ZWANGERSCHAP BIJ CHRONISCH NIERLIJDEN

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ORPADT nefrologiedag 2018

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“ 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, 1975,801-802

CKD stage 5

- ‘Show me a method of birth control more effective than end stage renal disease’, Roger Rodby MD, 1991

- ‘Even if a woman on CAPD ovulates, doesn’t the egg just float away?’, Rodby, 1992

Case 1

- 30-year old woman with ADPKD
- Creatinine 1.45 mg/dl (klaring van 48 ml/min/1,73m²)
- Blood pressure: vasexten 20 mg/d
- No proteinuria

How are you going to counsel?

Case 2

- Alport disease (COL4A5)
- Normal renal function
- Proteinuria before pregnancy : 0.3 g/d (treated with lisinopril 5 mg/d)

Pregnancy: counselling and shared decision making

Perspectives on pregnancy in women with CKD

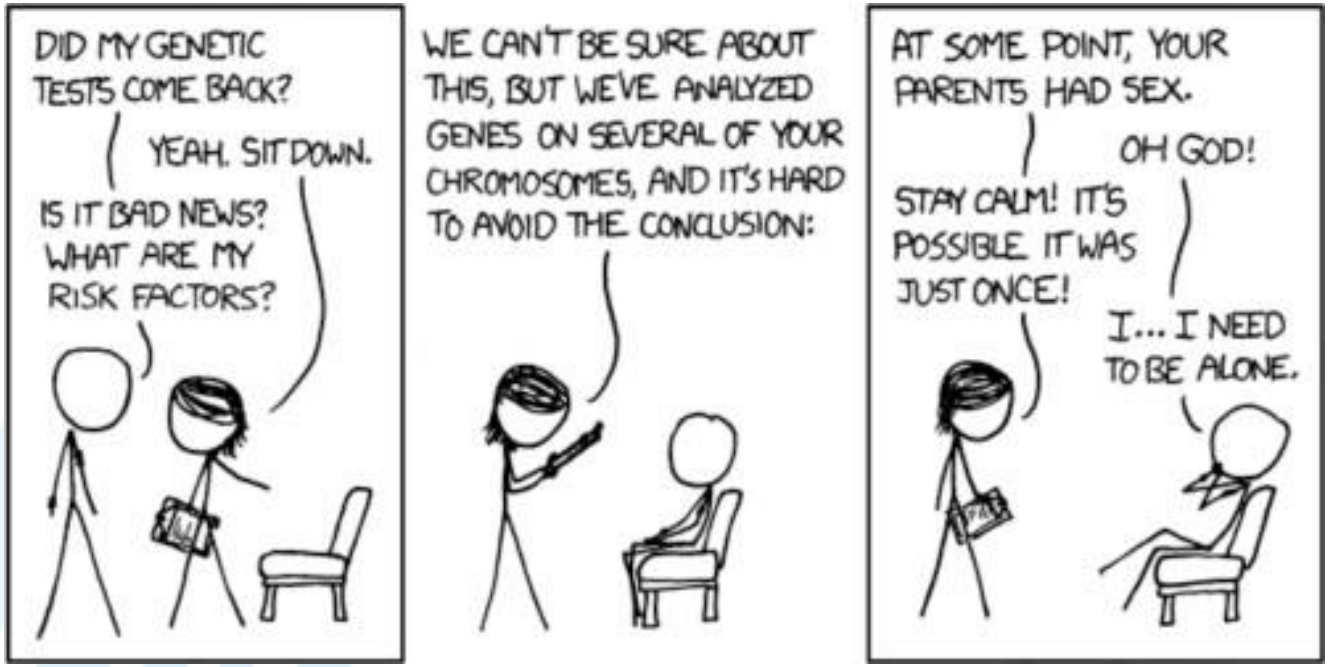
- Systemic review of qualitative studies:
  (15 studies, n= 257)
- 7 Major themes:
  - Pursuing motherhood
  - Failure to fulfill social norms
  - Fear of birth defects (ie IS) and transmitting genetic disease
  - Decisional insecurity and conflict
    - Fear of graft loss
    - Future??
  - Witholding emotional investments
  - Control and determination
  - Exacerbating disease

Tong A et al, NDT 2015; 652-660

Chronic kidney disease

- What is the underlying disease?
- Impact CKD on pregnancy
- Impact pregnancy on CKD

UNDERLYING DISEASE



GENETIC COUNSELLING

UNDERLYING DISEASE

ADPKD, familial focal sclerosis, CAKUT, Alport, VUR, …
But also post pregnancy FU if mother or father VUR: ultrasound postpartum

UNDERLYING DISEASE

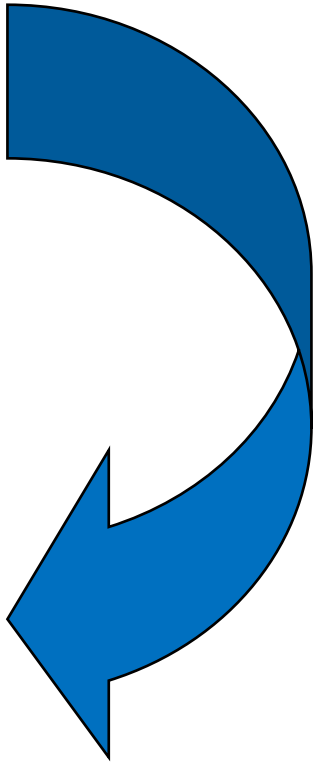
- Risk of complications: dependent of the underlying disease
  - Immunological or systemic disease: glomerulonephritis, diabetes, lupus: higher risk of adverse pregnancy-related events
  - Interstitial disease: higher risk of UTI

Chronic kidney disease

- What is the underlying disease?
- Impact CKD on pregnancy
- Impact pregnancy on CKD

IMPACT CKD ON PREGNANCY

- Renal insufficiency
- Chronic hypertension
- Proteïnuria



Maternal risks

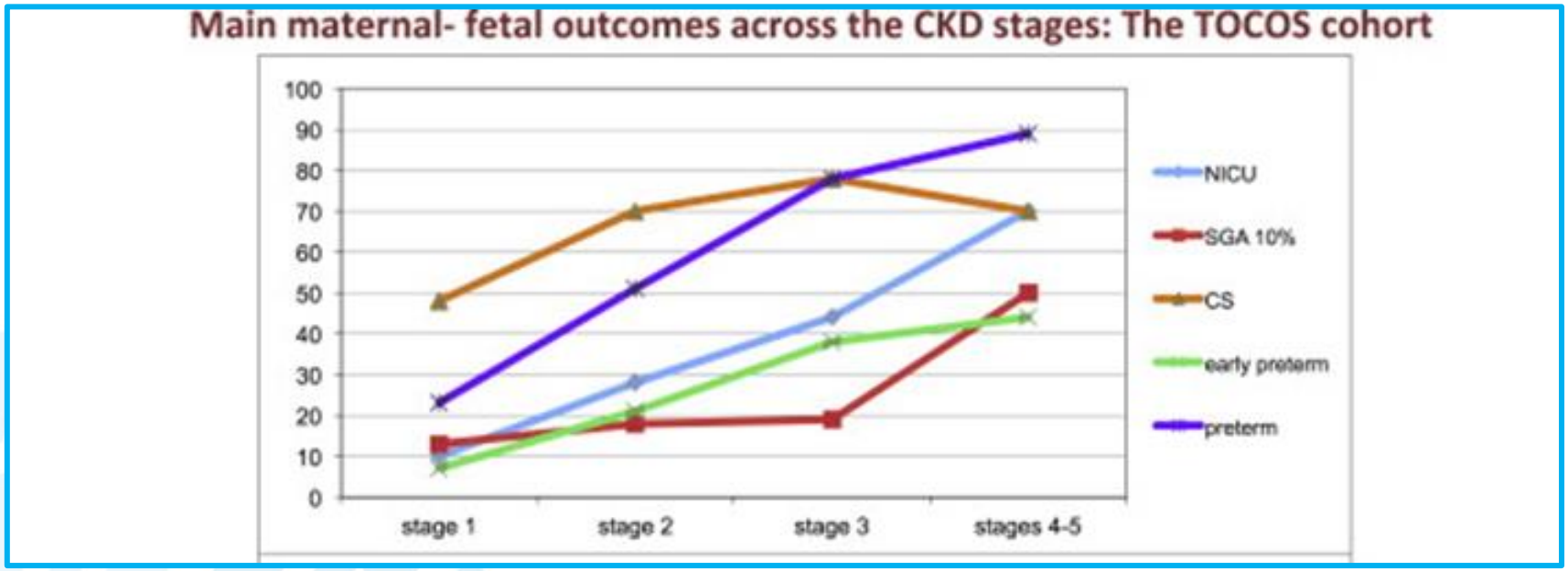
Foetal risks

Impact CKD on pregnancy

- Maternal risk:
  - hypertensive disorders of pregnancy (new onset or worsening; persistence after delivery)
  - C-section
- Child risk:
  - prematurity (with its sequelae),
  - inheritance of maternal disease, malformations
  - side effects of maternal therapy

IMPACT CKD ON PREGNANCY

- Fig. 2 Risk patterns in the various CKD stages in the ToCOS cohort (Torino *Cagliari* Observational Study), data collection on 504 live-born singleton deliveries in CKD patients followed up in the two largest facilities for CKD in pregnancy



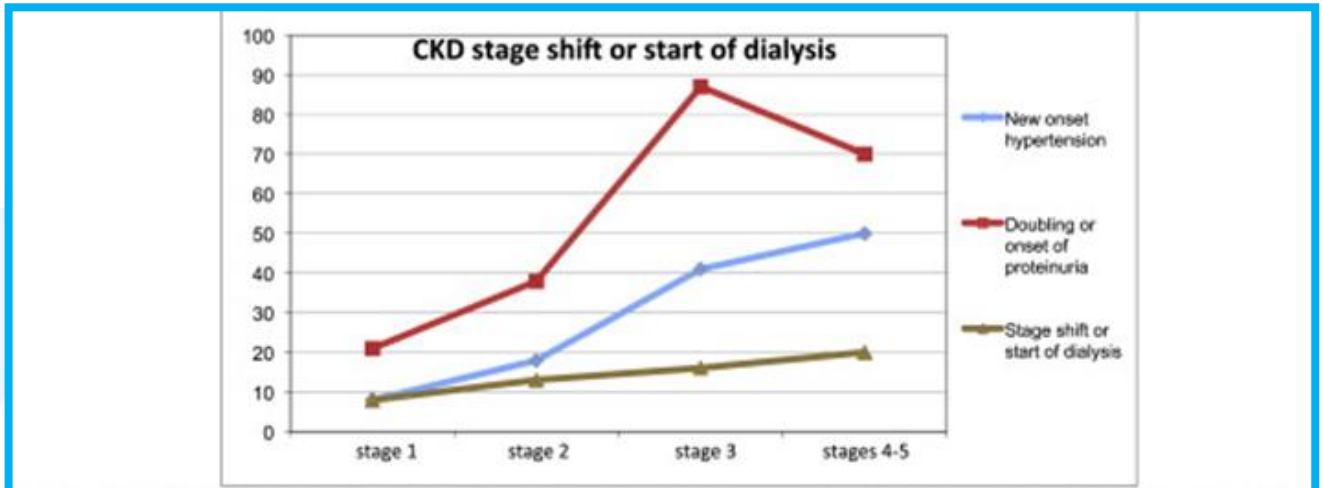
Piccoli GB; Best Practice & Research Clinical Obstetrics & Gynaecology, 2015

Chronic kidney disease

- What is the underlying disease?
- Impact CKD on pregnancy
- Impact pregnancy on CKD

IMPACT PREGNANCY ON CKD

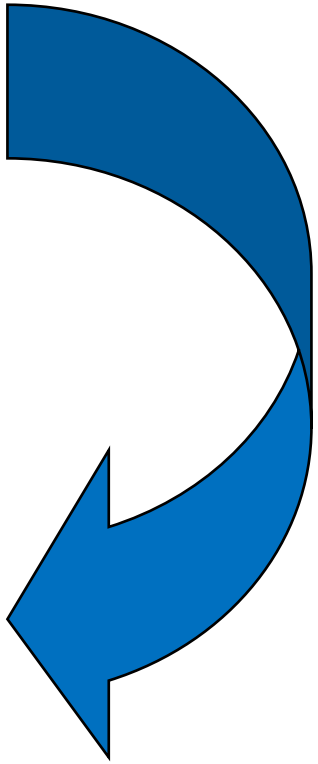
Fig. 2 Risk patterns in the various CKD stages in the ToCOS cohort (Torino *Cagliari* Observational Study), data collection on 504 live-born singleton deliveries in CKD patients followed up in the two largest facilities for CKD in pregnancy



Legend: NICU (neonatal intensive care unit), SGA (small for gestational age), CS (Caesarean section), early pre-term < 34 weeks and pre-term < 37 weeks
New onset hypertension and proteinuria: PE was not used as a definition, due to the overlapping features with CKD

Piccoli GB; Best Practice & Research Clinical Obstetrics & Gynaecology, 2015

- Renal insufficiency
- Chronic hypertension
- Proteïnuria



Maternal risks

Foetal risks

1+1=3

Pregnancy in chronic kidney disease: need for a common language

Giorgina B. Piccoli [1], Anne Conijn [2], Rossella Attini [2], Marilisa Biolcati [2], Carlotta Bossotti [2], Valentina Consiglio [1], Maria Chiara Deagostini [1], Tullia Todros [2]

[1] SS Nephrology, Biological and Clinical Sciences, University San Luigi, Orbassano - Italy
[2] Maternal-Fetal Unit, University of Turin, Turin - Italy

GENERAL RULES

- Counselling: patient tailored

TABLE I
WOMEN WITH RENAL DISEASE WHO SHOULD BE REFERRED FOR PRE-PREGNANCY COUNSELING

- Women with CKD stage 1-2 and adverse risk factors:
  - ➢ Significant proteinuria
  - ➢ Hypertension
  - ➢ Systemic diseases such as lupus or vasculitis
  - ➢ Previous adverse obstetric history
- Women with CKD stage 3 to 5 including women on dialysis
- Women with renal transplants
- Women with a family history of hereditary renal disease

CKD = chronic kidney disease.

Lightstone L J nephrol 2012

General rules: CKD stages 1 and 2

- Risk of pre-eclampsie (10%-20%)(5% normal)
- Risk of preterm delivery (11%-40%)
- Low birth weight (5-26%)
- Risk increase with presence of:
  - Proteinuria:
    - No PU: 30% develops PU
    - Nephrotic: thromboprophylaxis
  - Hypertension:
    - Dd preeclampsia: difficult (sFlt-1 and PGF)
    - FU of foetal growth to guide decision about delivery

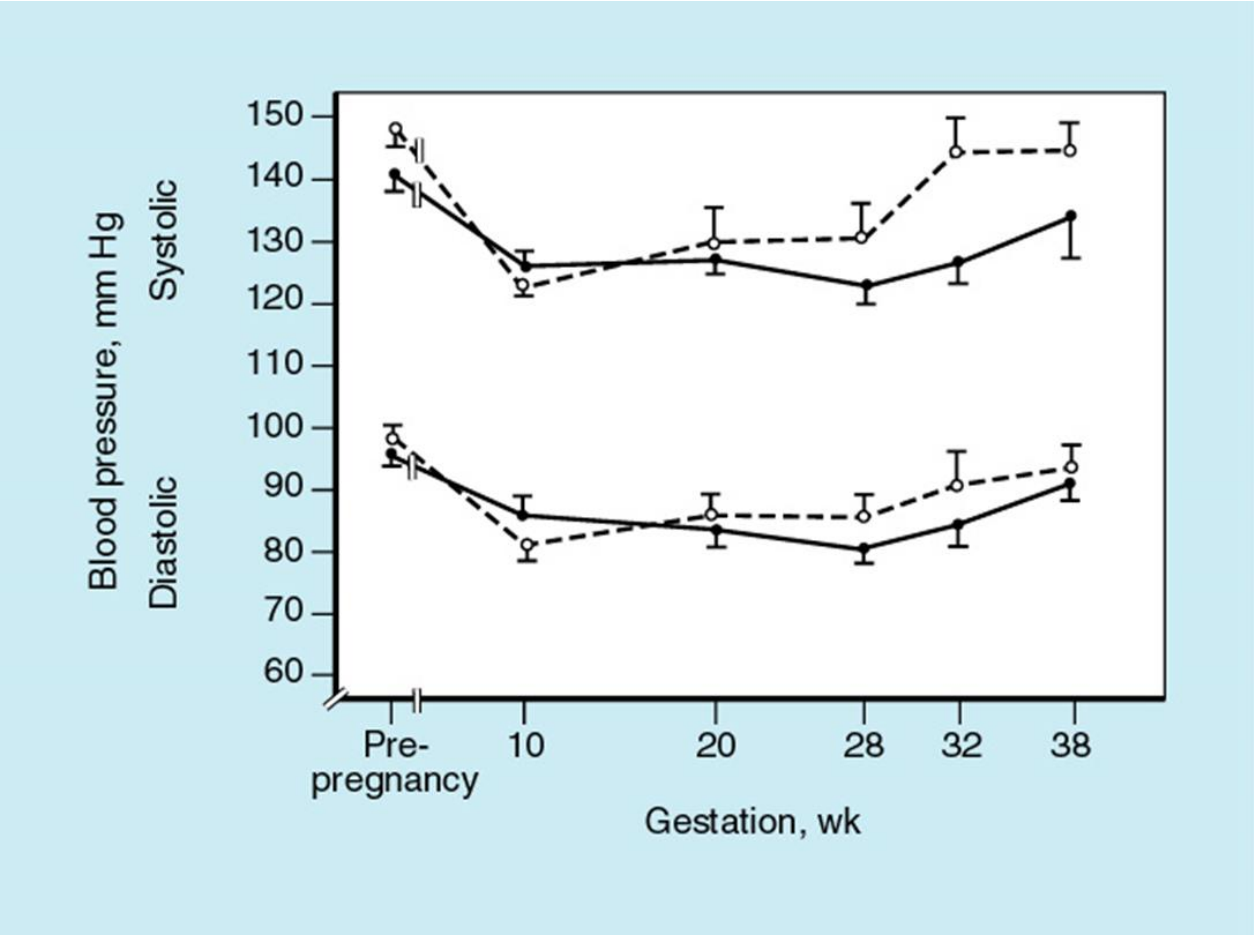
General rules: CKD stages 3 and 4

- Fetal loss is greater
- Preeclampsia: 40%-60%
- Prematurity: 39%-64%
- No creatinine reduction in the first trimester: suggestive of future complications
- Predictors: <40 ml/min/1.73 m^2 and proteinuria >1 g/24h
- Reduction in fertility

Therapeutic approach

- Timing of conception
  - Diabetes: adequately controlled blood pressure and glucose
  - Lupus nephritis: 6 m quiescent disease
  - “Woman: <35y and CKD 4-5 with deteriorating renal function: delay conception until transplantation”
  - “Woman: >35y and CKD 4-5 with deteriorating renal function:discuss with patient”

HYPERTENSION



HYPERTENSION(6%-8%)

- Pre-existing hypertension
- Pregnancy induced hypertension
- Pre-eclampsia/eclampsia

Target blood pressure < 160/105 mm Hg
Renal patients ≤ 140/90 mm Hg
Doch nieuwe studie mag tot 85 mm Hg diastole in niet nierpatiënten

ASPIRIN 80 MG (12 WEEKS)

Risk level		
High risk	History of preeclampsia, especially when accompanied by an adverse outcome Multifetal gestation Chronic hypertension Type 1 or 2 diabetes Renal disease Autoimmune disease (systemic lupus erythematous, antiphospholipid syndrome)	Recommend low-dose aspirin if ≥ 1 risk factors
Moderate risk	Nulliparity Obesity (body mass index >30 kg/m^2) Family history of preeclampsia (mother or sister) Sociodemographic characteristics (African American race, low socioeconomic status) Age ≥35 years Personal history factors (e.g., low birthweight or small for gestational age, previous adverse pregnancy outcome, >10-year pregnancy interval)	Consider low-dose aspirin if the patient has several of these moderate-risk factors
Low risk	Previous uncomplicated full-term delivery	Do not recommend low-dose aspirin

Low-Dose Aspirin Use for the Prevention of Morbidity and Mortality From Preeclampsia
U.S. Preventive Services Task Force Recommendation Statement
Release Date: September 9, 2014

Table 1 | The efficacy of different screening strategies plus aspirin therapy for the prevention of pre-eclampsia

Screening algorithm	Screen positive rate	No. of patients who would receive aspirin (per 10,000 unselected women)	Rate of pre-eclampsia in untreated population	Relative risk reduction with aspirin (95% CI)	No. of cases of pre-eclampsia that would be prevented (per 10,000 unselected women)	Refs
Rolnik et al.						
Pre-term pre-eclampsia	11%	1,100	4.3%	0.37 (0.2–0.71)	29	1
All pre-eclampsia	11%	1,100	11.4%	0.72 (0.54–0.98)*	35	1
USPSTF						
One or more high risk factors (all pre-eclampsia)	7.2%	720	19.4%	0.76 (0.62–0.95)	34	7
Two or more moderate risk factors (all pre-eclampsia)	20.4%	2,040	6.2%	0.76 (0.62–0.95)	31	7

*Calculated using data provided by Rolnik *et al.*[1] Assumes that the total number of pre-eclampsia cases is calculated by combining data for the primary outcome plus pre-eclampsia >37 weeks gestation.

Roberts and Himes, Nature Reviews nephrology 2017

Rolnik: An on line risk calculator using this algorithm is available at: https://fetalmedicine.org/research/assess/preeclampsia

Drug	Mechanism of action	Dose	Comments
Relative rest/No salt restriction			
Low dose ASA in all		80-100 mg/d ???	Start 12 weeks
Labetolol (Trandate)	a+ß-adrenergic receptor antagonists	100-400 mg (2-4/d) maximum dose 1200 mg	First choice No long term follow-up children hepatotoxicity/broncho spasm
Methyldopa (Aldomet)	a2-adrenergic receptor agonists	250-500 mg (2/d) maximum dose 2 g/d	Maternal side effects: fatigue, nasal congestion, dry mouth, postural hypotension, transaminitis…
Nifedipine LA (Adalat)	Ca^{2+}-block	30-120 mg/d	Mildly tocolytic? Aggrevate oedema/ headache
Ketanserin	serotinine-2-receptor blocker		In combination w/ aspirin→↓PET

HYPERTENSION: NOT RECOMMENDED

Drug	Mechanism of action	Comments
Atenolol	ß-adrenergic receptor antagonists	Side effects: bradycardia, apnoe, hypoglycemia, IUGR, …
ACE-inhibitor or ARB	May be used till pregnant Recent data no increase in teratogenicity if stopped in first trimester	Teratogenic in second and third trimester
Diuretics	May be continued if intake prepregnancy	Avoid (may limit physiological increase in plasma volume)

https://www.cybele.be/CybeleN/#t=intronl%2Fintrozw_n.htm

CYBELE

CYBELE

Verbergen

-Zoeken-

Inhoud Index Lexicon Lijst

- Gebruiksaanwijzing
- Inleiding
- Begin van een normale zwangerschap
- Farmacokinetische begrippen Borstvoeding
- Legende
- Repertorium per actief bestanddeel (INN)
  - Cardiovasculair stelsel
  - Gastro-intestinaal en uro-genitaal stelsel
  - Ademhalingsstelsel
  - Pijn en ontsteking
  - Zenuwstelsel
  - Hormonaal stelsel
  - Infecties
  - Immuniteit en tumoren
  - Uitw. gebr., huid
  - Uitw. gebr., andere
  - Mineralen en vitaminen
  - Diversen
- Repertorium per klasse
  - Cardiovasculair stelsel
    - Aritmie, antiaritmica, klasse IA
    - Aritmie, antiaritmica, klasse IB
    - Aritmie, antiaritmica, klasse IC
    - Aritmie, antiaritmica, klasse II
    - Aritmie, antiaritmica, klasse III
    - Aritmie, antiaritmica, klasse IV

Geneesmiddelen

voor en tijdens de
zwangerschap

en bij
borstvoeding

Cybele

PRO 2.0

KU Leuven
Clinical Pharmacology and Pharmacotherapy
Faculty of Pharmaceutical Sciences
FARMAKA vzw

Apr. Bérengère Couneson
Prof. em. Dr. Pharm. Gert Laekeman
Prof. em. Dr. Jan Van Damme
Apr. Paul Van Herzele

Uit verwondering ontluikt wijsheid
(Socrates)

Laatste bijwerking : 19/10/2017

Disclaimer

NL 10:26 21-10-2017

Therapeutic approach

- ACE-inhibitor and angiotensin 2 receptor blockers
  - Beyond first trimester: CONTRA-indicated
  - Blood pressure control with minimal proteinuria: switch to save therapy preconception
  - Proteinuria: stop while trying to conceive
  - Heavy proteinuria: discontinue after pregnancy confirmed

For the most important people of the world : the unborn and the newborn

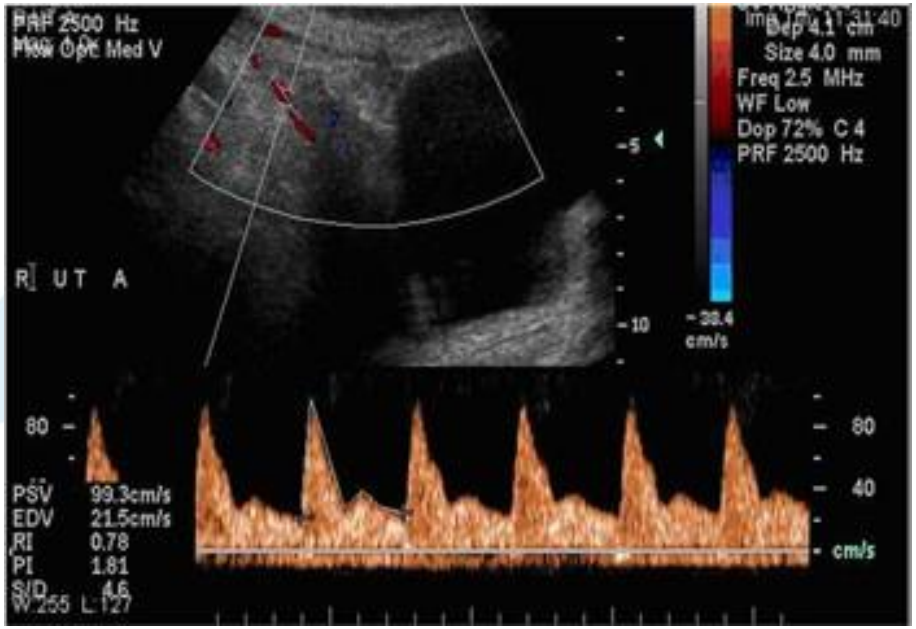
Show All

Cybele©		Geneesmiddelen tijdens zwangerschap & borstvoeding				
Bestanddeel	pre	0-3	4-6	7-9	peri	Borstvoeding
/cardiovasculair/antihypertensiva/ACEI						
Captopril (oraal)	(ja) III	(neen) II	neen II	neen II	neen II	(ja) II
Cilazapril (oraal)	(ja) III	(neen) II	neen II	neen II	neen II	(neen) III
Enalapril (oraal, parenteraal)		(neen) II	neen II	neen II	neen II	
Fosinopril (oraal)	(ja) III	(neen) II	neen II	neen II	neen II	(neen) II
Lisinopril (oraal)	(ja) III	(neen) II	neen II	neen II	neen II	(neen) III
Perindopril (oraal)	(ja) III	(neen) II	neen II	neen II	neen II	(neen) III
Quinapril (oraal)	(ja) III	(neen) II	neen II	neen II	neen II	(ja) II
Ramipril (oraal)	(ja) III	(neen) II	neen II	neen II	neen II	(neen) III
Zofenopril (oraal)	(ja) III	(neen) II	neen II	neen II	neen II	(neen) III
ACEI + hydrochloorthiazide	neen	neen	neen	neen	neen	neen
ACEI + indapamide		neen	neen	neen	neen	?
ACEI +amlodipine		neen	neen	neen	neen	?
ACEI +lercanidipine		neen	neen	neen	neen	?

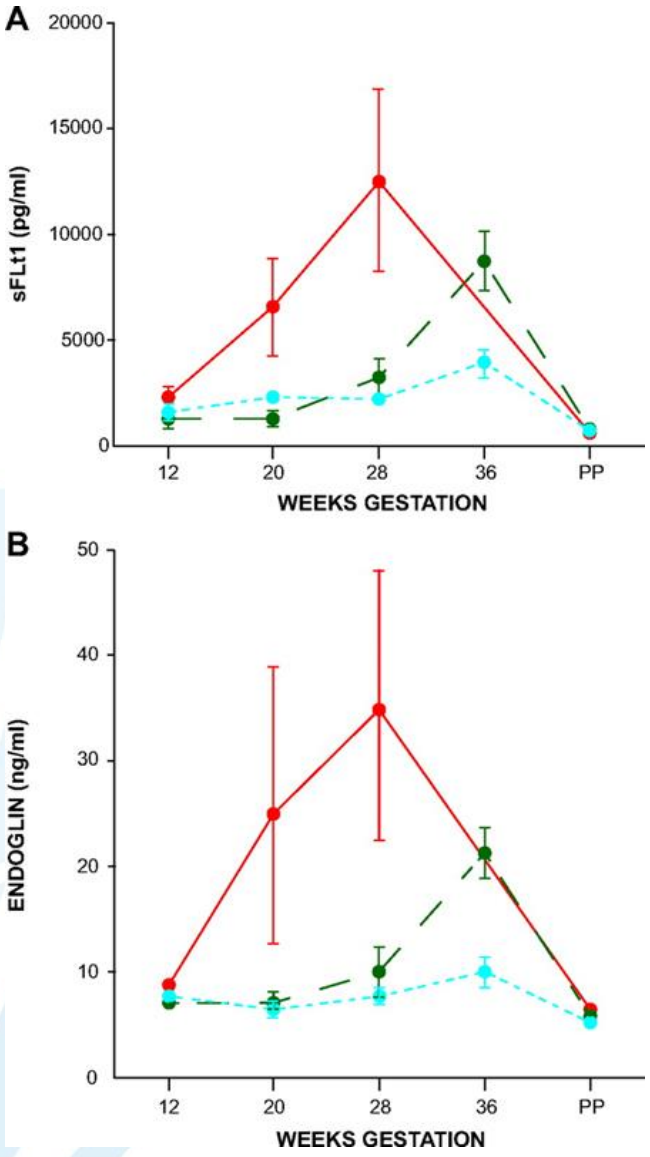
(c) 2017 CYBELE : geneesmiddelen voor en tijdens zwangerschap en borstvoeding - Disclaimer

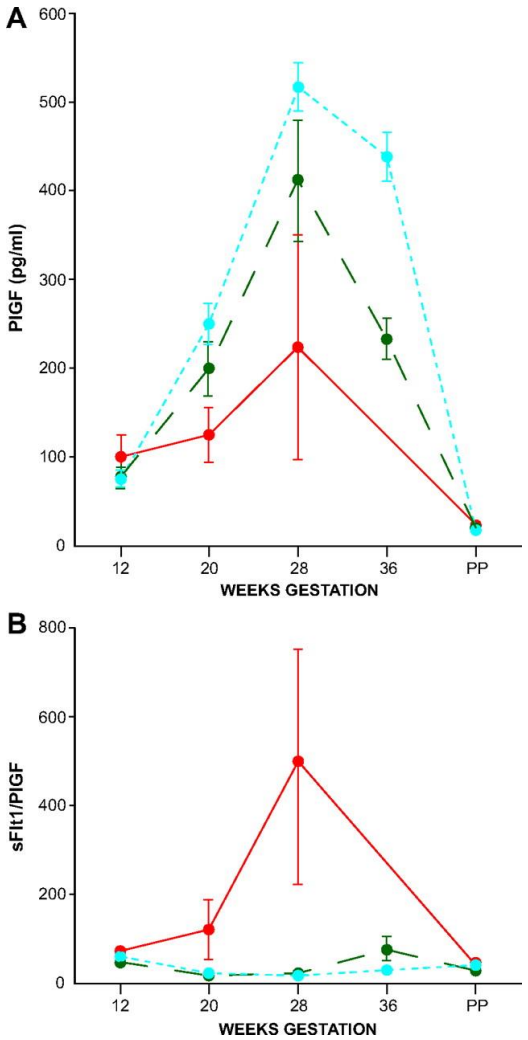
Prognostic approach

- Doppler of a uterinae at 20 weeks (Resistive and pulsatility index)
- Persistence of the notch



ANGIOGENIC FACTORS





Perni U et al. Hypertension. 2012;59:740-746

CKD stage 5

- ‘Show me a method of birth control more effective than end stage renal disease’, Roger Rodby MD, 1991

- ‘Even if a woman on CAPD ovulates, doesn’t the egg just float away?’, Rodby, 1992

CHILDREN ON DIALYSIS

- Pregnancy on dialysis is rare
- Fertility loss
  - 42% menstruation (59% irregular) ➔ late diagnosis
- Peritoneal dialysis: lower rate
  - Peritonitis
  - Lower implantation rate

CHILDREN ON DIALYSIS

Table 3. Main pregnancy outcomes: comparison between children born to mothers on dialysis and after transplantation (singletons only)

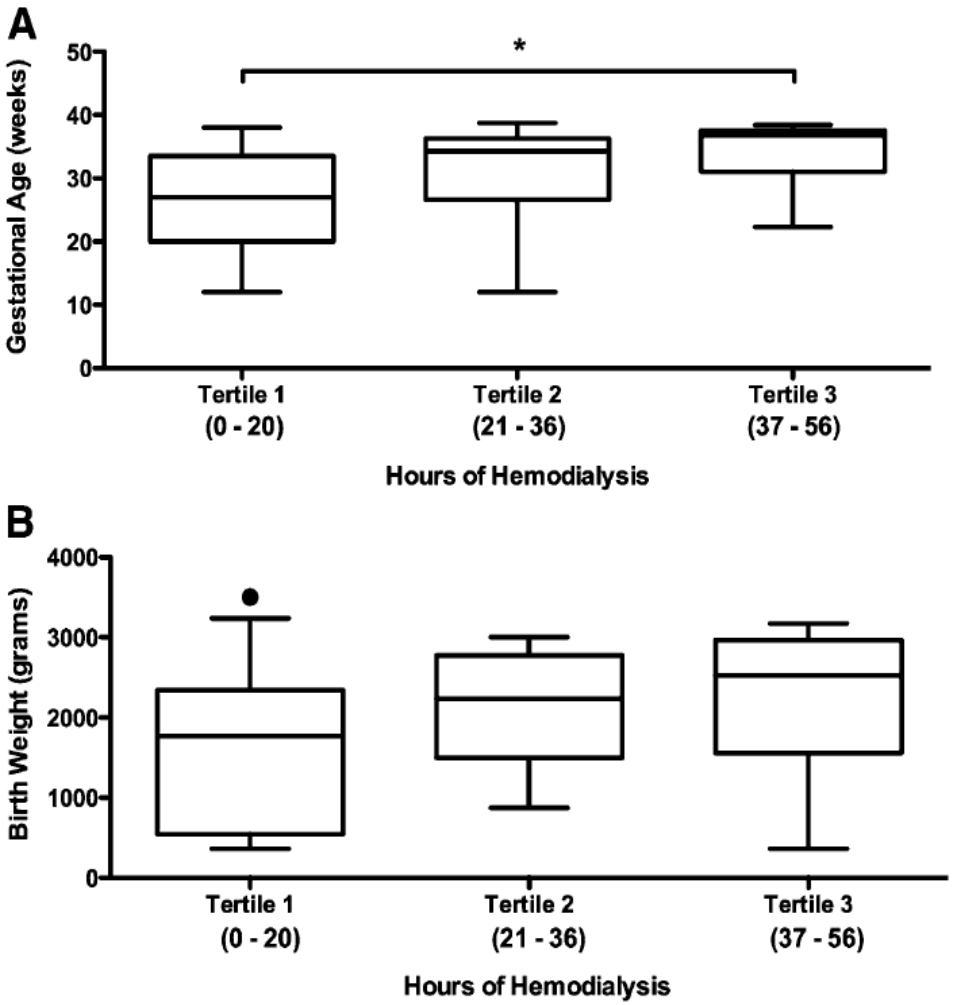
	Week of gestation (median, range)	Early pre-term % (<34 weeks)	All pre-term % (<37 weeks)	Weight (median, range)	SGA (<5 centile)	SGA (<10 centile)	Perinatal death
Dialysis patients	30 (26–37)	7/21 (33.33%)	19/21 (90.48%)	1200 (590–2250)	4/21 (19.05%)	7/21 (33.33%)	2/22 (9.09%)
Kidney transplant patients	36 (25–40)	27/107 (25.23%)	56/107 (52.34%)	2500 (820–4000)	9/101 (8.91%)	17/101 (16.67%)	0/110 –
P dialysis versus graft	<0.001	0.4307	0.0012	<0.001	0.2355	0.0030	0.0267

SGA, small for gestational age baby.

Higher RRF increases the probability of a successful pregnancy.
Better outcome with increase of dialysis dose
Low flow, slow ultrafiltration

Piccoli GB, Nephrol Dial Transplant 2014

Intensive Hemodialysis Associates with Improved Pregnancy Outcomes: A Canadian and United States Cohort Comparison



Hladunewich, JASN, 2014

Table 6. Management of pregnant women on intensive hemodialysis

Maternal Management	Fetal Surveillance
Preconception and first trimester	
Medication review to stop and replace teratogenic medications (*e.g.*, ACEIs, ARBs, and statins)	Cautious interpretation of first trimester screen to exclude Down syndrome (increased β-hCG and PAPP-A)
Double doses of water-soluble vitamins with increased folic acid supplementation (5 mg/d)	False-positive screens should be confirmed by careful US measurement of nuchal translucency, amniocentesis, or the Harmony Test (cellfree DNA in maternal blood)
Daily protein intake of 1.5–1.8 g/kg per day	
Low-dose aspirin for preeclampsia prevention may be appropriate in some women but is of unclear benefit	
Intensification of HD dose to ≥36 h/wk in women without residual renal function; women with residual renal function can have dialysis dose tailored to metabolic parameters	
Increase dialysate bath potassium concentration (3 mEq/L)	
Increase dialysate bath calcium concentration (1.5 mmol/L or 6 mg/dl)	
Liberalize dietary phosphate, with possible dialysate bath sodium phosphate supplementation	
Increase the dose of ESAs to approximate the physiologic anemia of pregnancy (10–11 g/L)	
Use of weekly maintenance or bolus therapy of iv iron therapy to maintain normal iron saturation	
Heparin to maintain circuit patency	
Second and third trimesters, including delivery	
Frequent volume assessments to avoid hypotension and manage ultrafiltration	Maternal serum screen (AFP, inhibin A, total hCG, and unconjugated estriol) between 15 and 18 wk
Target BP <140/90 mmHg postdialysis	Level 2 US to measure cervical length and assess for anomalies at 18–20 wk
Preeclampsia surveillance after 20 wk (consider admission for fetal/maternal monitoring for sudden increases of BP, *etc.*)	Placental US with Doppler assessment at 22 wk
Weekly platelets and liver function tests to assess for preeclampsia from 26 wk until delivery	Weekly US and BPP from 26 wk until delivery
	Planned induction after 37 wk where appropriate
Postpartum care	
Medication review to ensure that all medications are compatible with breastfeeding	Neonatal assessment and care
Avoid volume depletion to facilitate breastfeeding	Preservative-free heparin to avoid neonatal toxicity by benzyl alcohol
Maternal emotional support	

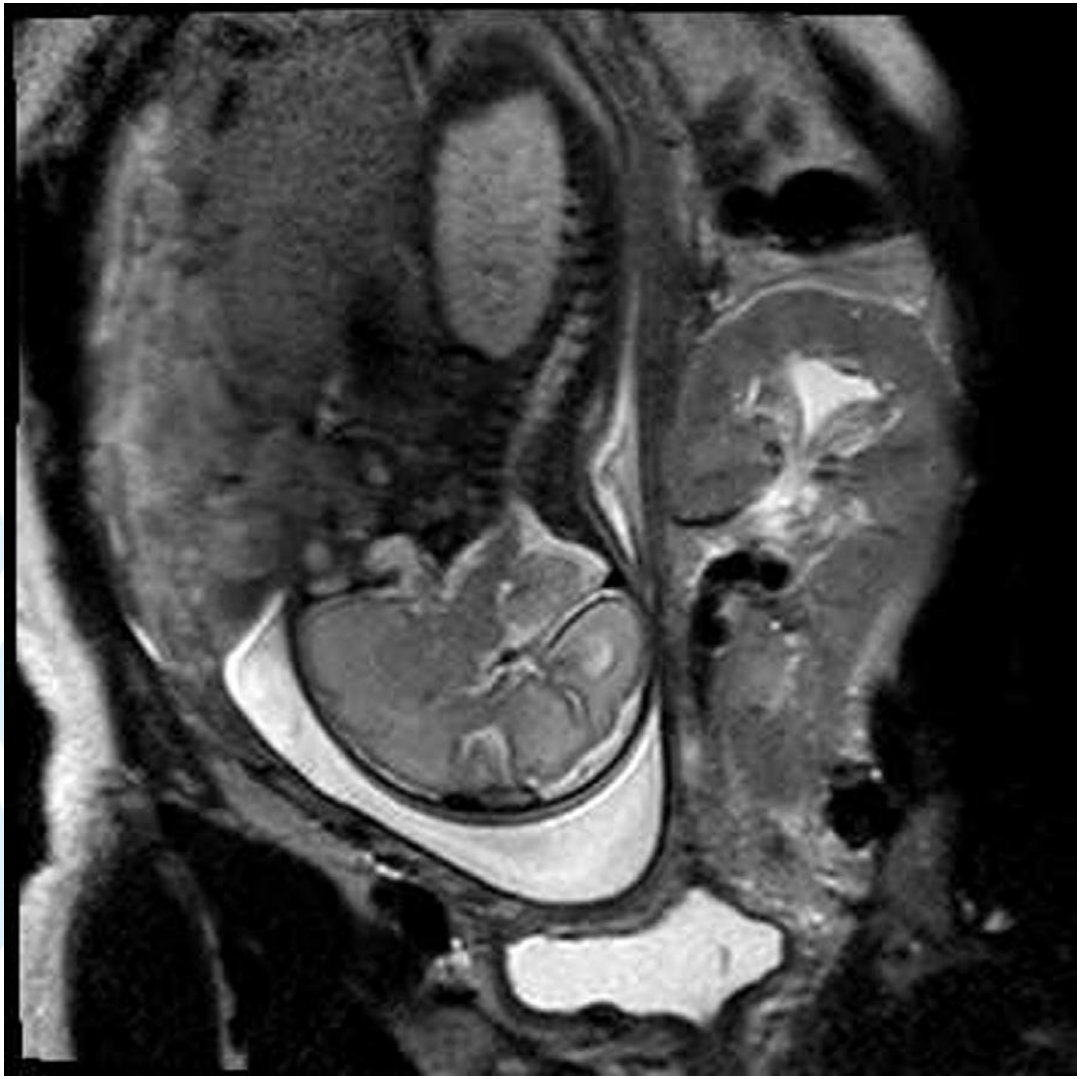
ACEI, angiotensin–converting enzyme inhibitor; ARB, angiotensin II receptor antagonist; β-hCG, β–human chorionic gonadotropin; PAPP-A, pregnancy–associated plasma protein-A; US, ultrasound; HD, hemodialysis; AFP, α-fetoprotein; hCG, human chorionic gonadotropin; BPP, biophysical profile.

Pregnancy and renal disease

- Physiological changes
- Renal complications of “normal” pregnancy
- Pregnancy in a renal patient
  - Chronic Kidney Disease
  - Transplantation

Case 4

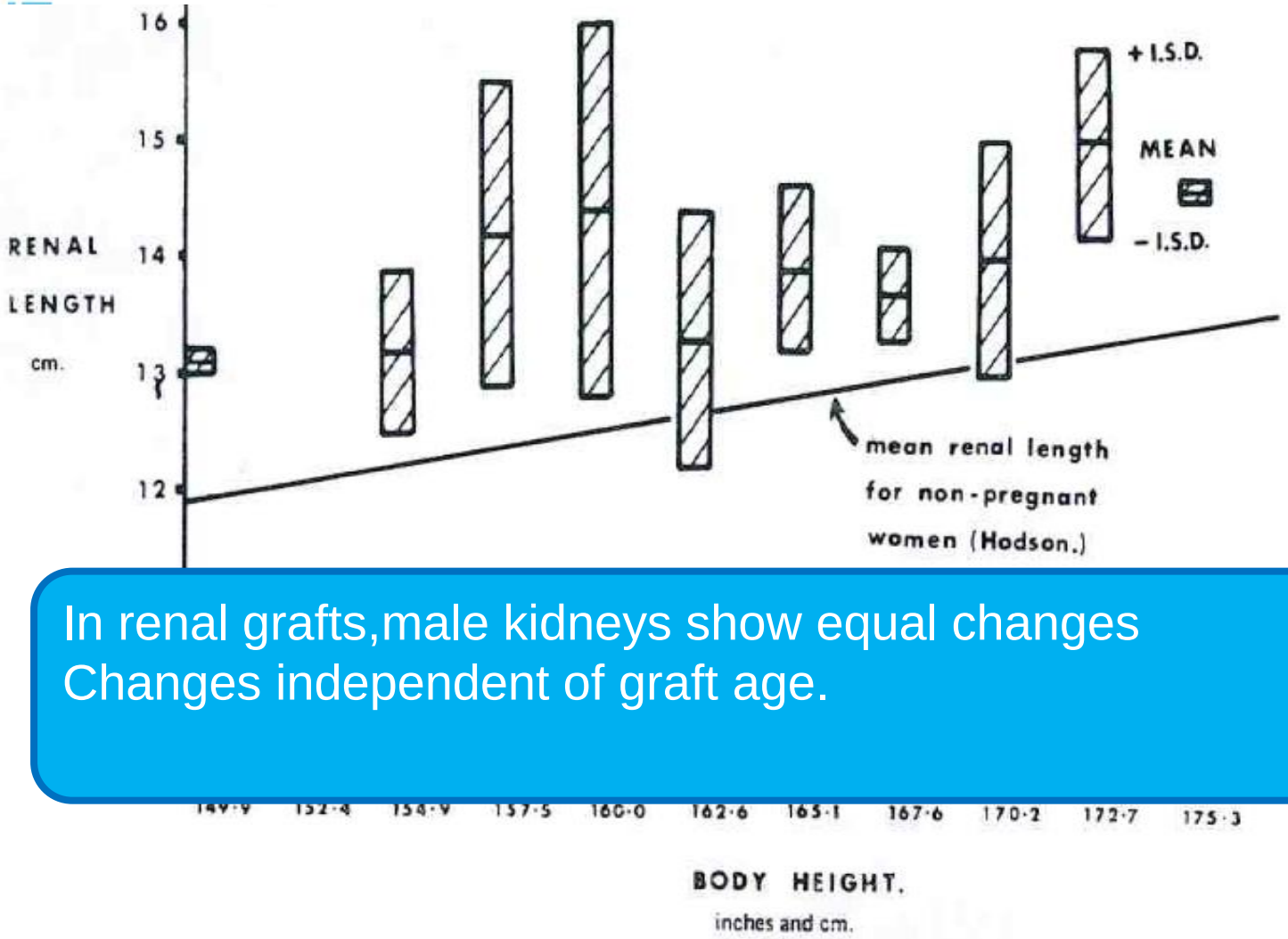
- 6 maanden geleden getransplanteerd
- Zwangerschapswens



TRANSPLANTATION

- Restoration of fertility. **Talk** about it
- 2-8% conceive
- Contraception
  - Barrier methods
    - IUD (intact immune system for efficacy)
  - Hormonal therapy
    - Progestin only: Cerazette
    - Depot progesterone

Consult gynecologist



In renal grafts,male kidneys show equal changes
Changes independent of graft age.

Figure 1-1. *Renal length in relation to body height, determined from roentgenograms taken during the immediate puerperium. (From Bailey, R. R., and Rolleston, G. L.: Kidney length and ureteric dilatation in the puerperium. J. Obstet. Gynaecol. Br.*

Kidney function and disease in pregnancy. Lindheimer, Katz, 1977

TRANSPLANTATION

- **Risk of renal transplant on pregnancy and risk of pregnancy on graft survival**
- **Immunosuppressive therapy**
- Antihypertensive therapy (as in non-transplant CKD)
- Hereditary risk (CKD)

Timing of pregnancy

- Stable transplant function
- > 2 y after transplantation (guidelines differ)
- 6 m after stop of cellcept (stable graft function)(minimum 6 w)

What is the effect on the graft?

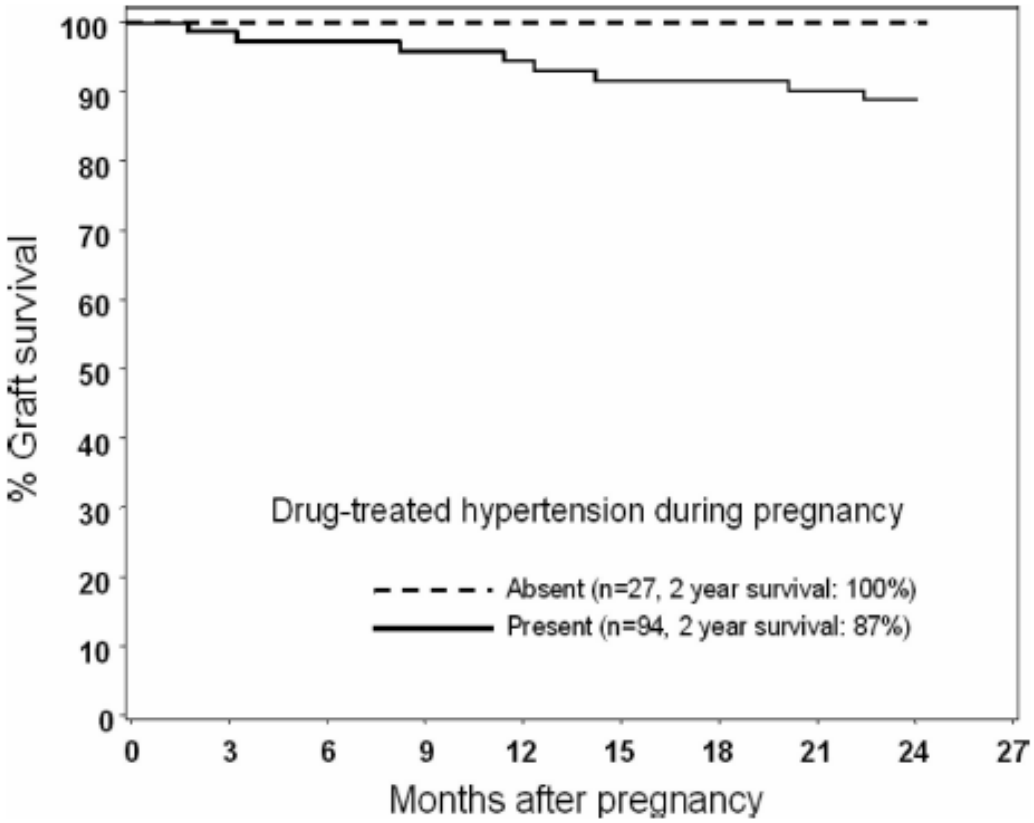
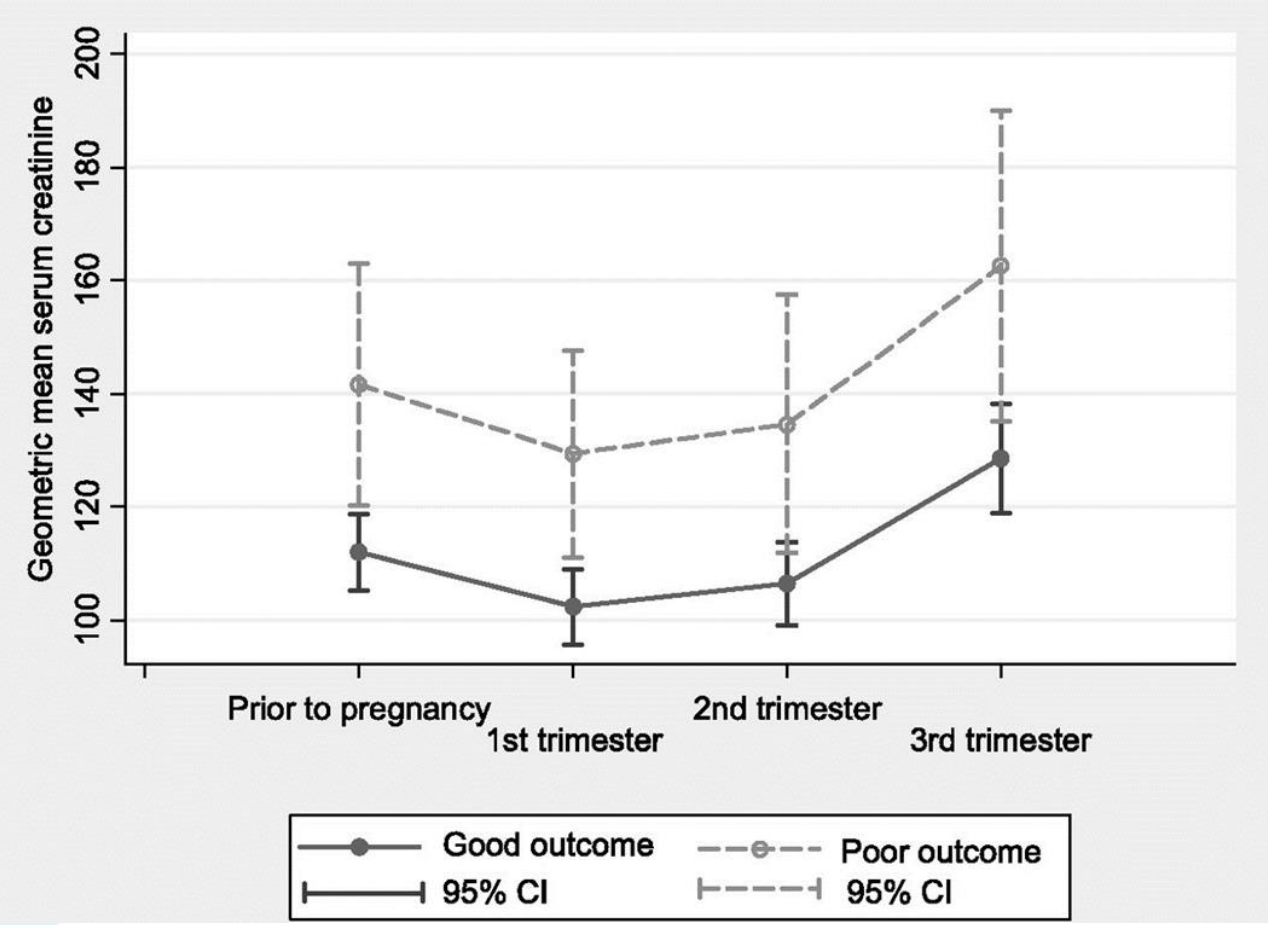


FIGURE 3. Kaplan–Meier survival curve comparing postpregnancy graft survival for patients with and those without drug-treated hypertension during pregnancy.

What is the effect on the graft?



Bramham K et al. CJASN 2013

IMMUNOSUPPRESSIVE THERAPY

Therapy	Transplacental passage	comments	safe	Breastfeeding
Prednisolone	Limited	(increase in oral clefts?) High dose: cataract, adrenal insufficiency, infection	Y	Y (not if prednisolone>60 mg)
Azathioprine	Y	Sporadic congenital abnormalities, transient immune alterations in neonates	Y	Y
MMF	Y	Contra-indicated (hypoplastic nails, shortened fifth finger, microthia, micrognathia, cleft lip and palate, heart defects)	NO	NO
Tacrolimus	Y	Hyperkalemia, renal impairment Diabetes mother, increase in dose	Y	Possibly safe
Cyclosporine	Y	Increase in dose	y	? Possibly safe
sirolimus	?	?	NO not to	?

TABLE 3. Results for multiple logistic regression model selection for the outcome variables "Success of pregnancy" and "Pre-term delivery" for kidney transplant recipients

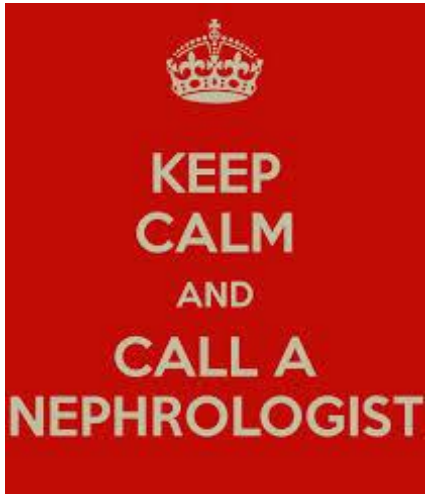
	Success of pregnancy (complete case analysis)[a]			
Prepregnancy factor	Total no. of pregnancies (no. of unsuccessful pregnancies)	Regression coefficient[b]	95% confidence interval	*P* value
Serum creatinine (μmol/L)	131 (24)	0.008	0.0002–0.02	0.03
Systolic blood pressure (mm Hg)	131 (24)	0.03	0.01–0.05	0.03

	Preterm delivery (analysis of entire cohort)[c]				
Factor	Factor level	No. of pregnancies (no. of preterm deliveries)	Odds ratio[d]	95% confidence interval	*P* value
Prepregnancy serum creatinine (μmol/L)	≤150 μmol/L	68 (27)	0.2	0.09–0.7	0.007
	>150 μmol/L[e]	32 (23)	1.0	—	—
	Not reported	21 (11)	0.4	0.1–1.5	0.2
Drug-treated hypertension during pregnancy	Absent	22 (2)	0.06	0.01–0.3	<0.001
	Present[e]	68 (42)	1.0	—	—
	Not reported	31 (17)	0.8	0.3–2.0	0.6

[a] R^2=14.9%.
[b] A positive (>0) regression coefficient indicates that an increase in the factor is associated with a greater risk of having an unsuccessful pregnancy.
[c] R^2=28.7%.
[d] An odds ratio that is less than 1.0 indicates that the factor level is associated with a lower risk of a preterm delivery compared to the baseline factor level.
[e] Baseline level.

Sibanda transplantation 2007

MULTIDISCIPLINARY APPROACH



The end