

Renal Disease in Pregnancy

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Overview

- The normal kidney in pregnancy
- Hypertension and pre-eclampsia
- Acute renal failure in pregnancy
- Chronic kidney disease and pregnancy
- End-stage renal disease and pregnancy
- Transplantation and pregnancy
- Pre-pregnancy counseling in renal disease

The kidney in pregnancy

- Kidney volume increases 30%
- ERPF increases 50-80%, primarily due to reduced RVR
- GFR \uparrow 40-50% at 13/40, baseline at 8-12 weeks post-partum
- SCr \downarrow 0.4-0.5mg/dl; normal pregnancy SCr 0.46 ± 0.13 mg/dl, BUN 8.7 ± 1.5 mg/dl, uric acid 2.5 – 4.0mg/dl
- Tubular Na⁺ reabsorption \uparrow 40-50% (20,160mEq/d \rightarrow 30, 240 mEq/d)
- SNa⁺ \downarrow ~5mEq/L / \downarrow Posm ~ 10mOsm/kg H₂O

GFR and ERPF in pregnancy

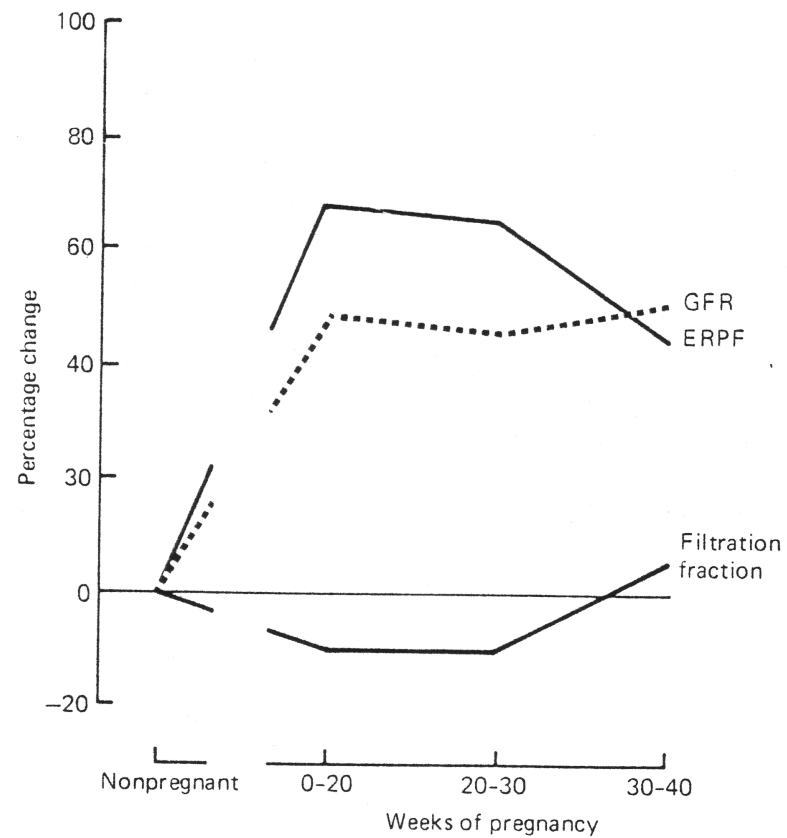


Fig. 1. Relative changes in renal hemodynamics during normal human pregnancy (based on mean data from Table 1).

Davison et al, KI 18, 1980; 152-161

Renal vasodilatation in pregnancy

ET via $ET\beta R$

EDRF (NO) $\Rightarrow \Rightarrow$

$\uparrow RPF$
($\downarrow \pi p$)

$\Rightarrow \Rightarrow \uparrow GFR$

Vasodilatory PG's
Relaxin

EDRF; Endothelial Derived Relaxing Factor, (NO)

ET; Endothelin

Q & A

Hct	31%	Sodium	132
WBC	9.0	Potassium	3.9
Plt	220	Chloride	95
BUN	5.0	Bicarbonate	20
SCr	0.6	SaO ₂	98%
UA	pH6.0, SG 1.020		

Which of the following is most likely based on the patient's electrolytes?

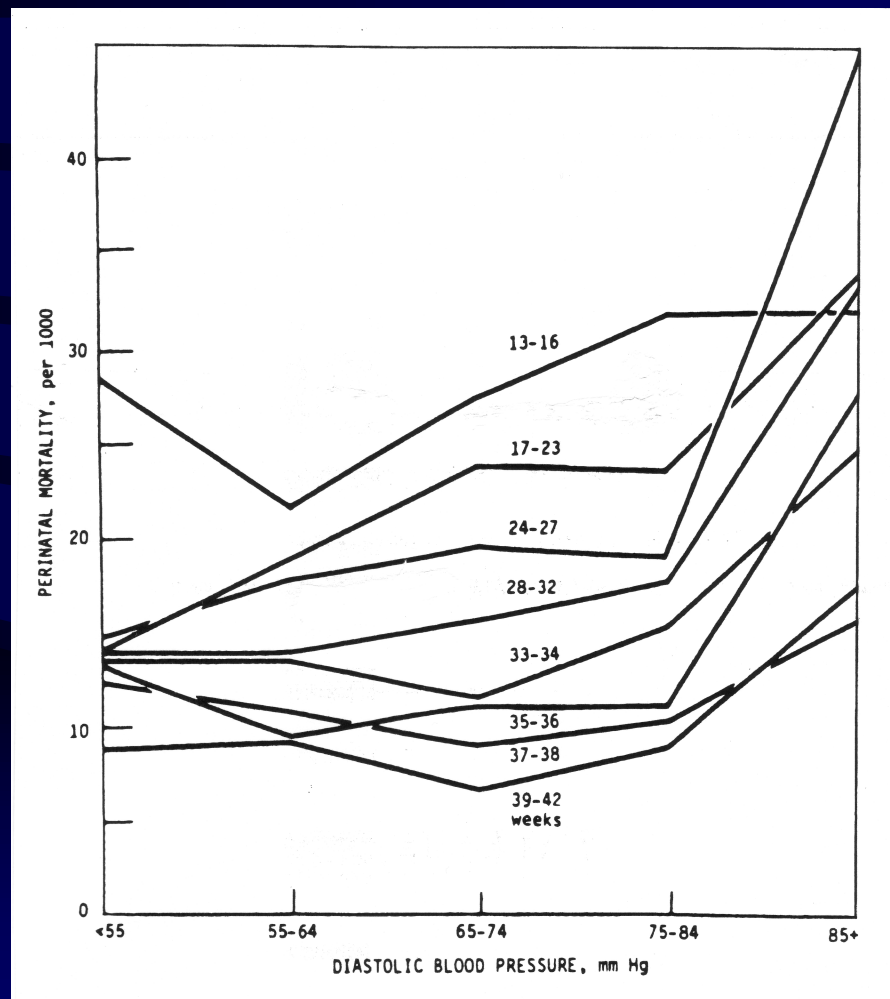
- A) Acute resp. alk. due to PE
- B) Met. acidosis due to GI disorder
- C) HyperCl met. acidosis due to RTA
- D) Normal values in a pregnant woman

Hypertension in pregnancy

- 1) Gestational hypertension
de-novo hypertension occurring alone after 20/40 which resolves post-partum. Risk factor for essential hypertension in later life.
- 2) Chronic hypertension
- 3) Pre-eclampsia
- 4) Chronic hypertension with superimposed pre-eclampsia

US NHBPEP, 1990

Hypertension and adverse outcomes in pregnancy



Hypertension and adverse outcomes in pregnancy

- Progressive increase in perinatal mortality with each 5mmHg increment in MAP
- $\text{MAP} \geq 90\text{mmHg}$ during 2nd trimester correlates with increased incidence of IUGR, pre-eclampsia
- If BP = 120/80, MAP = 93mmHg ie: 'normal' blood pressure in pregnancy associated with adverse outcomes
- 1/3 pregnant women with $\text{MAP} \geq 90\text{mmHg}$ in 2nd trimester progress to pre-eclampsia cf. 2% of pregnant women with $\text{MAP} < 90\text{mmHg}$ in second trimester

Chronic hypertension and pregnancy

Definition

- BP $>140/90$ pre-pregnancy, present $<20/40$, persists for $>12/52$ post partum

Mild – moderate $>140/90$ - $<179/110$

Moderate – severe $>180/110$

- Affects 1-5% of pregnancies, more common with increased age, obesity, AA, +FHx
- 25-30% risk for progression to pre-eclampsia

Chronic hypertension and pregnancy

	Mild-Moderate	Moderate - severe	Superimposed pre-eclampsia
Perinatal mortality			
Placental abruption	↑ 0.7-1.5%	↑ 5-10%	?
IUGR	↑ 8-16%	↑ ↑ 30-40%	?
Prematurity	↑ 12-34%	↑ ↑ 62-70%	↑ ↑ ↑ >70%
Superimposed pre-eclampsia	↑ 10-25%	↑ ↑ 50%	—

Chronic hypertension and pregnancy – risk stratification

Low Risk mild-moderate essential HTN, <4 yrs duration, no h/o pre-eclampsia. Can become high risk as pregnancy progresses

High Risk severe hypertension, HTN >4yrs, secondary HTN, h/o pre-eclampsia/perinatal loss, end-organ damage, maternal age >35, diabetes, vascular disease, renal disease

Chronic hypertension and pregnancy – evaluation/risk stratification

- **H&P:** duration/severity of HTN, treatment/compliance, obstetric history, prior evaluation for secondary causes/end organ damage, comorbidities
- **Data:** UA/UCx, chem 7, 24hr urine protein, 24hr urine creatinine clearance (supranormal)
If long-standing HTN, poor control/compliance - evaluate for end-organ damage: EKG, echocardiogram ?LVH
- **Screen for secondary HTN:** renal US, cortisol, TFT's, PRA/aldo (?↓K), 24hr urinary metanephrines/plasma metanephrines, ?MRA for RAS/FMD

Chronic hypertension and pregnancy – goals of therapy

- Low risk
 - No compelling evidence that treatment alters outcome but does reduce rate of exacerbation of hypertension.
 - No evidence that improved BP control reduces rate of superimposed pre-eclampsia or placental abruption
 - Control of hypertension does not affect gestational age at delivery
- High risk (no trials)
 - BP control may alter short and long-term outcome in women with end-organ damage, renal disease, vascular disease and diabetes
 - Even mild hypertension treated in this group.

Chronic hypertension and pregnancy - treatment

- During pregnancy
 - 1 = methyldopa / labetalol
 - 2 = CCB / hydralazine (not monotherapy)
 - 3 = thiazide diuretic

No ACE inhibitor/ARB after conception/1st trimester

Early delivery for severe hypertension

Bed rest
- During lactation
 - Labetalol/propranolol/methyldopa
 - Sustained release verapamil/nifedipine

ACE inhibitors/ARB's in pregnancy

- 2nd and 3rd trimester exposure; fetal and neonatal renal dysfunction - oligohydramnios, neonatal anuria and renal failure, death
- Other effects: renal tubular dysplasia, pulmonary hypoplasia, prolonged neonatal hypotension, PDA, traumatic developmental abnormalities due to oligohydramnios
- Fetal toxicity not seen if limited to use in 1st trimester ; if planned pregnancy d/c prior to conception, if unplanned and d/c before 10 weeks – outcome generally good

Chronic hypertension and pregnancy – treatment of hypertensive urgency

Hydralazine	IV	5mg, then 5-10mg q30min or infusion 0.5-10mg/h
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Labetalol	IV	20mg then 20-80mg q20- 30min/max 300mg or infusion 1-2mg/min
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(Nifedipine)	PO/SL	5-10mg PO, q30min x 1, then 10-20mg every 2-6 hrs
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Relatively contraindicated, category D, agent of last resort
(Nitroprusside) IV 0.5-10mcg/kg/min

Q & A

Hct	33%	BUN	11
SCr	0.7	Uric acid	4.1
UA	tr prot	Uprot	125mg/24hr
Cr Cl	160ml/min		

Which of the following is not correct?

- A) ramipril should be stopped
- B) another antihypertensive should be started
- C) she has an approximately 25% risk for pre-eclampsia
- D) better BP control will diminish the risk for pre-eclampsia

Q & A

Na	146	K	2.5
BUN	8	SCr	0.8
Uric acid	4.0	Cl	108
Uprot	150mg/24hr		
8am ald.	50ng/dl	Noon ald.	22ng/dl
renin	4ng/ml/hr	renin	4ng/ml/hr

What is the most likely diagnosis?

- 1) malignant hypertension
- 2) 1^o aldosteronism due to adrenal adenoma
- 3) renal artery stenosis
- 4) pre-eclampsia
- 5) 1^o aldosteronism due to bilateral adrenal hyperplasia

Pre-eclampsia

- De novo hypertension after 20/40 plus:
 - New onset proteinuria

And/or at least one of the following:

- Renal insufficiency or oliguria
- Abnormal LFT's, RUQ/epigastric pain
- Neurologic manifestations; HA, visual dist., ↑reflexes
- Hematologic abnormalities; ↓plts, DIC, MAHA
- Fetal growth restriction

Chronic hypertension with superimposed pre-eclampsia

Chronic HTN without proteinuria <20/40

- PE = new onset proteinuria

Chronic HTN with proteinuria <20/40

- PE = exacerbation of BP to severe range in previously well controlled pt., with one or more additional diagnostic criteria for pre-eclampsia ie: HA, epigastric pain, reduced visual acuity, elevated LFT's, ↓plts etc

Pre-eclampsia

- Cause? – unknown
 - Abnormal placentation
 - Maternal endothelial dysfunction
 - Genetic factors
 - Increased maternal inflammatory response
 - Immunologic factors
 - Infectious diseases
- Predicting pre-eclampsia – no good markers
- Prevention
 - Low dose aspirin, vitamin C & E, Ca²⁺, fish oil
 - Trial of magnesium sulfate prophylaxis ongoing

Pre-eclampsia - management

Delivery if viable / termination if remote from term

Temporizing measures if stable maternal/fetal unit and benefit of increased fetal maturity outweighs risk

Antihypertensive therapy: PO or IV (not diuretics)

- threshold for therapy? $>160/105$

Seizure control – magnesium sulfate

- Superior to anticonvulsants and nimodipine
- Risk of toxicity with renal impairment
- Never compared to BP control per se in trials

Q & A

Hb	10	Uric acid	4.0
BUN	10	SCr	0.8
UA	no protein		
Normal physical exam			

Which of the following therapeutic options is most appropriate?

- A) Prescribe enalapril
- B) Prescribe hydralazine and HCTZ
- C) Admit to hospital
- D) Prescribe methyldopa

Acute renal failure in pregnancy

- *Any etiology; pre-renal, renal, post-renal*
- Pyelonephritis/UTI
- ATN/cortical necrosis
oligoanuria, gross hematuria, flank pain
- Acute fatty liver of pregnancy: 60% ARF
- Obstruction
- Thrombotic microangiopathy

ARF in pregnancy – thrombotic microangiopathy

Fulminant PE, HELLP

Preceding HTN, proteinuria
>20/40, late 3rd trim., intrapartum
HTN+++, renal failure +
Coagulopathy / DIC
LDH ↑ (500-800)

Severe liver dysfunction
Hepatic subcapsular hematoma

TTP

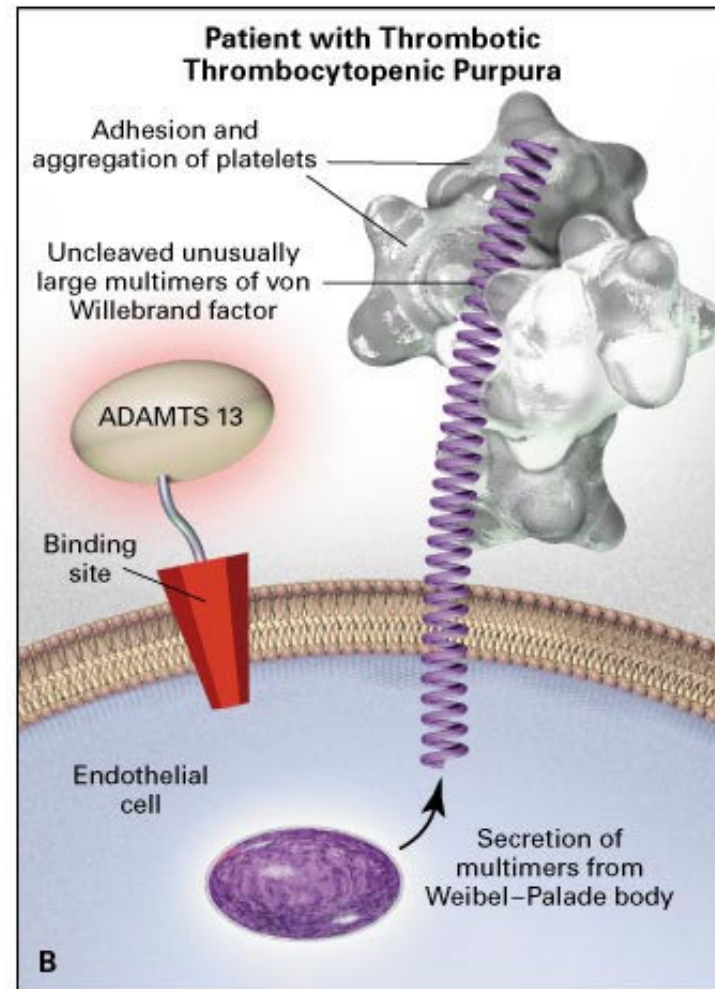
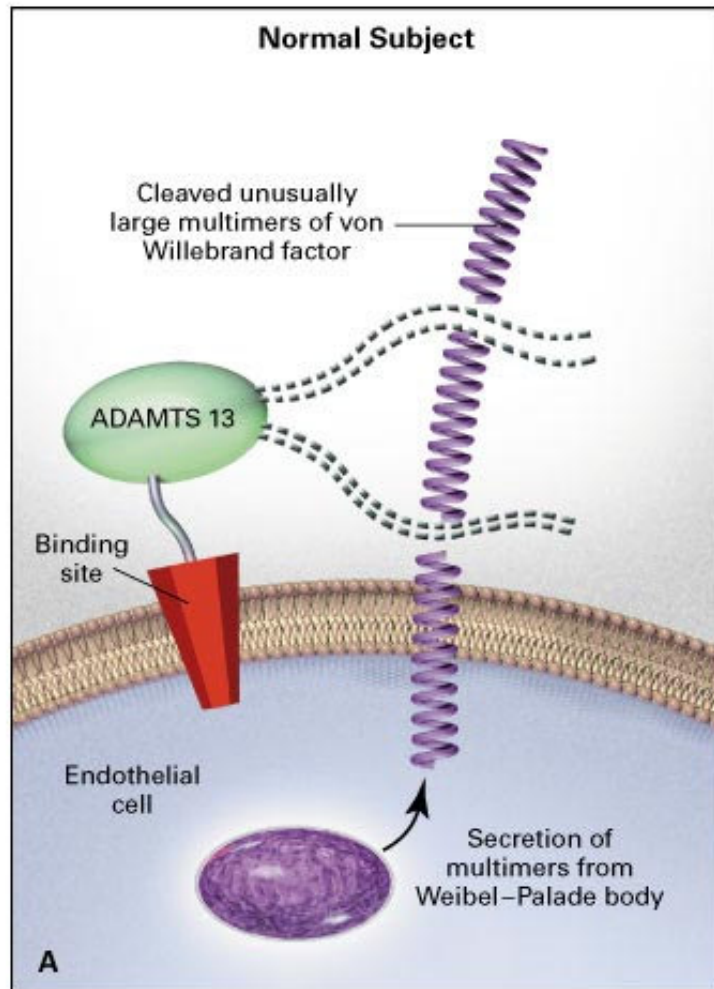
Any trimester, 2d-4wk post-part.
HTN+ / ++, renal failure ++ / +++
No coagulopathy
LDH ↑↑ (>1000)

Fever prominent
Profound ↓plts, ↓Hct

ARF in pregnancy – thrombotic microangiopathy

“ Acute post-partum renal failure is one of the strangest complications of an apparently uncomplicated pregnancy and delivery.....occasionally the same syndrome strikes during pregnancy.....Renal failure is usually irreversible although Finkelstein saw 2 patients make an excellent recovery.....heparin improved some cases but not others”

Lancet ii, 1975, 801-802



Moake JL, Thrombotic Microangiopathies, NEJM 2002; 347: 589-600

Q & A

Hct	40	SCr	1.7
WBC	7.0	Bili	2.7
Plt	70	AST	500
LDH	500	Haptoglobin	14
UA	2+ prot	Uric acid	8.3
Smear	schistocytes, helmet cells		
Retics	5%	FSP	20mg/dl (<10)

What is the most likely diagnosis?

- A) TTP
- B) Malignant HTN
- C) Acute GN
- D) Acute pancreatitis
- E) Fulminant pre-eclampsia

Renal biopsy in pregnancy

- Complication rate no different than that in non-pregnant women in pregnant women biopsied <34/40
- Biopsy during pregnancy restricted to:
 - sudden decline in renal function <32/40, ?RPGN – may be steroid responsive
 - symptomatic nephrotic syndrome <32/40, ?steroid responsive (more controversial)
 - active urinary sediment ?SLE – for classification of lesion to direct therapy / prognosis

CKD and pregnancy

Historically (before 1975) pregnancy discouraged for women with CKD and early termination advised

“ children of women with renal disease used to be born dangerously or not at all – not at all if their doctors had their way.....nature takes a helping hand by blunting fertility as renal function falls ”

Lancet ii, 1975, 801-2

CKD and pregnancy

- Considerations
 - Effect of renal disease on pregnancy outcomes
 - Effect of pregnancy on renal disease

CKD and pregnancy

- Preserved/mildly reduced renal function, Cr \leq 1.4
 - good outcome for pregnancy and renal disease
- Moderately impaired renal function, Cr 1.4 – 2.8
 - risk progression of renal failure, increased fetal risk
- Severe renal insufficiency, Cr $>$ 2.8
 - high fetal/maternal morbidity/mortality, low likelihood of successful outcome, pregnancy discouraged
- High grade proteinuria and severe hypertension
 - also important risk factors for progression of renal disease in pregnancy, worse outcomes

CKD and pregnancy

Etiology of renal disease and outcomes in pregnancy:

- Best outcomes; chronic interstitial disease (eg:reflux)
- Worse outcomes (for any given degree of renal impairment); lupus (?) and MPGN
- Women with scleroderma and polyarteritis nodosa discouraged in past from attempting pregnancy but case reports of successful outcomes with quiescent disease.

CKD and pregnancy – diabetic nephropathy

- 6% of pregnant women with type I DM have overt diabetic nephropathy (<20/40: Uprot>300mg/d, macroalbuminuria >300mg/d, alb/creat. ratio >0.3mg/mg)
- Microalbuminuria also associated with an increased risk of adverse fetal-maternal outcomes
- **Effect of nephropathy on pregnancy:** prematurity(22%), IUGR (15%), pre-eclampsia
- **Effect of pregnancy on nephropathy:** exacerbation of proteinuria and hypertension. Return to baseline post-partum with well preserved renal function.

CKD and pregnancy – diabetic nephropathy

- Pre-eclampsia is the most frequent complication of pregnancy in women with diabetic nephropathy
- Perinatal survival 95% in pregnancy with overt nephropathy (cf 99% general obstetric population)
- **Pre-conceptual management:**
 - Staging of disease; 24 hr Uprot. /Cr Cl, eye exam (SCr >2.0 and Uprot >2g/24hr relative contraindications)
 - Counseling re: risks to mother and fetus
 - Good glycemic/BP control, for at least 6mths pre-conception
 - ACE inhibitors pre-conception – protective benefit carries over into pregnancy. Substitute for CCB (?) during pregnancy.

CKD and pregnancy - ADPKD

- Exacerbation of HTN, increased risk of pre-eclampsia
- Genetic counselling re: risk to offspring, screening of offspring (PKD 1 disease: >20, but negative US does not exclude disease until pt >30-35, negative CT at 25 excludes clinically significant disease)
- Prenatal genetic testing for PKD1 disease (C16) - available
- No increased incidence of simple UTI during pregnancy
- Association between women who have had ≥ 3 pregnancies and worse renal function (Gabow et al)

CKD and pregnancy - Lupus

- Rate of relapse not different between pregnant women and concurrent controls (9-60%).
- Major factor determining a pregnancy related exacerbation is the stability of the disease before conception.
- If in remission for >6mths pre-conception, low incidence of clinical flare during pregnancy.
- In a prospective study of planned pregnancy in women with inactive SLE, live birth rate was 96%.
- Prematurity common.
- Irreversible decline in renal function uncommon.
- Assess for disease activity once each trimester, more frequently if active disease in 6mths pre-conception

CKD and pregnancy - Scleroderma

- Before 1971; 12 case reports of pregnancy in scleroderma – 35% maternal mortality – renal/pulmonary disease
- Incidence of pregnancy in scleroderma increasing with increasing maternal age (peak onset of this disease 30-50)
- Fertility? – no data. Increased incidence of spontaneous abortion? – probably. Pregnancy outcome? – no data
- Scleroderma renal crisis vs pre-eclampsia vs TTP etc
- High morbidity in women who develop renal crisis during pregnancy. Women with active renal disease or early diffuse disease counseled against pregnancy.

CKD and pregnancy

“ secondary syphilis must not be missed as a rare but curable cause of nephrotic syndrome in pregnancy ”

Lancet ii, 1975, 801-2

Q & A

BUN	28
SCr	2.2
Uric acid	5.1
UA	4+ protein

Which of the following about this patient's course is correct?

- a) She is not at high risk for pre-eclampsia
- b) She is not at high risk for premature birth
- c) She has a 1-2% risk for developing more severe CKD
- d) Her fetus is at risk for IUGR

End-stage renal disease and pregnancy

- Reduced fertility / infertility common in pts on RRT
 - elevated prolactin, reduced estrogen, anemia, anovulation
- Contraception is advised for all women of childbearing age receiving RRT
- Rates of conception – few data; ?1/200
- If candidates, women are strongly advised to wait until after transplantation before trying to conceive, may be considered for pre-emptive transplantation.
- Outcome also determined by comorbidities; HTN, DM

ESRD and pregnancy

- Significant risk for; spontaneous abortion, IUGR, preterm delivery, pre-eclampsia, and some increased risk of fetal abnormality (mild dysmorphogenesis)
- Successful outcome rates?- improved over time; 50% in pts on HD pre-conception, 80% in pts initiating dialysis after conception
- Prematurity and low birth weight occur in almost all successful pregnancies

ESRD and pregnancy

Management of women who require RRT

- General principal, “more dialysis is better”, empiric
- If CAPD, consider change to HD, esp. if minimal residual renal function, but not mandatory
- If pre-ESRD may need to institute dialysis after conception to mimic physiologic augmentation of renal function in pregnancy.
- HD 5-6d/wk, avoid intradialytic hypotension, EPO \pm Tx for anemia, control of hypertension / Increase PD exchanges – some combination of day and night exchanges usually required
- Other considerations: preservation of access, estimation of dry weight, dietary protein intake, \uparrow PRA

ESRD in pregnancy

“ One day we will reach a point where physicians regard childbearing as a goal of treatment for dialysis patients of childbearing age rather than as an accident to be handled when it occurs. Our understanding of how to care for those women has not yet reached the point where we can justify treating infertility in dialysis patients”

S. Hou, PDI 21, 2001; S3

Renal transplant and pregnancy

- National Transplant Database Pregnancy Register, NT DPR (UK)
- National Transplantation Pregnancy Register, NTPR (USA)

>14,000 pregnancies reported worldwide

Renal transplant and pregnancy

- Transplantation restores fertility
- 1/50 women of childbearing age with a functioning transplant become pregnant
- Of pregnancies that continue beyond the 1st trimester, 92% result in a live birth
- Outcome dependent on co-morbidities, presence or absence of hypertension, renal function at conception, degree of proteinuria (</>1g/day).
- In women with stable well-preserved graft function, pregnancy per se does not appear to adversely affect graft function.

Renal transplant and pregnancy

	CsA Sandimmune	Neoral Gengraf etc	Tacro Prograf
Livebirths (n)	350	57	17
Gestational age (mean)	35.9	35.8	33
Birthweight (mean,g)	2485	2449	2151
Premature (<37/40) %	52	51	63
Low birth wt. (<2500g) %	46	54	63
Caesarian %	51	48	44
Neonatal complications %	40/1	49/0	53/6

Modified from Armenti et al, Graft 2000; 3: 59-63

Pancreas-kidney transplant and pregnancy

- NTPR reported 10 pts in 1998:
 - CsA based regimens
 - 75% premature
 - 83% low birth weight
 - 66% delivered by CS
 - Increased incidence of UTI, HTN etc

Renal transplant and pregnancy

- Delay conception for at least 1 year (ideally 2) post-transplant or 12mths from last episode of rejection, or until stable graft function/stable immunosuppression for 12 mths, and until drugs contraindicated in pregnancy have been withdrawn
- Advise against pregnancy in women with moderate-severe graft dysfunction/poorly controlled BP/ 24hr Uprot >500mg
- All these pregnancies are high-risk
- Increased incidence of UTI and graft pyelonephritis, anemia, worsening proteinuria (usually transient)
- No increased incidence of acute rejection.

Renal transplant and pregnancy

Safety of immunosuppressive agents in pregnancy:

- **Steroids**; safe, lower dose – better outcome
- **Azathioprine (D)**, **cyclosporine (C)**; large body of experience – not teratogenic
- **MMF(C)**; teratogenic
- **Tacrolimus (C)**; several large series, appears safe,
- **Rapamune/Sirolimus(C)**; unknown, considered unsafe

CsA levels can fall in pregnancy – need monitored more closely

Breast-feeding not recommended

Renal transplant and pregnancy

- No definite pattern of abnormality among offspring
- Possible increased incidence of urinary tract abnormalities in offspring (10%)
- Long-term follow-up; general health and physical assessment unremarkable *for gestational age*
- 16% developmental delay / need for educational support (cf 11% of children in US schools)

Pre-pregnancy counseling in renal disease

Nephrologist

Medical/renal history
Staging of renal dz., HTN, DM
Transplantation

Risks to mother/fetus

Discuss optimal timing
Med. changes pre-conception
All information in written format

High-risk obstetrician

OB/gyn. history
Genetic history
Psychosocial
Contraception
Fertility

Risks to mother/fetus

Renal disease in pregnancy

“ What advice should we give to a woman with chronic renal disease who is contemplating pregnancy?....dogmatic prohibition does not seem justified today.... Instead, obstetricians and physicians must batten down the hatches and prepare to ride out the storm together with those determined to set sail.”

Lancet ii, 1975, 801-2