Chronic Kidney Disease (CKD) and Pregnancy

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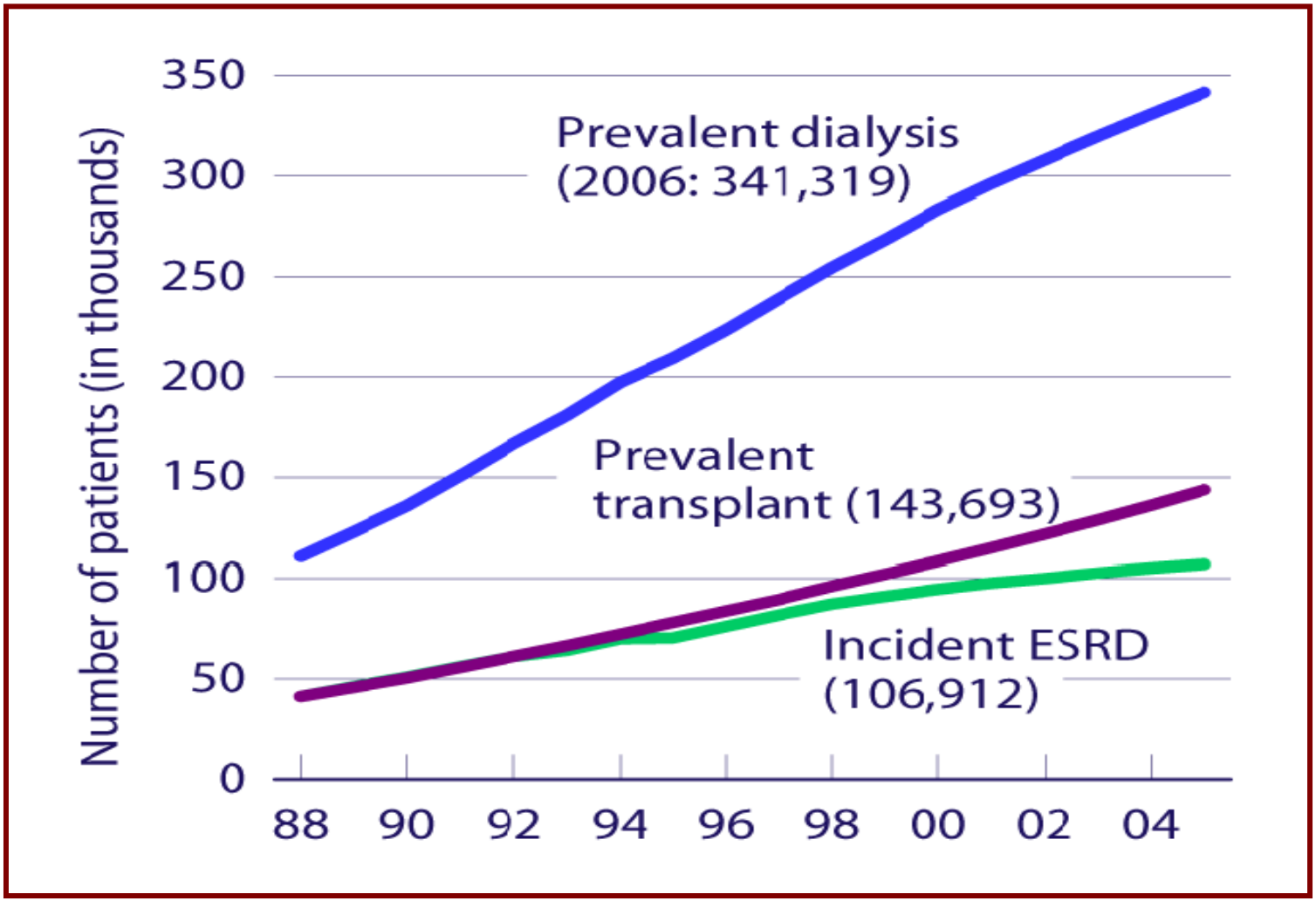
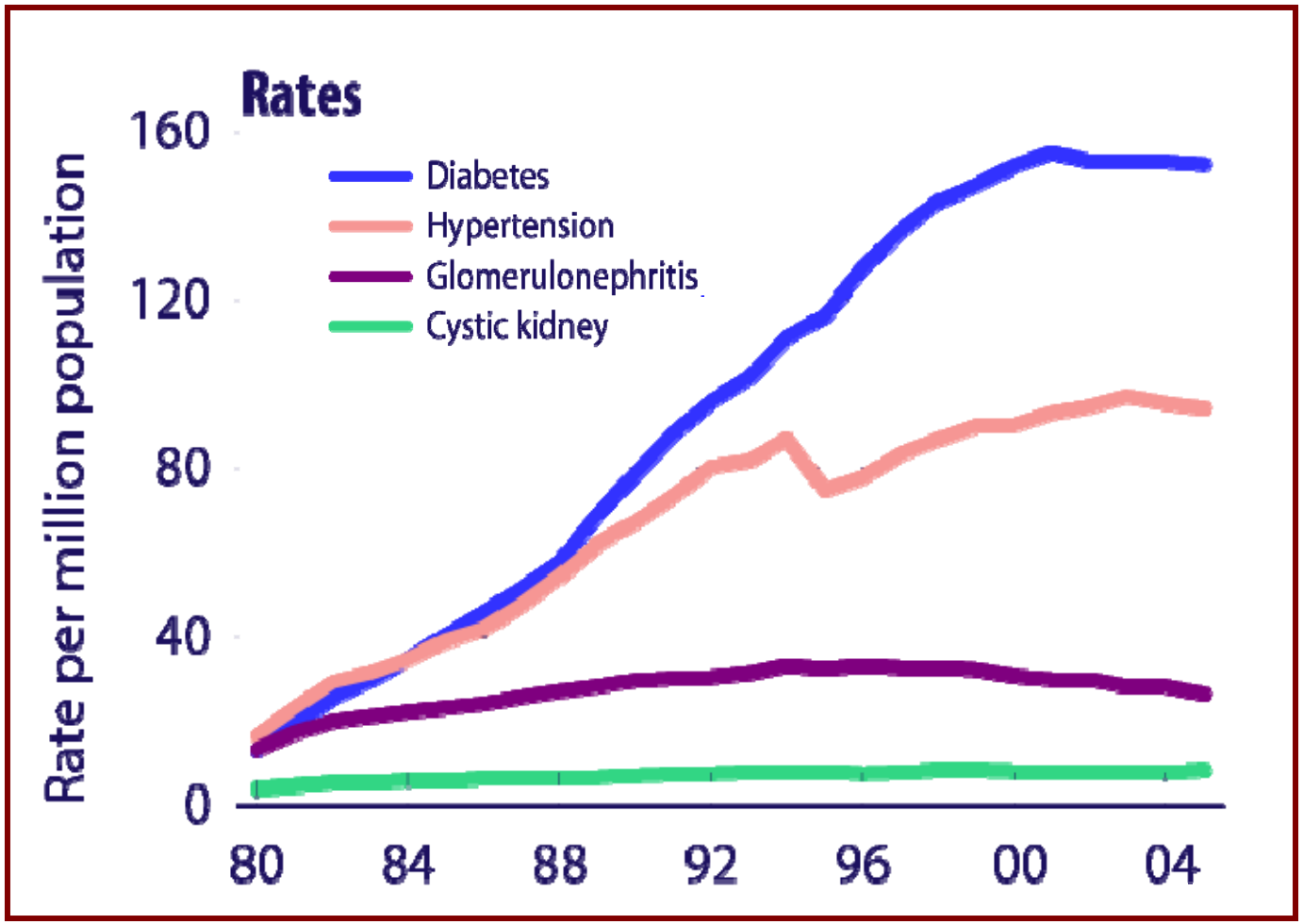
The 'Epidemic' of *End Stage* Kidney Disease



Global epidemic of type 2 diabetes
154 million worldwide- will double in 20 yrs



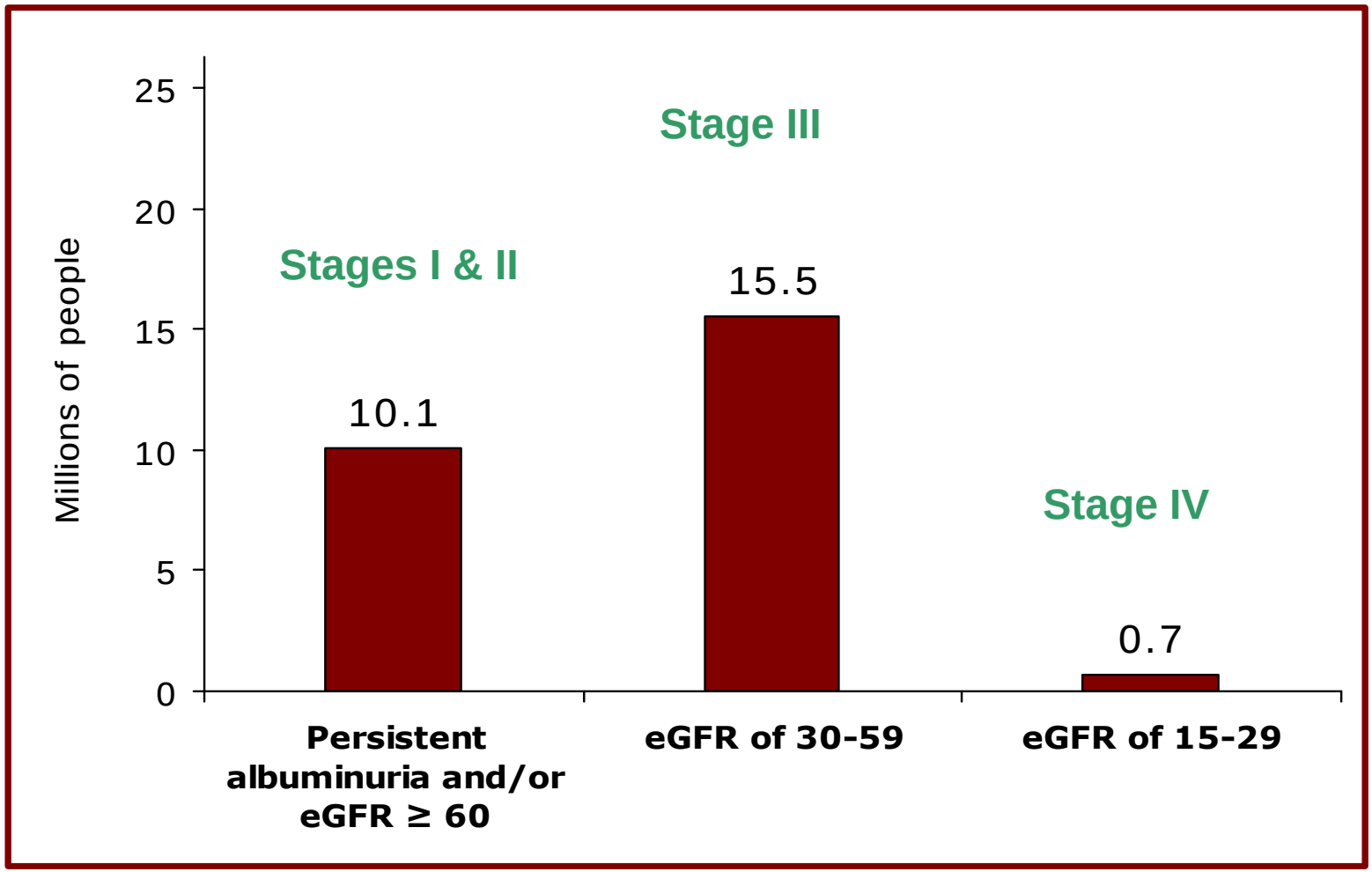
Incident ESRD rates, by primary diagnosis, adjusted for age, gender, & race.

USRDS 2007

ESRD: The 'Tip of the Iceberg'

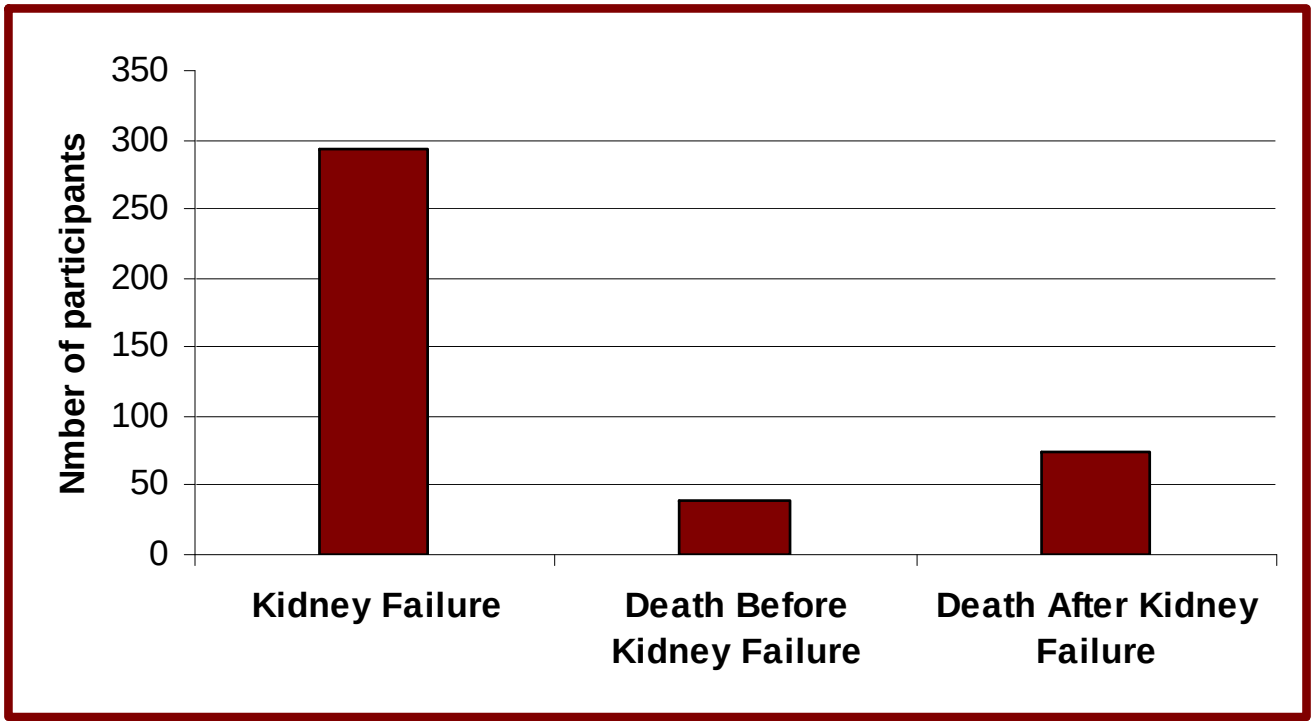
Patients with CKD: 50X those with ESRD

26 Million Americans have 'CKD'



JAMA 2007

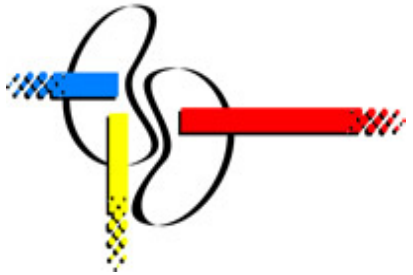
People with CKD Progress to ESRD: Especially those Middle Aged and Younger



Long term (7 year) follow up of non-diabetic CKD; mean GFR=39, mean age=52 year old).

Levey, et al., 2006

Global Epidemic of Kidney Disease



- ESRD increasing 8% per year (population growth is 1.3%)
- 1.4 million people (15% of world population) are receiving hemodialysis
- Renal replacement therapy *is not available* to most patients in developing world

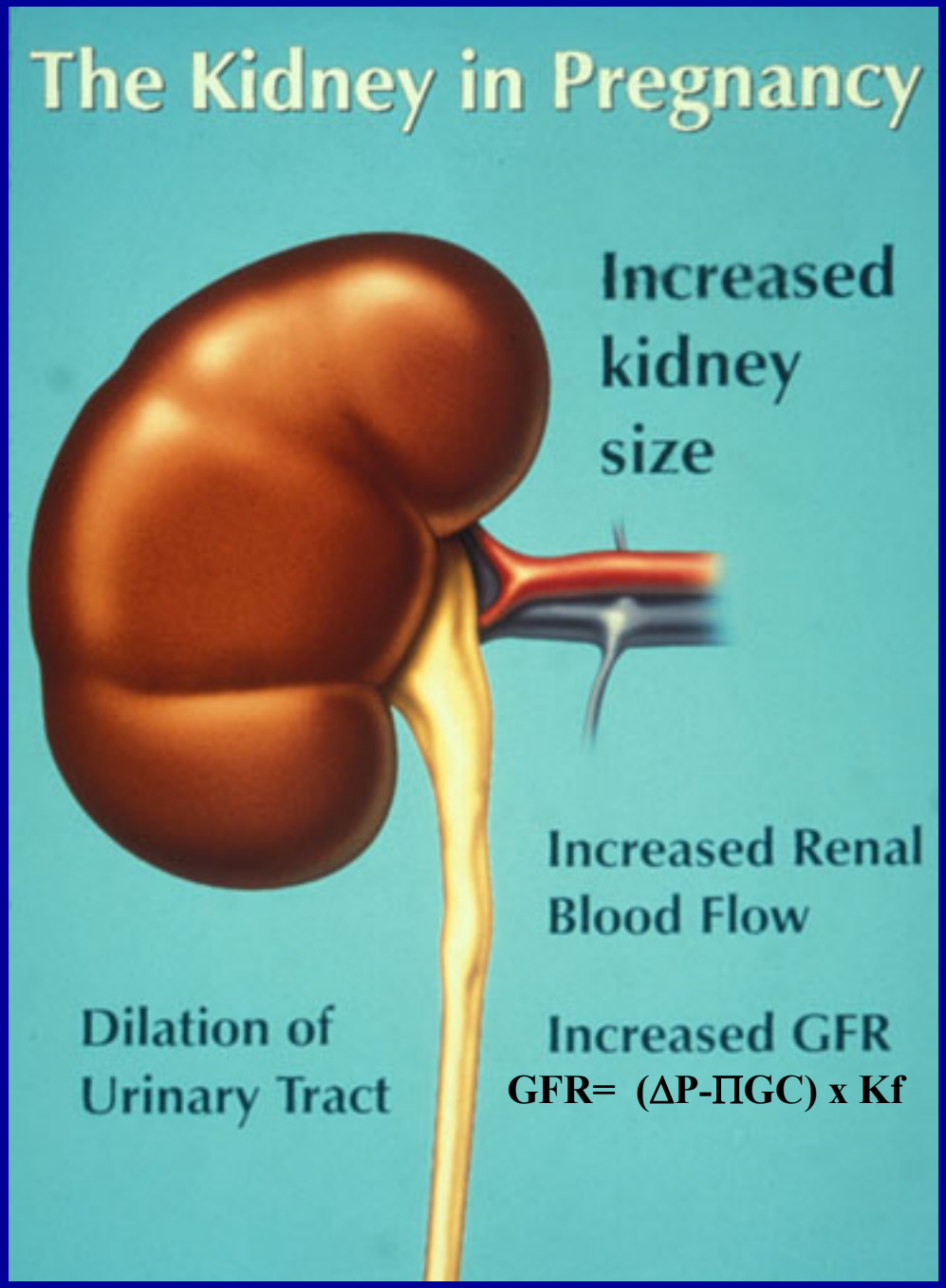
Chronic Kidney Disease in Pregnancy: Goals of Obstetric Physician

- Good Obstetric Outcomes: Maternal and Fetal

- Prevent progression of kidney disease

CKD and Pregnancy

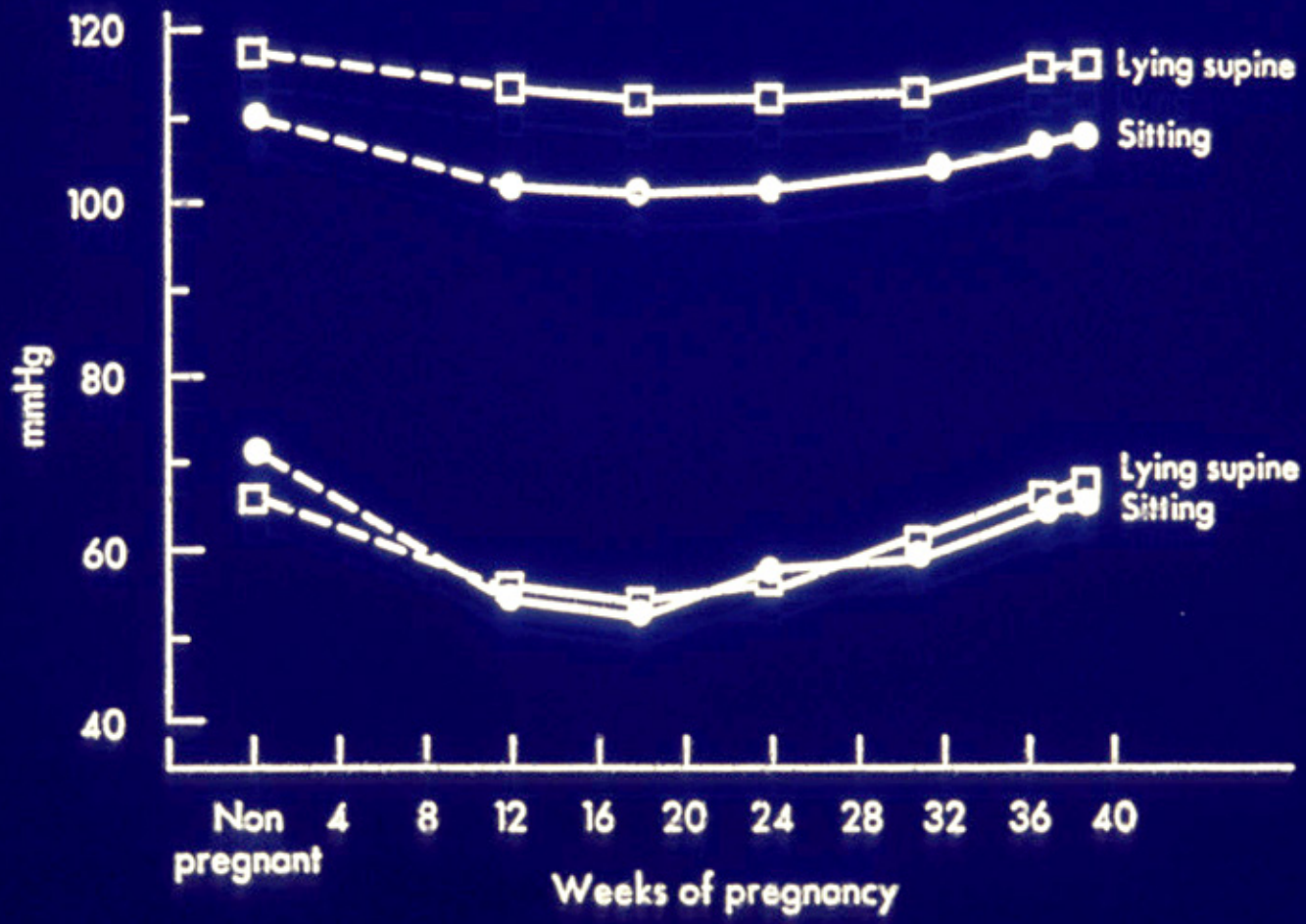
- Renal adjustments to pregnancy
- Obstetric and renal outcomes
- Diabetic kidney disease
- Lupus
- Glomerulonephritis
- Polycystic kidney disease
- Dialysis and Transplant

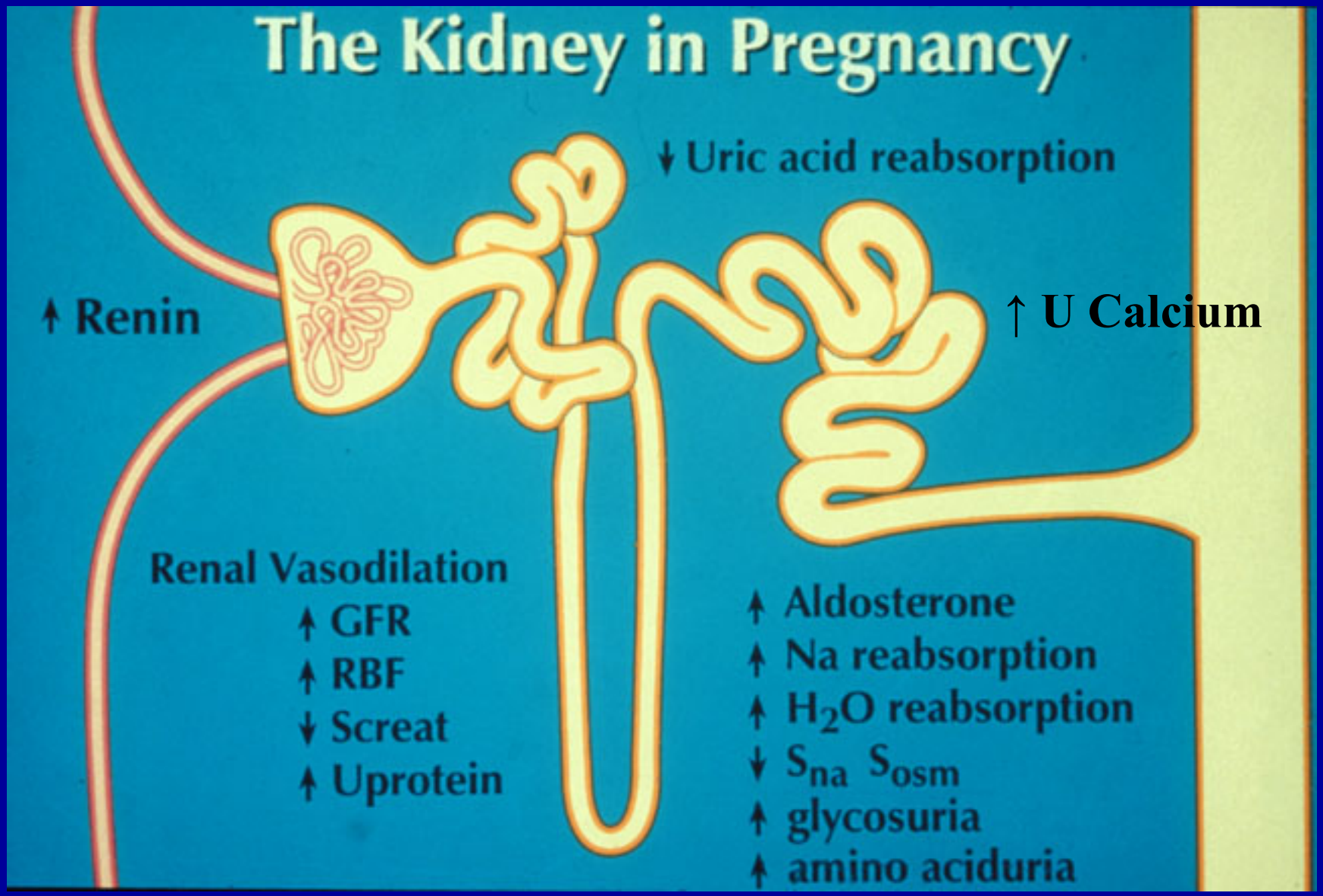

The Kidney in Pregnancy
Increased kidney size
Increased Renal Blood Flow
Increased GFR
GFR= (ΔP-ΠGC) x Kf
Dilation of Urinary Tract

Hemodynamic Changes in Pregnancy

- Vasodilation begins early in pregnancy
- Stimulus may be estrogen mediated enhanced NO production
- ? Ovarian relaxin

Systolic and Diastolic Blood Pressure During Pregnancy




The Kidney in Pregnancy
↓ Uric acid reabsorption
↑ Renin
↑ U Calcium
Renal Vasodilation
↑ GFR
↑ RBF
↓ Screat
↑ Uprotein
↑ Aldosterone
↑ Na reabsorption
↑ H_2O reabsorption
↓ S_{na} S_{osm}
↑ glycosuria
↑ amino aciduria

Assessment of GFR and Proteinuria in Pregnancy

- GFR estimating equations (e.g. MDRD) are not valid for pregnancy
- Creatinine clearance is gold standard
- Serum creatinine is useful, although sensitivity for mildly reduced GFR is low
- Proteinuria: ACR, PC ratio; 24 hour urine protein

Stages of Chronic Kidney Disease

e GFR defined by Modified MDRD equation

Stage 1: kidney damage; eGFR> 90 ml/min

Stage 2: kidney damage; eGFR 60-90 ml/min

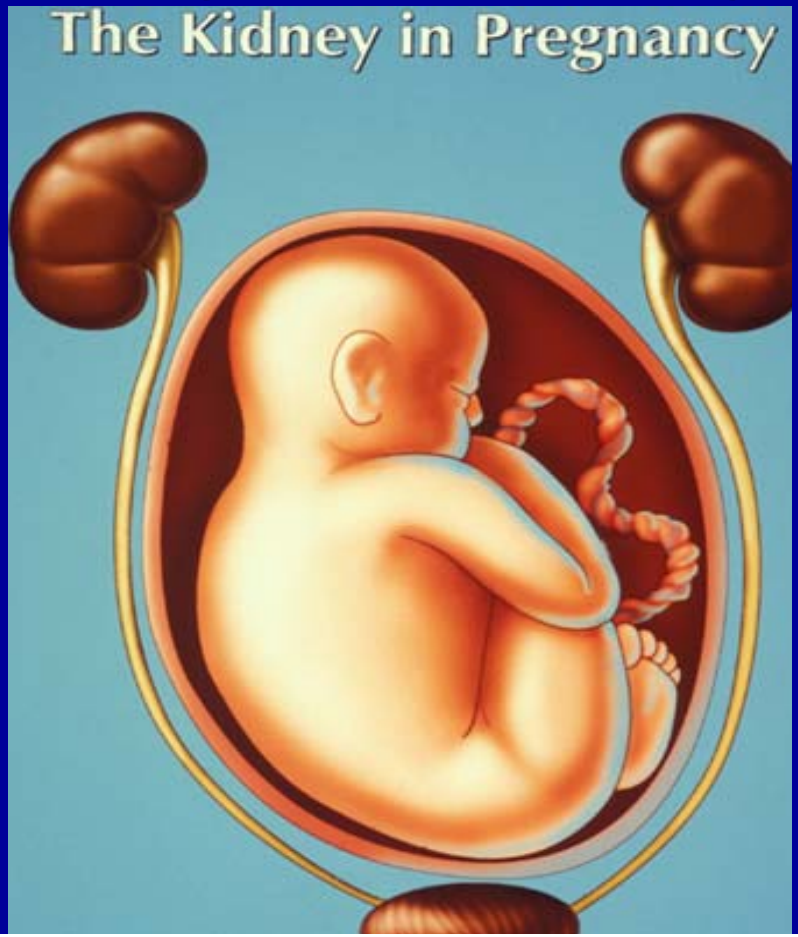
Stage 3: moderate decrease; eGFR 30-59 ml/min

Stage 4: severe decrease; eGFR 15-29 ml/min

Stage 5: Kidney Failure; eGFR < 15 ml/min

Is CKD Related to Pregnancy Outcomes?

Reproductive and Renal Function are Strongly Linked:
Healthy pregnancy is dependent on physiologic renal adjustments



Fertility is Associated with Kidney Function

Women with ESRD are often infertile

- Anovulatory cycles
- Elevated prolactin and impaired hypothalamic-pituitary function

Healthy Kidneys – Healthy Pregnancy

- The significant hemodynamic and hormonal adjustments made by the kidney are essential for fetal growth and development
- Women with impaired kidney function have adverse pregnancy outcomes in proportion to the degree of GFR reduction and hypertension

Pregnancy Outcomes in Women with Moderate or Severe Renal Insufficiency

Jones and Hayslett, 1996, NEJM

Number of Pregnancies	82
Age	28±6
Glomerulonephritis	40%
Interstitial Nephritis	43%
Baseline Serum Cr (mg/dl)	1.9± .8
Mean Arterial Pressure	99± 17
Proteinuria	77%

Pregnancy Outcomes with Moderate to Severe CKD *(Jones, Hayslett)*

- 60% pre term delivery
- 37% IUGR
- 7% Fetal loss
- Maternal hypertension and proteinuria: 50%

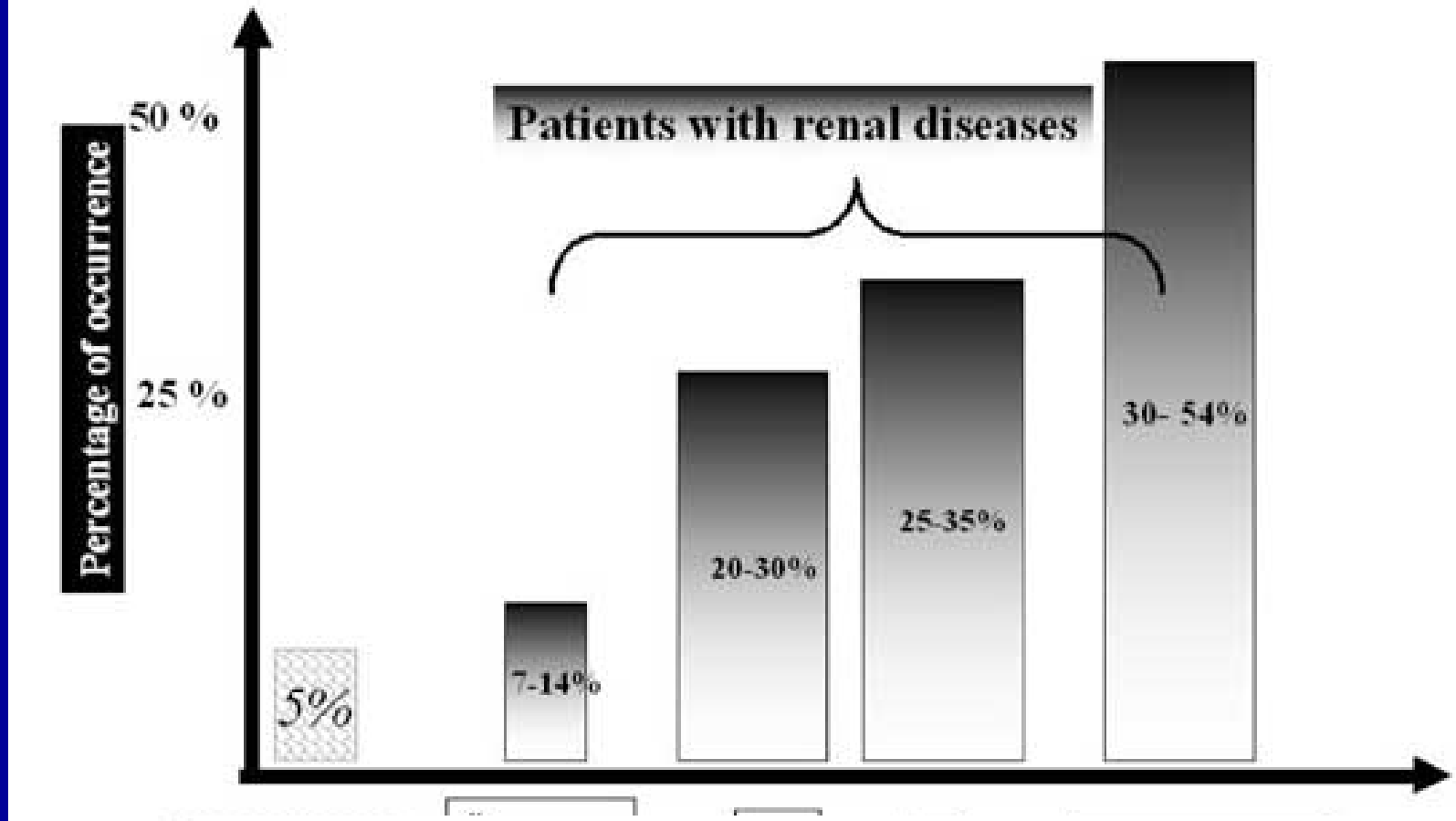
Pregnancy Outcomes in Stage 1 and 2 CKD

Piccoli et al. 2010

	Stage 1 CKD (eGFR> 90)	Stage 2 CKD (eGFR 60-90)
Delivery< 37 wks	33%	40%
Delivery <34 wks	15%	14%
SGA	13%	7%

91 women with CKD, 2000-2009

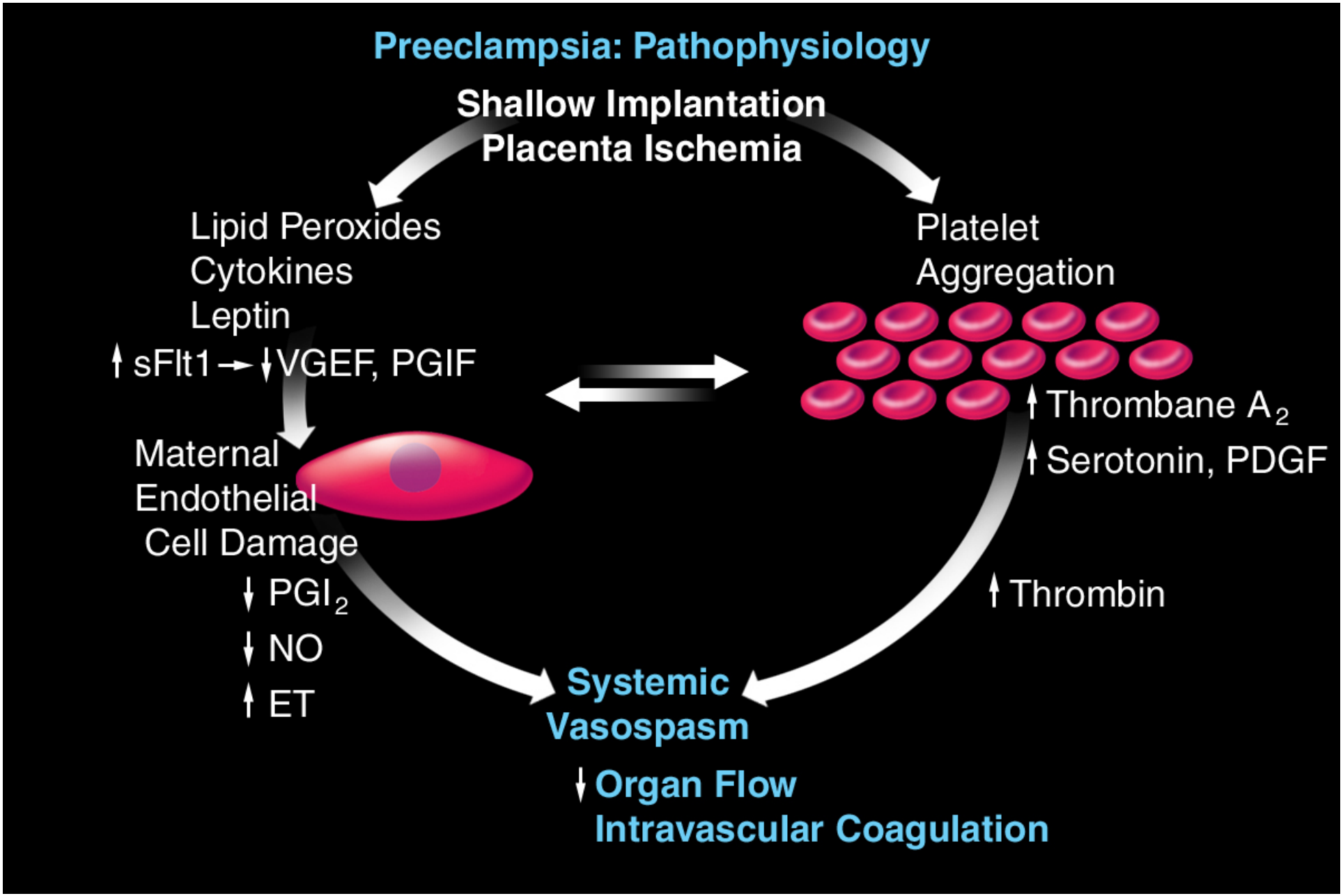
Risk of Preeclampsia Increases with Advanced CKD



Adapted from Stratta et al 2006

Are Adverse Pregnancy Outcomes with CKD all Due to Preeclampsia?

- When preeclampsia is 'superimposed' on preexisting hypertension or renal disease the risk for stillbirth, fetal growth restriction, placental abruption, premature delivery, and maternal mortality and morbidity increase significantly
- In absence of maternal hypertension or preeclampsia pregnancy outcomes are significantly better


Preeclampsia: Pathophysiology
Shallow Implantation
Placenta Ischemia
Lipid Peroxides
Cytokines
Leptin
↑ sFlt1 → ↓ VGEF, PGIF
Maternal
Endothelial
Cell Damage
↓ PGI2
↓ NO
↑ ET
Platelet
Aggregation
↑ Thrombane A2
↑ Serotonin, PDGF
↑ Thrombin
Systemic
Vasospasm
↓ Organ Flow
Intravascular Coagulation

Why Does CKD Increase Risk of Preeclampsia?

- Shared *risk factors* among CKD, hypertension, and preeclampsia (e.g. metabolic syndrome, inflammation, SNPs in RAS, obesity)
- Chronic vascular disease leading to diminished placental perfusion
- What is the role of reduced GFR? Inflammation? Hypertension?

Pregnancy Outcomes After Kidney Donation

Ibrahim et al AJT 2009

- 1085 women; 3213 pregnancies
- Pre donation pregnancies (n=2519) compared with post donation pregnancies (n=490)
- 377 pre and post donation pregnancies

Pre Donation vs Post Donation Pregnancy Outcomes *(Ibrahim et al)*

	Pre Donation	Post Donation
Pre term Del	4 %	7.1%
Fetal Loss	11.3 %	19.2%
Gest DM	0.7%	2.7%
Maternal HTN	0.6%	5.7%
Preeclampsia	0.8%	5.5%
Proteinuria	1.1%	5.3%

P = 0.0001

Summary

- Renal adjustments to pregnancy are profound, and apparently necessary for normal gestation
- There is a direct relationship between degree of renal dysfunction and adverse pregnancy outcome
- Even mildly reduced GFR is associated with pre term birth, fetal loss, preeclampsia

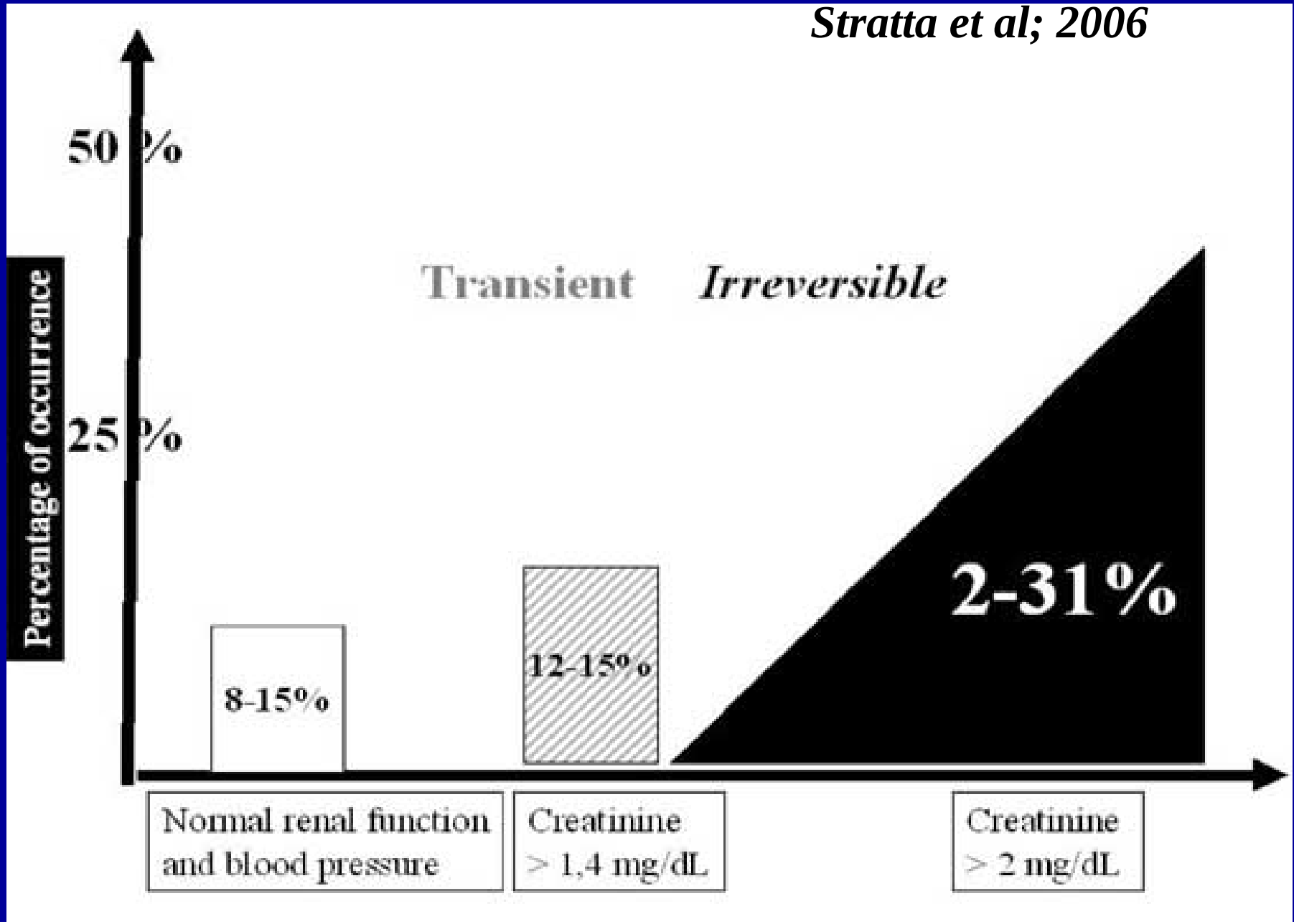
How Does Pregnancy Influence Renal Disease?

- Hemodynamic changes – No evidence for hyperfiltration (increased GC Pressure)
- ? Increased inflammatory response
- Increased urinary protein excretion
- Preeclampsia
- Possibility of permanent loss of function

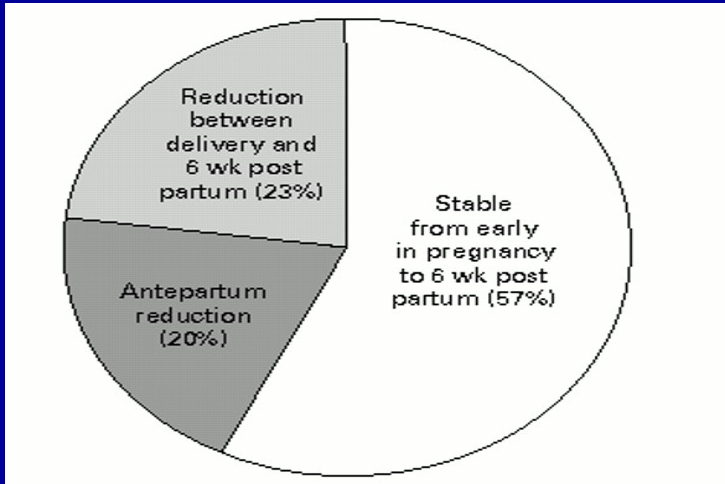
What is the Impact of Physiologic Changes of Pregnancy on Long Term Renal Function?

- Animals with normal kidneys – repetitive pregnancy does not cause renal damage : reduce R_A and R_E, no increase in P_{GC} (Baylis et al)
- Women with mild renal insufficiency (creat < 1.4 mg/dl) demonstrate similar renal hemodynamic changes
- Animal models of CKD: heterogeneity in renal responses to pregnancy (Baylis et al)

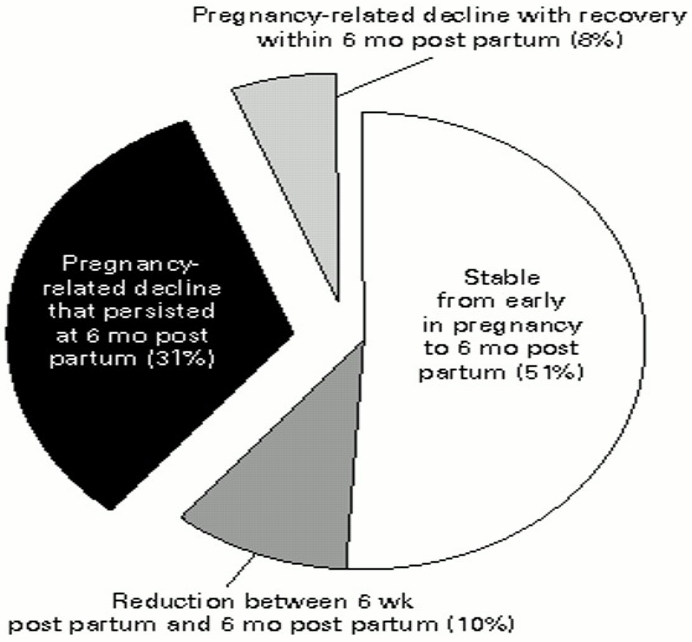
Risk of Worsening of Renal Function in Pregnancy by GFR



Irreversible Reduction in GFR at 6 Months Post Partum in 31%



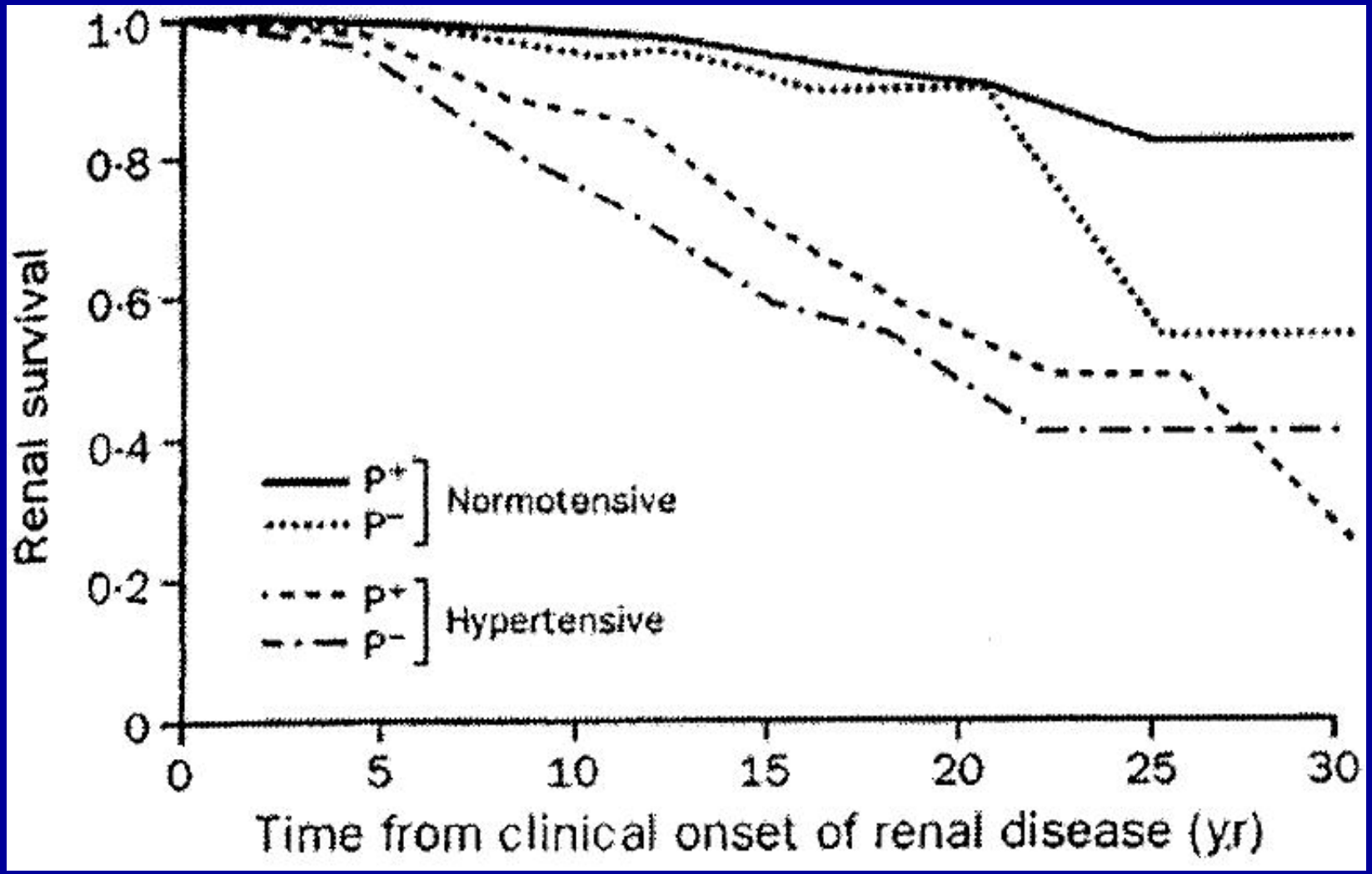
Glomerular Filtration Rate during Pregnancy



Glomerular Filtration Rate 6 mo Post Partum

Jones and Hayslett
NEJM 1996

Influence of Pregnancy on Long Term Course of GN Hypertension is an Important Confounder



Jungers P et al Lancet 1995

CKD and Pregnancy
Take Home Message (Summary)

- Outcome related to GFR, Proteinuria, and BP:
  - Favorable if Scr < 1.4 mg/dl, proteinuria < 1 g/d *(Imbasciati et al 2007; Rene e Gravidanza)*
  - Favorable in absence of hypertension
  - Little evidence for relationship between histologic diagnosis and outcome

Type 1 Diabetes

- Pregnancy and renal outcomes are better in early stages: normal GFR, microalbuminuria
- Preeclampsia, preterm birth, and SGA are increased even when GFR is normal
- Overt Nephropathy (macroalbuminuria, reduced GFR): Serious Maternal and Fetal morbidity and mortality

Diabetic Nephropathy in Pregnancy: Rx

- First trimester glycemic control is important
- ACE inhibitors and ARB's are contraindicated, increased proteinuria is common in pregnancy

Lupus is Associated with Poor Pregnancy Outcomes

- 'Active' SLE at conception
  doubles fetal loss (25%)
  triples pre term births (75%)
  (Clowse et al. 2005)

- 4 fold increase in stillbirth
  30% preterm birth, 28% LBW
  20-30 % Hypertension/preeclampsia

  (Dhar et al. 2005)

Pregnancy in Women with Preexisting Lupus Nephritis

Imbasciati et al; NDT, 2009

- 113 pregnancies, all biopsied, renal function normal at baseline
- Fetal loss – 13%
- 30% preterm birth; 25% IUGR

Pregnancy and Preexisting Lupus Nephritis

Imbasciati et al.

- 34 renal flares; most treatable; 3 deterioration in GFR, one ESRD

Predictors of Pregnancy Outcomes:

- Hypocomplementemia, low dose aspirin

Predictors of Adverse Renal Outcomes:

- Proteinuria > 1g; GFR < 60 (OR 9)
- Partial remission (OR 3)

Lupus Flare vs Preeclampsia?

	SLE	PE
Proteinuria	+	+
Hypertension	+	++
Azotemia	++	+
RBC Casts	**+**	**-**
Low C3,C4	**+**	**-**
Abnl LFTs	**-**	**+/-**
Low platelets	+	+/-
Low WBC	+	-

Lupus Nephropathy: Summary

- Possibility of flare during pregnancy increases morbidity
- Conception should be discouraged when disease is ‘active’
- Antiphospholipid antibodies are associated with poor pregnancy outcome
- Cyclophosphamide and mycophenalate are contraindicated in pregnancy

CKD in Pregnancy

- Anatomic/congenital: Reflux, solitary kidney
- GN; IgA, FSGS, Vasculitis (SLE, Wegener's)
- PKD
- Interstitial nephritis

CKD First Diagnosed During Pregnancy

- Any mild renal disease may become clinically apparent for the first time during pregnancy because of hemodynamically mediated increase in proteinuria, closer monitoring of BP and U/A
- Examples: FSGS, Reflux nephropathy, chronic pyelo, ADPKD, SLE

Renal Evaluation During Pregnancy

- Serology
- Function
- Ultrasound
- Biopsy: < 30-32 weeks
  deteriorating function
  morbid nephrotic syndrome;
  Bx may be associated with significant morbidity

Intrinsic Renal Disease vs Preeclampsia (gestational age> 20 wks)

	Preeclampsia	Renal Disease
BP	> 140/90 mm Hg	variable
Uprot	>300 mg/d	variable
Serum Cr	.8-1.2 mg/dl	>1.0 mg/dl
Uric acid	>5.5 mg/dl	variable
LFTs	may be increased	normal
Platelets	may be decreased	usually normal
UA	protein, +/- RBC,WBC	variable

Pregnancy Outcome In ADPKD

Chapman et al, 1994 JASN

- 235 ADPKD compared with unaffected relatives
- Preexisting hypertension and preeclampsia were major determinants of adverse maternal and fetal outcomes
- Multiple pregnancies were associated with lower GFR

Management of Chronic Renal Disease During Pregnancy

- Preconception counseling; DC ACE-I, ARB's
- Multidisciplinary Approach
- Frequent monitoring of BP (q 1-2 weeks) and renal function (q month)
- Balanced diet (moderate Na, protein)
- Maintain BP 120-140/80-90 mm Hg
- Watch for preeclampsia

Antihypertensive Drugs Safe in Pregnancy

- Methyldopa (clonidine, if side effects to MD)
  - Starting dose 250 BID
  - Maximum of 500 QID
- Labetolol (and other beta blockers)
  - Starting dose 100 BID
  - Maximum 200 QID
- Nifedipine XL (other NDHP CCBs have been used)
  - Starting dose 30 OD
  - Maximum 90 OD
- ? Amlodipine; no data!
  - 2.5 to 10 mg OD

CKD in Pregnancy: Summary

- ADPKD may be diagnosed during pregnancy
- Kidney biopsy is rarely indicated during pregnancy
- Increased creatinine without proteinuria is usually not preeclampsia
- Proteinuria without hypertension is usually not due to preeclampsia

Dialysis and Pregnancy

- **Asamiya et al (KI 2009)**
  28 pregnancies; only 2 full term (average, 32 weeks)
  18 infants survived one year
  BUN should be <= 48mg/dl
  Hb should 9-11
  better outcomes associated with increased dialysis, EPO, transfusions

- **Luders et al (AJKD 2010):**
  52 pregnancies, 87% success rate (32 wks)
  preeclampsia major risk factor for adverse outcome

Transplantation and Pregnancy

- Prognosis depends on BP and baseline renal function (< 1.5 -2 mg/dl; nl BP)
- Controversy whether pregnancy accelerates graft loss
- Patients are advised to wait 1-2 years post transplant
- CN inhibitors associated with HT, prematurity
- MMF, Rapa: not recommended
- Azathiaprine, prednisone: preferred regimen

Summary and Conclusions

- The Kidney is a ‘reproductive organ’
- Outcome of pregnancy related to renal function, BP, proteinuria: relationship between histology and pregnancy outcome is not clear
- Superimposed preeclampsia is responsible for most of the morbidity and mortality in pregnancy
- Need for multicenter studies/registries
- Basic research to understand the relationship of CKD to preeclampsia and pregnancy outcomes

‘Sex and the Kidney’

Carrie: “Do you think this business about preeclampsia is for real?”

Miranda: “ I heard that if you have CKD your chances of having a healthy pregnancy are reduced?”

Charlotte: “What’s CKD?”

Samantha: “I don’t know but it doesn’t sound like fun!”