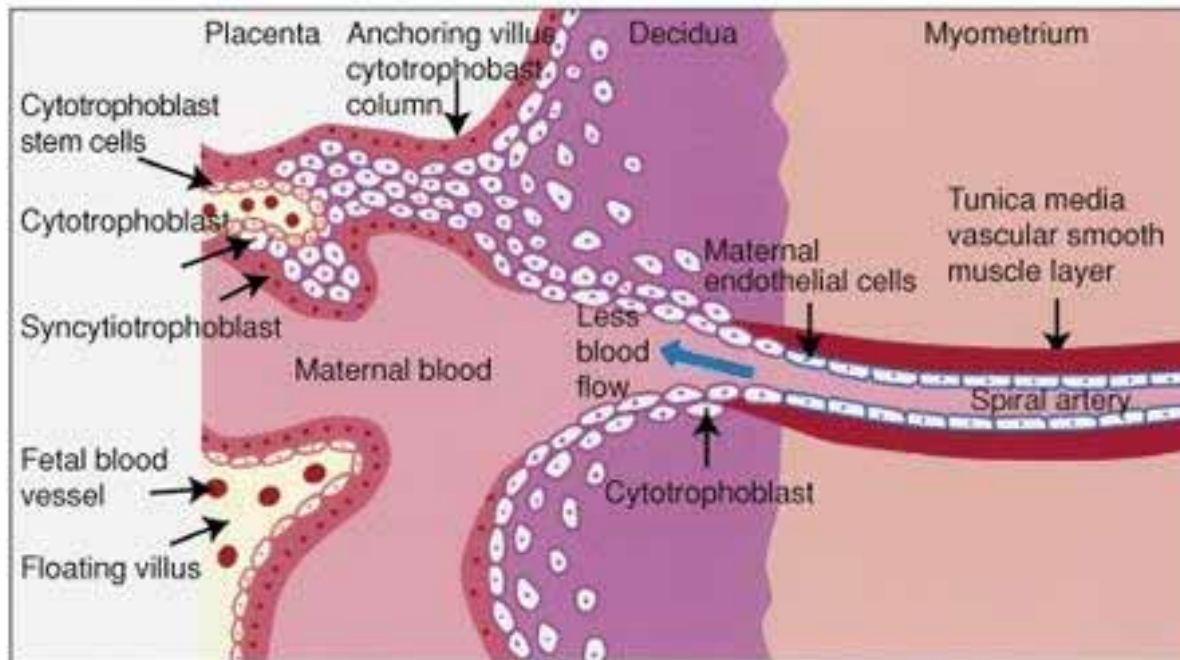
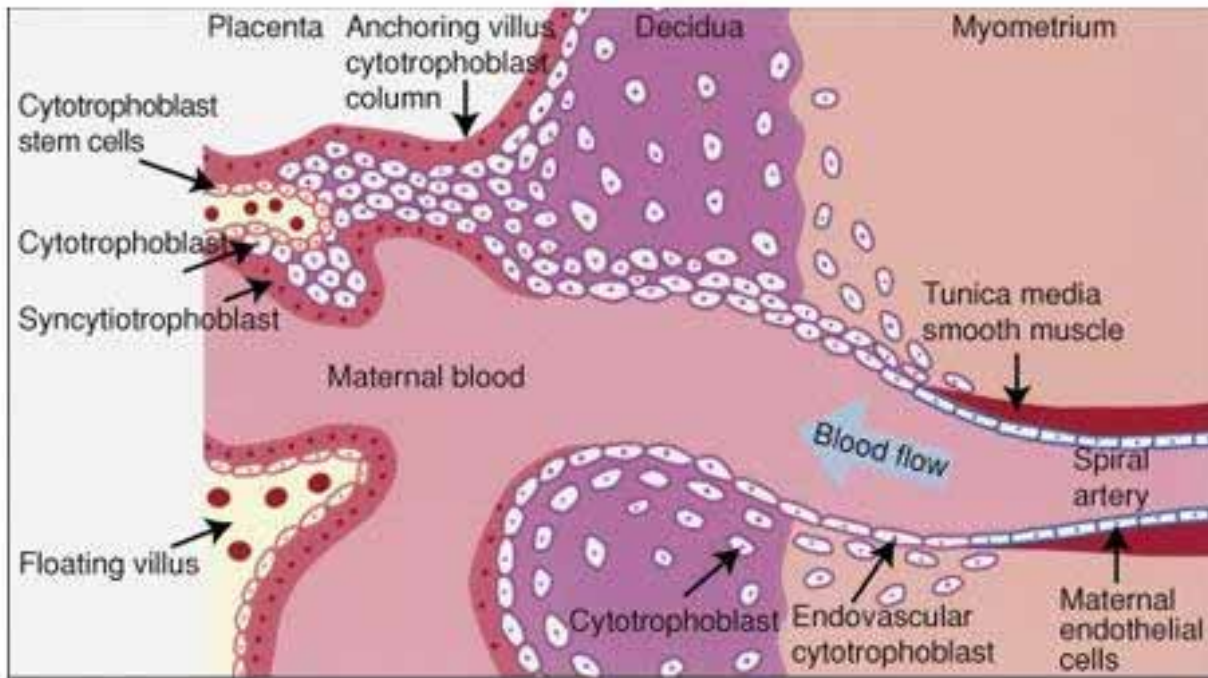
IgM deposition in preeclampsia Immunofluorescence microscopy in preeclampsia showing diffuse IgM deposition. This represents **nonspecific** entrapment of larger proteins in the more permeable glomerular capillary wall, rather than the formation of discrete immune complexes. There is, for example, generally no deposition of IgG. Courtesy of Helmut Rennke, MD.

HELLP Syndrome

- Severe variant of preeclampsia
- **H**emolysis
- **E**levated **L**iver enzymes
- **L**ow **P**latelets
- ~ 1 per 1000 pregnancies
 - Maternal mortality 1%
 - Placental abruption 16%
 - Acute renal failure 8%
 - Subcapsular liver hematoma, retinal detachment 1%

Proposed Pathophysiologic Mechanisms of Pre-Eclampsia

- **Abnormal placentation and placental ischemia**
- Circulating pro-angiogenic factors and their inhibitors
 - VEGF, PlGF, sFlt-1
- Endothelium-derived relaxing factors and inhibitors: Nitric oxide and ADMA
- Circulating Angiotensin II AT1 receptor autoantibodies
 - AT-1AA activate Ang II AT1 receptor



Angiogenic factors: Vascular Endothelial Growth Factor (VEGF) and Placental Growth Factor (PIGF)

Antiangiogenic factors: soluble fms-like tyrosine kinase 1 (sFlt-1) and soluble endoglin (sEng)

Circulating Proangiogenic Factors & Their Inhibitors

- Soluble fms-like tyrosine kinase 1 (sFlt1)
 - Naturally occurring VEGF and PlGF antagonist
 - Increased placental expression and excretion in preeclampsia
 - Maynard et al. (2003) hypothesized that excess circulating sFlt1 secreted by the placenta in preeclampsia led to endothelial dysfunction, hypertension and proteinuria

Hypothesis for the role of sFlt1 in preeclampsia

Remodeling of maternal spiral arteries does not occur



(?) Placental hypoperfusion



(?) Placental Ischemia



sFlt1 Increases



Free VEGF and PlGF decrease



Systemic maternal endothelial dysfunction

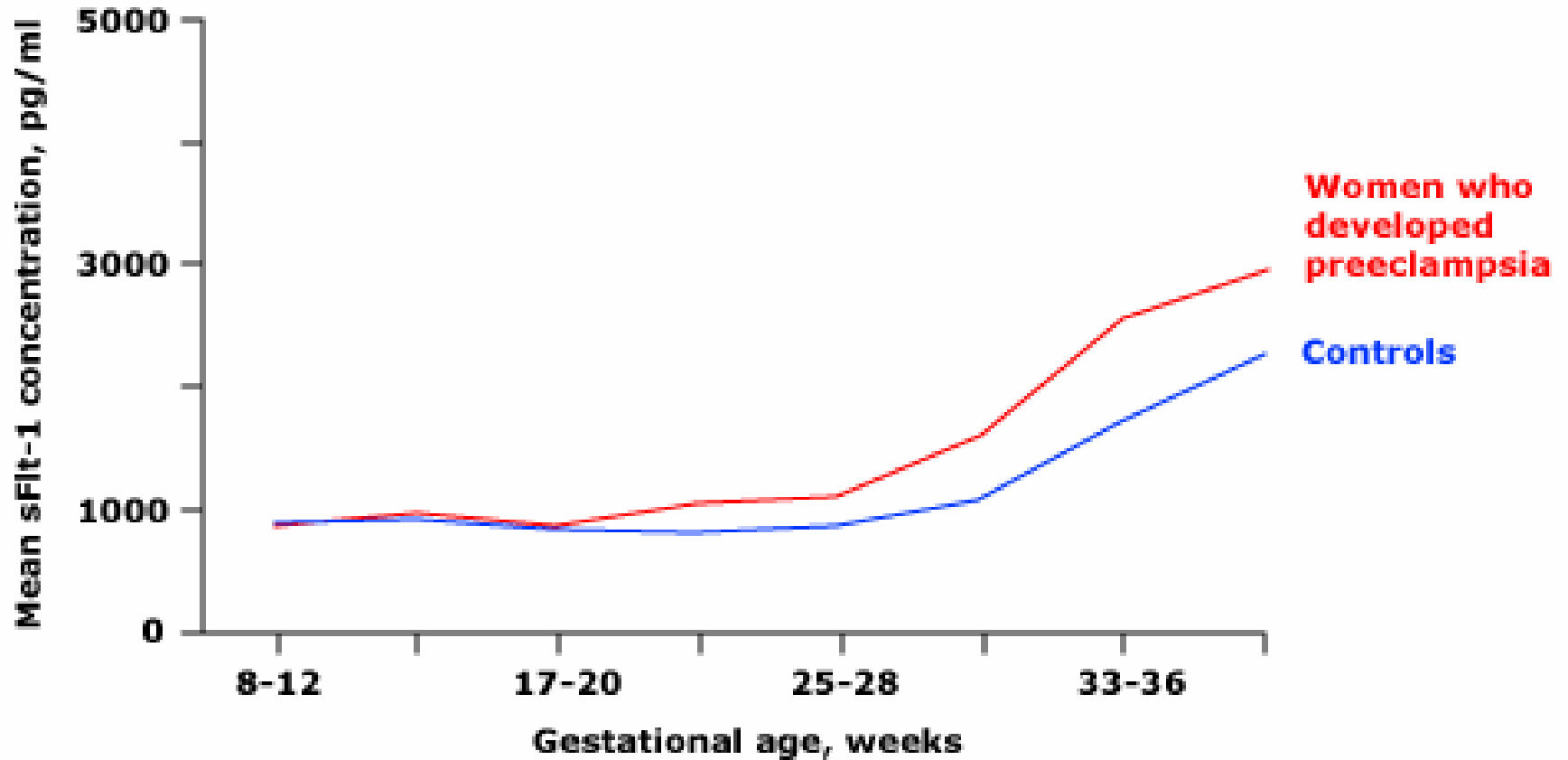


Thrombosis of arterioles
Hypertension
Dysfunction of multiple organs,
especially kidney, liver, and brain

Circulating Proangiogenic Factors & Their Inhibitors

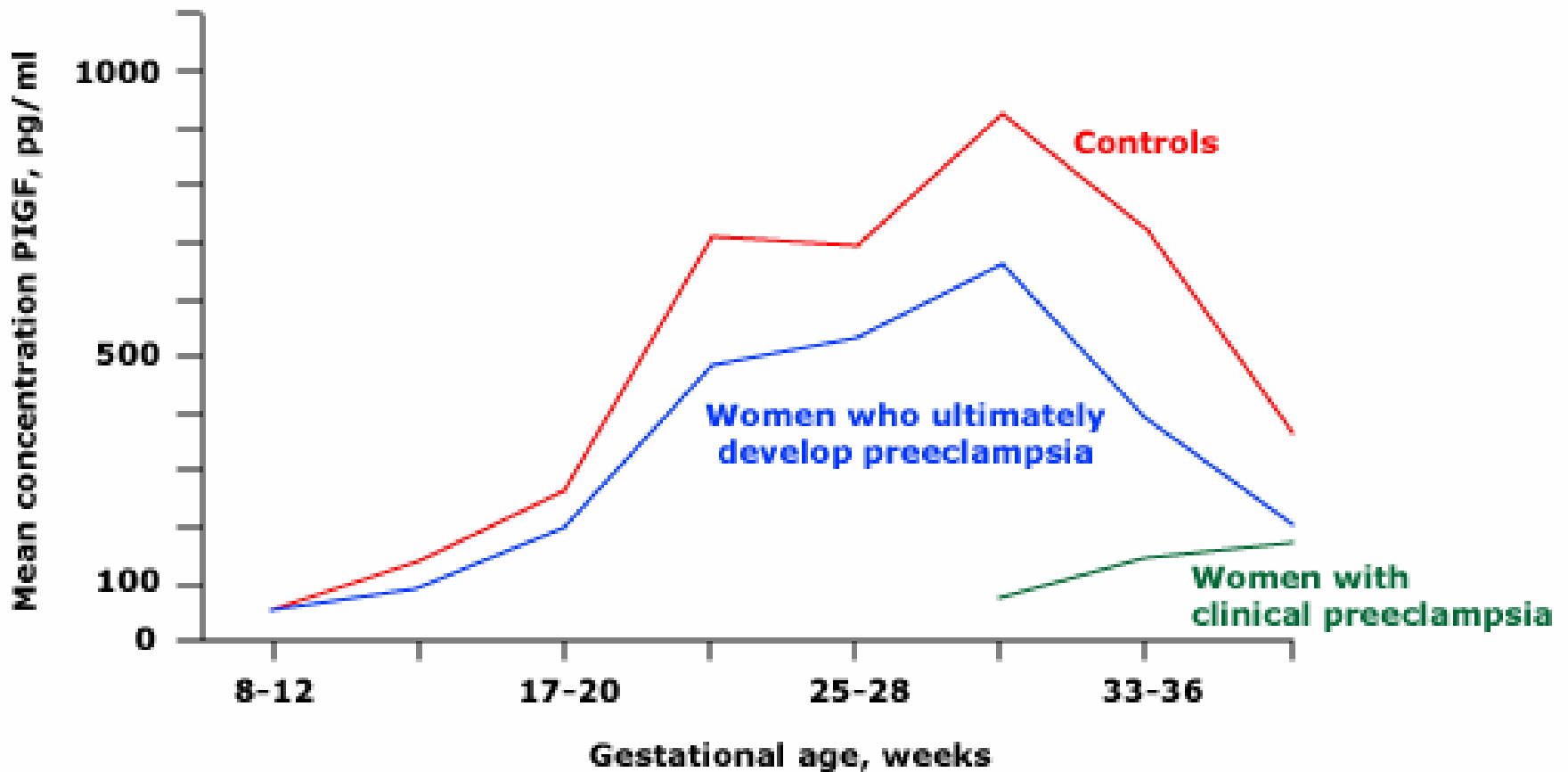
- Levine et al. (2004)
 - Nested case-control study within the Calcium for Preeclampsia Prevention Trial
 - Each woman with preeclampsia matched to normotensive control (120 pairs)
 - Measured serum concentrations of total sFlt-1, free PlGF, and free VEGF
 - sFlt-1 increased beginning 5 weeks before the onset of preeclampsia

Concentration of sFlt-1



Modified from: Levine, RJ, Maynard, SE, Qian, C, et al. N Engl J Med 2004; 350:672.

Concentration of PIGF in various groups



Modified from: Levine, RJ, Maynard, SE, Qian, C, et al. N Engl J Med 2004; 350:672.

Endothelium-Derived Relaxing Factors & Their Inhibitors

- Asymmetric dimethylarginine (ADMA)
 - May directly interfere with NO and induce endothelial dysfunction in pregnant women
 - May be overcome by raising the concentration of L-arginine
 - Savvidou et al. (2003) hypothesized that endothelial dysfunction and ADMA precede and contribute to the development of preeclampsia
 - Monitored uterine blood flow by doppler
 - Measured forearm ischemia-reperfusion
 - Measured ADMA levels

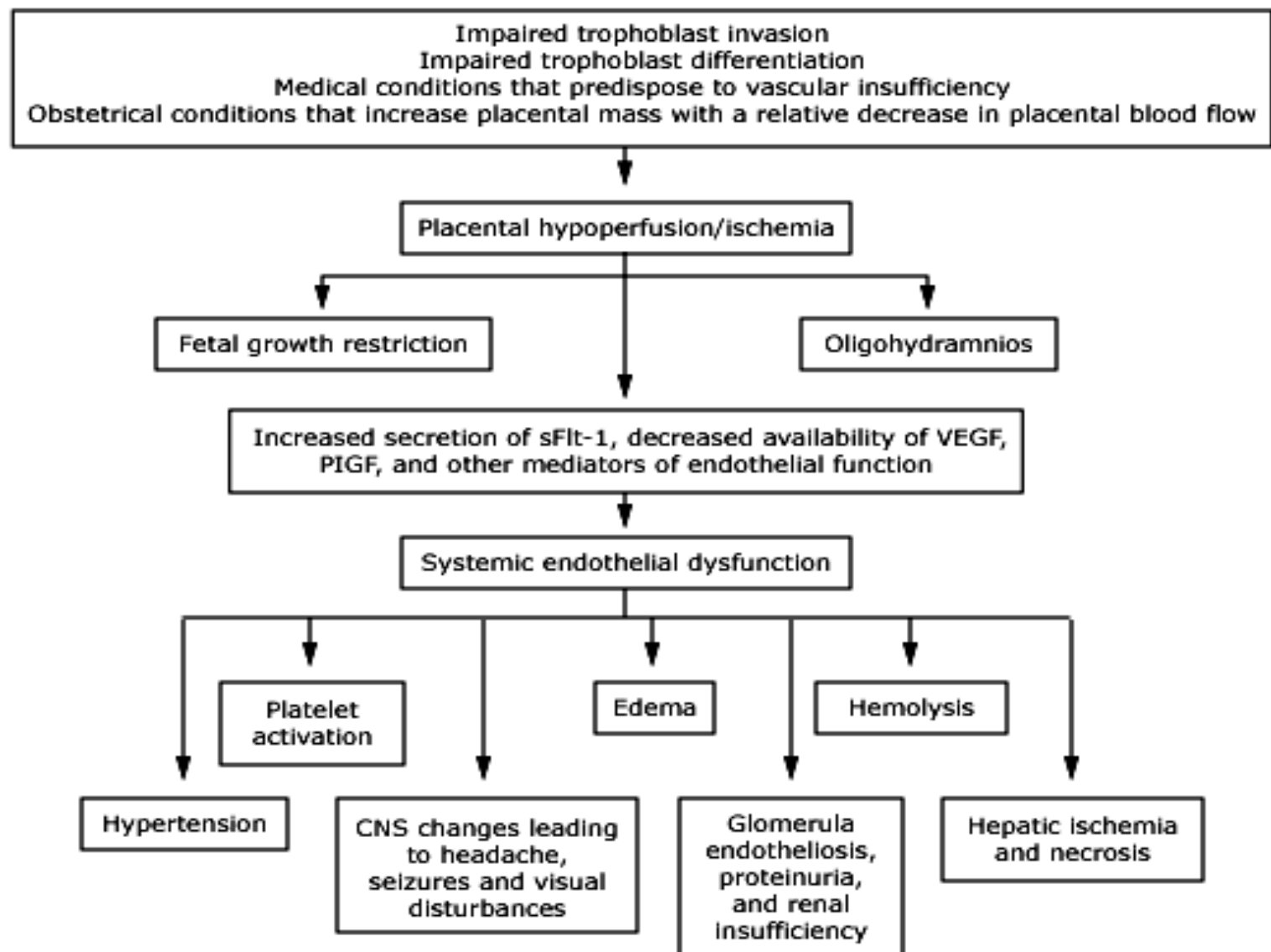
Endothelium-Derived Relaxing Factors & Their Inhibitors

- Rytlewski et al. (2005)
 - 61 preeclamptic women randomized to 3 g of L-arginine or placebo daily for 3 weeks in addition to standard therapy
 - SBP, DPB and MAP significantly lower in the L-arginine group (SBP 134 vs 143, DBP 81 vs 86, MAP 101 vs 108, $P < 0.01$)
 - May be due to increased synthesis of NO as measured by 24-urine nitrite excretion
 - No change in urinary protein excretion

Circulating Autoantibodies

- AT-1AA
 - Autoantibodies activate the angiotensin II AT1 receptor
 - Arise at the time symptoms develop and subside within 6 wk after delivery
 - May lead to increased plasminogen activator 1 (PAI1) production
 - Cause human trophoblasts to produce ROS by activating NADPH oxidase-leading to shallow trophoblast invasion
 - Demonstrated in both patients with preeclampsia and transgenic rat model of preeclampsia

Model for Pathogenesis of Preeclampsia



Prevention

- Dietary manipulation
 - Salt restriction
 - Calcium supplementation
 - Fish oil
- Low-dose aspirin
- Antioxidants
 - Vitamins C and E

Treatment of Pre-Eclampsia

- Bedrest for mild disease
 - BP <140/90, proteinuria <500 mg/d, normal renal function, serum uric acid <4.5
- Delivery (>32 weeks) = DEFINITIVE TREATMENT
 - Progressive worsening organ dysfunction (renal, hepatic, pulmonary, CNS, hematologic)
 - HELLP syndrome
 - Seizures
 - Uncontrollable HTN
 - Inadequate fetal growth

Treatment of Pre-Eclampsia

- Treatment (cont'd)
 - Antihypertensive medications for maternal safety (DBP <110 mmHg)
 - Eclampsia prophylaxis
 - Diazepam
 - MgSO₄
 - Cautious volume expansion (<500-1000 mL)
 - Platelet infusion for Platelets <20-40,000
 - FFP for microangiopathy or coagulopathy
 - HD for acute renal failure

Antihypertensive Therapy

- **Recommended**

- Hydralazine

- 5 mg iv initial dose with goal DBP 90-100 mmHg
 - Can repeat with 5-10 mg at 15-20 minute intervals

- Labetolol

- 20 mg iv bolus followed by 40mg, then 80mg every 10 minutes but not to exceed 220 mg total dose

- **Not Recommended**

- Nifedipine

- Nitroprusside

- Fetal cyanide toxicity can occur after 4 hours

- Diuretics

Long-Term Consequences

- Counseling for future pregnancies
 - Rate of preeclampsia in subsequent pregnancies is 25%
 - Recurrence rate for preeclampsia before 30 weeks is $\geq 40\%$
 - Recurrence rate for HELLP syndrome is 5%
 - Recurrence rate for eclampsia is 2%
- Long-term prognosis
 - Recurrent pregnancy hypertension a risk for chronic hypertension
 - Preeclampsia does not cause chronic hypertension but may predispose to future CVD

Urinary Tract Infections

- Frequency of UTI similar to non-pregnant women but consequences of infection more serious in pregnancy
- Higher prevalence of UTI's in DM, sickle cell disease
- Untreated, 30% progress to pyelonephritis
 - Dilated collecting system
 - Presence of vesicoureteral reflux
 - Glucosuria, aminoaciduria promote bacterial growth

Risks Associated with UTI in Pregnancy

- Maternal
 - Bacteremia
 - Septicemia
 - Decrease in renal function
- Fetal
 - Mid-trimester abortion
 - Increased perinatal mortality if UTI within 2 weeks of delivery
 - Pyelonephritis associated with IUGR, prematurity

Treatment of UTI in Pregnancy

- Treat even if asymptomatic; obtain UCx
- Duration
 - Cystitis: 3-7 days
 - Pyelonephritis: 10-14 days
 - Repeat urine culture 1 week after antibiotic course completed then q1month
- Drugs
 - Amoxicillin
 - Nitrofurantoin 100 mg po qhs for prophylaxis (except G6PD deficiency)
 - Avoid sulfonamide (hyperbilirubinemia), TMP (anti-folate → neural tube defects in 1st trimester)

Causes of ARF in Pregnancy

- **Pre-renal azotemia → ATN**
 - Volume depletion: vomiting, diarrhea, diuretics
 - Edema-forming states: cirrhosis, nephrosis, CHF
 - Other: hyperemesis gravidarum, uterine hemorrhage
- **Obstruction**
 - Gravid uterus
 - Uterine incarceration
 - Hydramnios
 - Nephrolithiasis
- **Intrinsic Renal Disorders**
 - Acute GN
 - AIN
 - Infection: pyelonephritis, septic abortion
 - Renal cortical necrosis
 - ATN: nephrotoxic drugs, rhabdo, abruptio placentae, uterine hemorrhage, septic shock, intrauterine fetal death, amniotic fluid embolism
- **Causes Unique to Pregnancy**
 - Acute Fatty Liver of Pregnancy
 - Pre-Eclampsia/Eclampsia
 - HELLP syndrome
 - Microangiopathic Syndromes (HUS/TTP)

Acute Tubular Necrosis (ATN)

- Most often a complication of sepsis or hypotension
- Early pregnancy
 - Septic abortion + shock
 - *E. coli*, *Clostridium perfringens*
 - Volume depletion
 - Hemorrhage from spontaneous abortion, hyperemesis gravidarum
- Late pregnancy – pre-eclampsia/HELLP syndrome or uterine bleeding from abruptio placentae

Renal Cortical Necrosis

- Risk factors
 - Abruptio placentae, septic abortion, severe pre-eclampsia, amniotic fluid embolism, retained fetus
- Triad
 - Anuria (suspect if severe oliguria or anuria persists > 1 wk)
 - Gross hematuria
 - Flank pain
- Diagnosis
 - US: hypoechoic or hypodense areas in the renal cortex
 - CT: ischemic zone in the cortex below the renal capsule
 - Renal arteriogram: patchy blood flow or absent nephrogram
- Outcome
 - Often requires hemodialysis
 - Majority never recover renal function or recover renal function transiently with later development of ESRD

TTP

- Classic Pentad
 - Microangiopathic hemolytic anemia
 - Thrombocytopenia, purpura
 - Fever
 - Neurologic dysfunction
 - Renal dysfunction (mild)
- May occur at any time during/after pregnancy but most often in 2nd/3rd trimester
- Treatment
 - Plasma exchange: 1.5-2.0 total body volume exchanges, replacement with FFP

TTP, HUS, and Pre-Eclampsia

| Feature | TTP | HUS | Pre-Eclampsia (HELLP) |
|--------------------------------------|-------------------------|--------------------|---------------------------|
| Microangiopathic hemolytic anemia | Frequent | Frequent | Rare |
| Thrombocytopenia | Frequent | Frequent | Occasional |
| Neurologic dysfunction | ++ | 0 | Occasional |
| Fever | ++ | 0 | 0 |
| Renal dysfunction | Variable Mild to mod | Frequent Severe | Frequent Mild to mod |
| HTN | Occasional | Frequent | Frequent |
| Purpura | Common | Rare | Rare |
| Low plasma fibrinogen | Rare | Rare | Variable |
| Elevated fibrin degradation products | Variable | Variable | Variable |
| Onset | Any time | Post-partum | 3 rd Trimester |

Acute Fatty Liver of Pregnancy

- Clinical Characteristics
 - Nausea, vomiting, jaundice
 - Elevated LFT (ALT, AST) → fatty infiltration hepatocytes without inflammation or necrosis on liver biopsy
 - Bleeding (prolonged PTT), consumptive coagulopathy (hypofibrinogenemia)
 - Thrombocytopenia
 - Hypoglycemia
 - Hyperuricemia
 - Severe renal failure
- Presents in the 3rd trimester
- Treatment – treat DIC; delivery with recovery 1-2 days after delivery

Pregnancy in Women With Renal Disease

Fetal and Maternal Outcomes in Women With or Without Kidney Disease, 1989 to 2001

| Outcome | Kidney Disease (n = 911) | No Kidney Disease (n = 4,606) | P |
|------------------------------|-----------------------------|-------------------------------------|--------|
| Adverse fetal outcomes | 166 (18.22) | 438 (9.51) | <0.001 |
| Adverse maternal outcomes | 125 (13.72) | 197 (4.28) | <0.001 |

NOTE. Values expressed as number (percent).

Facts

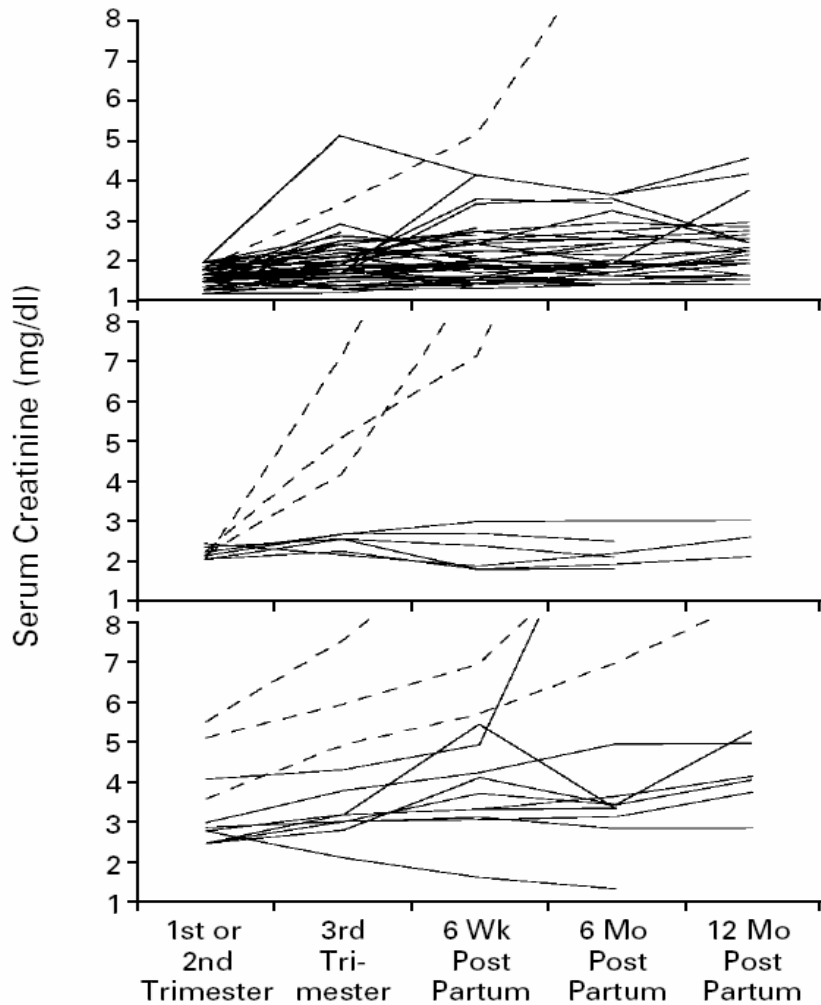
- Majority of women are beyond childbearing age
- Libido decreased/not sexually active
- As renal function declines, fertility rates decline proportionately
- The frequency of conception is decreased in women with renal insufficiency and markedly decreased in dialysis patients (0.5% per year)
- Return of fertility in 1-12 months is the rule in transplant recipients (not known if the recovery is complete)

Outcome of Pregnancy in Women with Moderate or Severe Renal Insufficiency

- 67 women (82 pregnancies)
- All had initial serum creatinine of at least 1.4 mg/dl and gestations continued beyond first trimester
- Increase in serum creatinine, blood pressure (from 28% to 48%) and proteinuria (from 23% to 41%) in the third trimester
- Pregnancy-related loss of maternal kidney function 43%
- Complications: preterm delivery (59%) and growth retardation (37%)
- Infant survival rate 93%

Jones D, et al. NEJM 1996

Serum Creatinine During and After Pregnancy



Scr < 2.0 mg/dl at the onset of gestation
Accelerated decline in GFR in 2%
49 pregnancies

Scr 2.0-2.4 mg/dl
Accelerated decline in GFR in 33%
9 pregnancies

Scr ≥ 2.5 mg/dl
Accelerated decline in GFR in 33%
12 pregnancies

Jones DC, et al. NEJM 1996

Chronic Kidney Disease and Pregnancy

- Proteinuria generally increases in women with glomerular disease and preexisting proteinuria
- Heavy proteinuria early in pregnancy associated with an increased rate of fetal loss, prematurity, and IUGR
- Nephrotic-range proteinuria late in pregnancy does not adversely affect fetal outcome

How Does Pregnancy Influence Renal Disease?

- Hemodynamic changes – hyperfiltration
- Increased urinary protein excretion
- Pre-Eclampsia more common in pt with renal disease
- Possibility of permanent loss of function

Renal Diseases Associated With Poor Renal Prognosis in Pregnancy

- Reflux nephropathy
- MPGN
- IgA nephropathy
- FSGS

Pregnancy Outcomes in Diabetic Nephropathy

- Adverse fetal outcomes predicted by level of proteinuria (Ekblom et al, 2001)
- In patients with well established DM nephropathy and decreased GFR, higher incidence of adverse outcomes
 - Prematurity
 - Congenital abnormalities
 - Low birth weight
 - Respiratory distress syndrome

Progression in Diabetic Nephropathy

| Author | N | Follow-up | % ↓ GFR | Progression | ESRD |
|--------------------|----|-----------|--------------------|-------------|------|
| Kitzmilller (1981) | 26 | 2 years | 22% | No | 22% |
| Reece (1988) | 31 | 3 years | 38% | No | 13% |
| Purdy (1996) | 11 | 2 yrs | 100% (SCr >1.4) | Yes | 63% |

*In general proteinuria, HTN, GFR returned to baseline after delivery except in Purdy et al.

Management of Diabetic Nephropathy During Pregnancy

- Discontinue ACEi/ARB pre-conception
- Tight glucose control – multiple injections, dietary supervision
- Antihypertensive therapy – methyldopa, labetalol
- RTC q 2 weeks
- Labs q 1 month

Systemic Renal Diseases: SLE

- Predictors of poor outcome
 - Active disease at conception
 - Disease first appears during pregnancy
 - Increased antiphospholipid antibodies
 - HTN, severe CRI, proteinuria in 1st trimester
- Disease course during pregnancy is unpredictable
 - Frequency of SLE exacerbations during pregnancy varies with the state of disease activity pre-conception
 - Encouraged to delay pregnancy until disease quiescent >6 months

Antiphospholipid Antibody in Pregnancy

- Fetal loss (40%) in 1st and 2nd trimester
- APL Ab interfere with embryonic implantation
- Arterial and venous thrombosis (renal and placental vessels)
- Pre-eclampsia
- Renal vasculitis, thrombotic microangiopathy
- Consider Rx with low dose SQ heparin, low dose ASA or dipyridamole

SLE Flare vs. Pre-Eclampsia

| Clinical Features | SLE Flare | Pre-Eclampsia |
|-------------------|-----------|---------------|
| Proteinuria | + | + |
| HTN | + | + |
| RBC casts | + | - |
| Azotemia | + | + |
| Low C3, C4 | + | - |
| Abnormal LFT | - | +/- |
| Low platelets | + | +/- |
| Low WBC | + | - |

ESRD and Pregnancy

- Successful outcome
 - Older studies: 23%; recent data: 40-70%
- 40% spontaneous abortions in 2nd trimester
- Most infants born premature (32 weeks) with low birth weight, higher incidence of congenital and developmental problems
- Improved outcome with residual renal function
- No difference in outcome between CAPD vs. HD

Management Guidelines

- Biocompatible and non-reuse dialyzers
- Minimize shifts in intravascular volume, avoid hypotension (target weight: difficult, weight gain: 1 pound/week after the 1st trimester)
- Target diastolic blood pressure: 80-90 mmHg range
- Avoid dialysis-induced alkalosis, hypo/hypercalcemia and hyperkalemia
- Allow high protein intake (1.8 g/kg/day)
- Anemia should be treated (EPO/Iron/folate)

Management Guidelines

- EPO dose increase by 50%
- Maintain a predialysis BUN of ≤ 50 mg/dl
- Increasing the dialysis dose: frequent dialysis sessions or daily dialysis (?reducing the risk of polyhydramnios and dialysis-induced hypotensive episodes, better results with dialysis ≥ 20 hours per week)
- Treatment of premature labor (avoid NSAIDs if possible)

Kidney Transplantation and Pregnancy

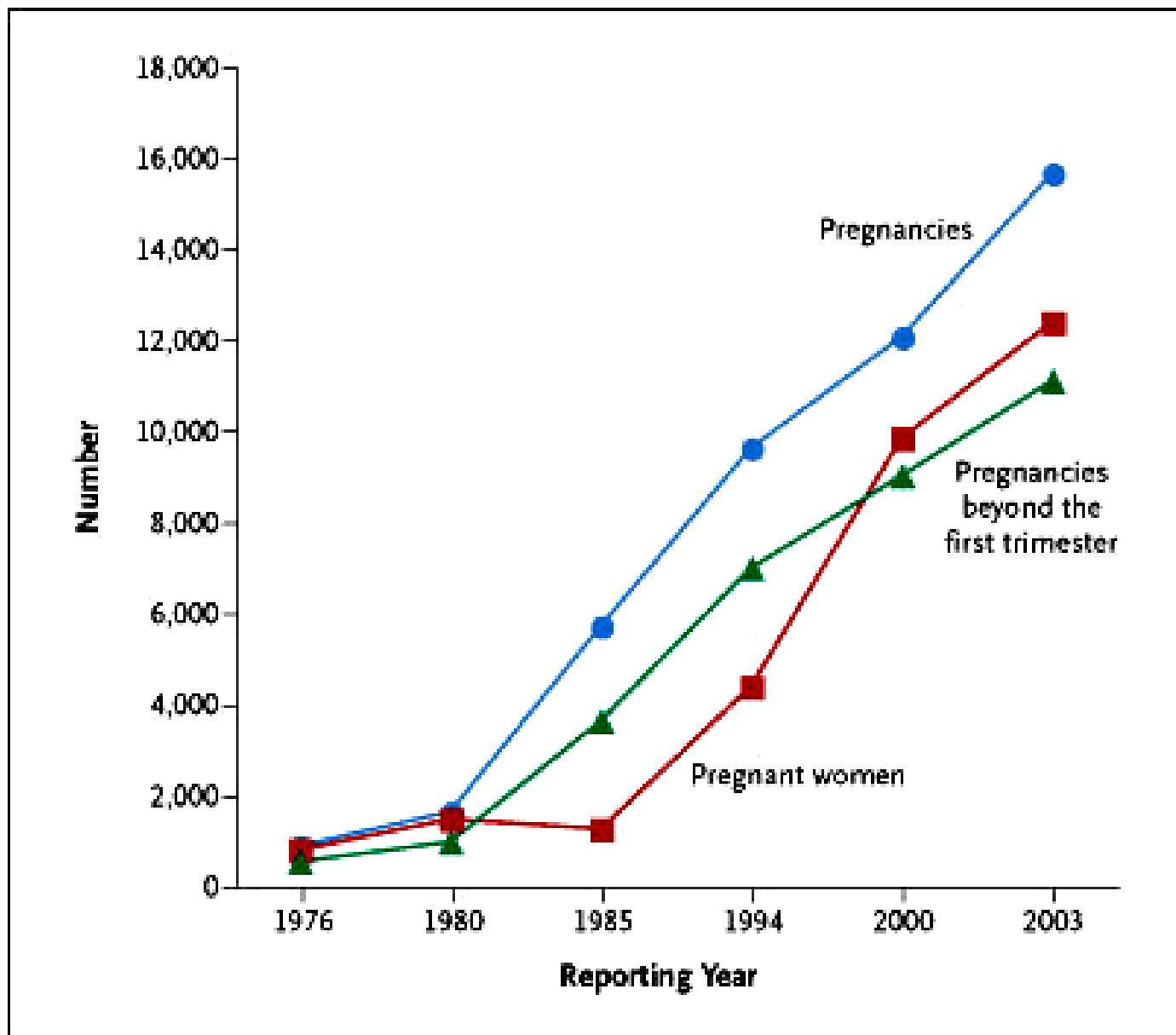
- Over 14,000 pregnancies have been documented since 1958 worldwide
- More than 1500 pregnancies in kidney transplant recipients reported to NTPR (National Transplantation Pregnancy Registry-established in 1991)
- More than 1100 pregnancies fathered by male transplant recipients reported to NTPR

Armenti VT, et al. Clin Transplants 2006

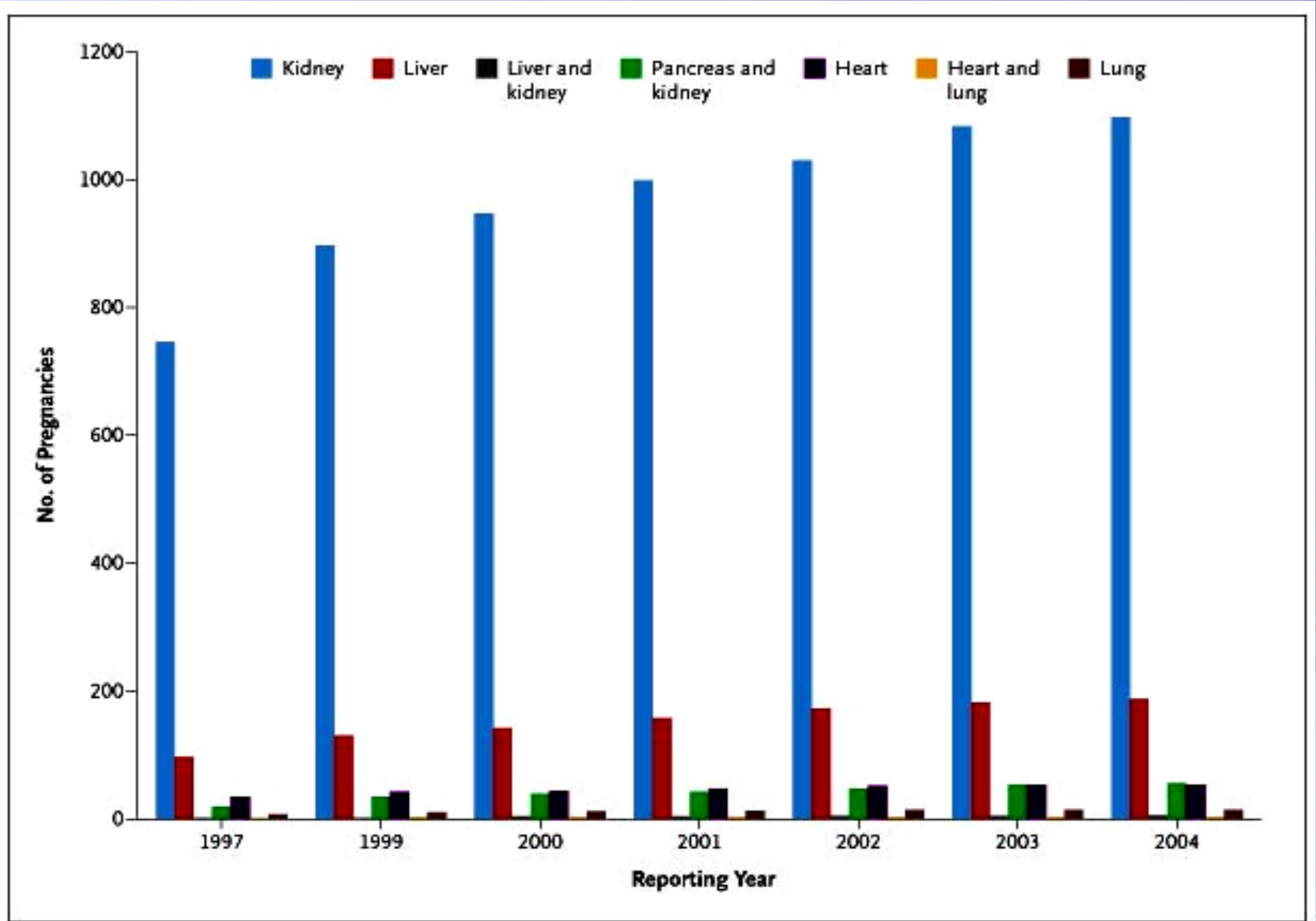
Important Date

March 2008

- The 50th anniversary of the first post-kidney transplant pregnancy from March 1958 reported by Joseph Murray and colleagues in 1963 (NEJM)



McKay D and Josephson M, NEJM 2006



McKay D and Josephson M, NEJM 2006

Questions

- Is pregnancy advisable in transplant recipients?
- Will pregnancy be complicated?
- Will the baby be healthy?
- Will there be any long-term harm (mother and the baby)?

Influence of Renal Allograft Function on Pregnancy Outcome

| Serum creatinine | Complicated pregnancy | Successful outcome | Long-term obstetric problems |
|----------------------------|------------------------------|---------------------------|-------------------------------------|
| ≤125 μmol/L (1.4 mg/dL) | 30% | 97% | 7% |
| ≥125 μmol/L (1.4 mg/dL) | 82% | 75% | 27% |

Estimates are based on data from 7110 pregnancies in 5370 women (1961-2000) that attained at least 28 weeks gestation.

Davison JM and Bailey DJ. J Obstet Gynaecol Res 2003

Maternal Conditions/Risks

- Hypertension: worsens (25-73%)
- Preeclampsia: up to 28%
- Risk of ectopic pregnancy: not increased
- Worsening renal function
 - Acute rejection: 2-14%
 - Obstruction
- Increased likelihood of operative delivery: 30-59% C-section
- Graft loss after delivery: 4-13% within 2 years after delivery
- Diabetes: not common

Pregnancy Outcomes

- Spontaneous Abortion: 14%
(similar to general population)
- One in five transplant recipients:
elective termination of pregnancy
- Live birth: 70% in kidney, kidney-
pancreas, and liver transplant,
slightly lower rates in lung and
heart transplants

Pregnancy Outcomes

| | Renal transplantation | Primary renal disease | <i>P</i> value |
|---------------------------|-----------------------|-----------------------|----------------|
| Pregnancies | 73 | 59 | — |
| Spontaneous abortions | 17 (23%) | 9 (15%) | NS |
| Therapeutic abortions | 7 (9.6%) | 2 (3.4%) | NS |
| Births | 49 | 48 | — |
| Neonates | 50 | 48 | — |
| Superimposed preeclampsia | 9 (19%) | 10 (21%) | NS |
| Preterm delivery | 29 (60%) | 10 (21%) | 0.001 |
| IUGR | 25 (52%) | 8 (17%) | 0.001 |
| Cesarean delivery | 18 (37%) | 13 (27%) | NS |
| Hospitalization in NICU | 17 (35%) | 3 (6%) | 0.01 |
| Stillbirths | 1 (2%) ^a | 0 | NS |

| | Renal transplantation (n = 48) ^a | Primary renal disease (n = 48) ^a | <i>P</i> value |
|------------------------------|--|--|----------------|
| Major malformations | 2 (4.2%) | 2 (4.2%) | NS |
| Mild errors of morphogenesis | 10 (20.8%) | 8 (16.6%) | NS |

^aNumber of live births.

Potential Risks to Children Born to Transplant Recipients

- Preterm birth (14-83% vs 5-15% in general population)
- Intrauterine growth retardation (IUGR) and low birth weight (19-67% vs 5-13% in general population)
- Congenital abnormalities (no increase with CsA, chromosome aberrations with AZA)
- Adrenocortical insufficiency
- Hyperkalemia, renal dysfunction
- Immunologic abnormalities, malignancies
- Infections (CMV, hepatitis B and C, sepsis)

Fetal Safety for Commonly Used Immunosuppressive Drugs

| | Pregnancy Category |
|-------------------|--------------------|
| • Corticosteroids | B |
| • Cyclosporine | C |
| • Azathioprine | D |
| • Tacrolimus | C |
| • Rapamycin | C |
| • MMF | C |

A-no risk, B-low risk, C-risk can not be ruled out, D-known risk, X-contraindicated

Immunosuppressive Drugs

- **Tacrolimus**: toxicities dose-dependent, transient neonatal hyperkalemia, cardiomyopathy in twins
- **MMF** (12 pregnancies): hypoplastic nails, short fingers, no chromosomal abnormalities
- **Rapamycin** (2 pregnancies): teratogenic in rats

BP Medications

- ACE inhibitors (D) are **contraindicated** in pregnancy (very low dose only in patients with severe, unresponsive hypertension)
- Stillbirth, renal tubular dysplasia, oligohydramnios, hypoplastic lungs, limb contractures, neonatal anuria and neonatal death, patent ductus arteriosus
- Less experience with ARBs-not recommended



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Major Congenital Malformations after First-Trimester Exposure to ACE Inhibitors

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ACE inhibitors restricted to the first trimester of pregnancy, an exposure that was previously considered to be safe, was associated with a risk of a major congenital malformation that was **2.7 times as great as the risk** with no fetal exposure to ACE inhibitors or other antihypertensive medications. Pre-specified subgroup analyses identified significantly increased **risks of malformations of the cardiovascular and central nervous systems**. “In a post hoc analysis, we also found a significantly increased risk of kidney malformations”.

BP Medications

- **Methyldopa (C):** safe
- **Beta blockers(C):** probably safe, fetal bradycardia, respiratory depression at birth
- **Labetalol (C):** safe, less bradycardia than beta blockers
- **Calcium channel blockers (C):** profound hypotension when used with magnesium, reserve for severe hypertension
- **Hydralazine (C):** safe, no increase in birth defects
- **Minoxidil (C):** limited experience, hypertrichosis in the infant

Kidney Transplantation and Pregnancy

- High-risk pregnancy
- Good prognosis:
 - 1-2 years waiting time
 - Scr < 1.5 mg/dl and stable
 - Normal blood pressure (target level?)
 - No proteinuria or minimal proteinuria (level?)
 - No recent acute rejection episode
 - Low-dose prednisone (≤ 7.5 mg/d)
 - No recent infections especially CMV
 - Normal blood glucose level

Recommendations

- Counseling at the pretransplant evaluation and after transplantation
- **Waiting time:** at least 1 year recommended
- Vaccination: pre-transplant or pre-pregnancy (influenza, Hep B, tetanus)
- Follow-up with high-risk OB
- Close follow-up for acute rejection and frequent blood work for immunosuppressive drug level monitoring
- Good blood pressure and blood glucose control

Recommendations

- Treatment of anemia and UTIs
- Fetal surveillance: close follow-up
- C-section for usual indications
- **Breast-feeding:** controversial, not recommended but not absolutely contraindicated, recent reports: might be OK with tacrolimus
- **Follow-up of offspring:** Long-term consequences of immunosuppressive agents?

Recommendations

Future research:

- Prospective observational studies and support of the current registries
- Other organ transplants-organ/recipient specific guidelines
- Impact of pregnancy on short and long-term graft function
- Target blood pressure and best BP meds to use
- The optimal immunosuppressive regimen during pregnancy and breast-feeding
- New immunosuppressive drugs and safety
- The long-term effects of immunos on the offspring