



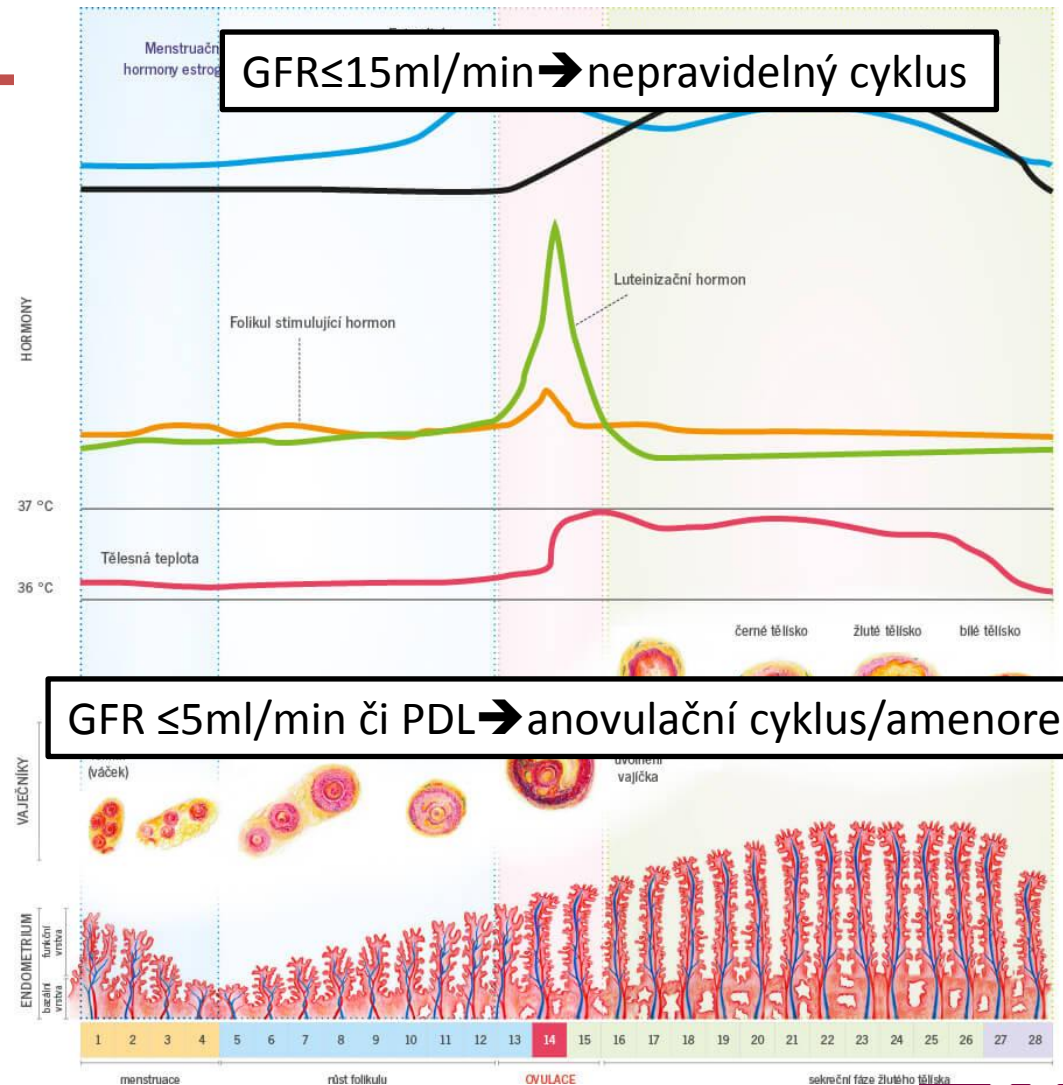
## **Těhotenství na dialýze a po transplantaci**

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KMN 10.-11.11.2017

# Fertilita a CKD– hypogonádotropní hypogonádismus

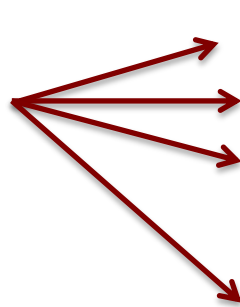
- ↓↓ estradiol
- ↓↓ progesteron
- ↘ FSH
- ↑ LH (+prodloužený plazm. poločas),  
hladina koreluje se sér. krea



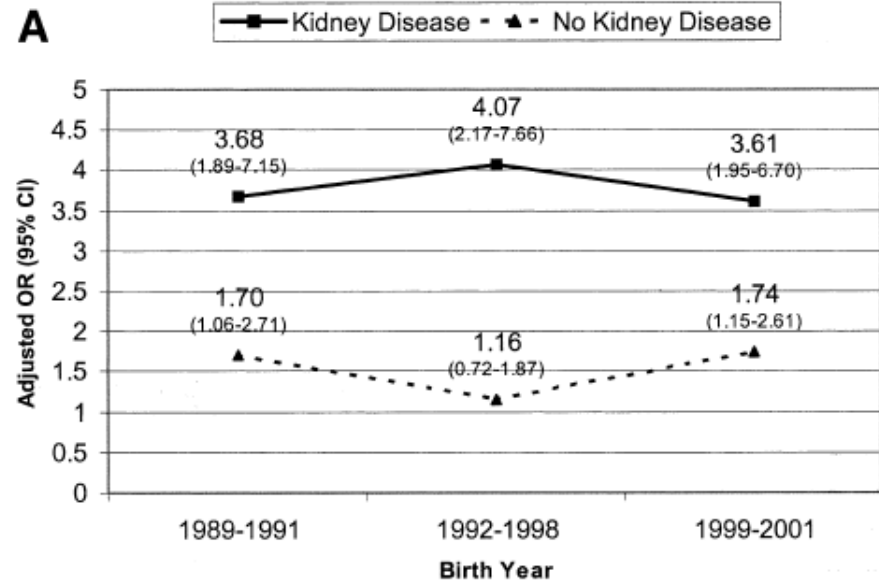
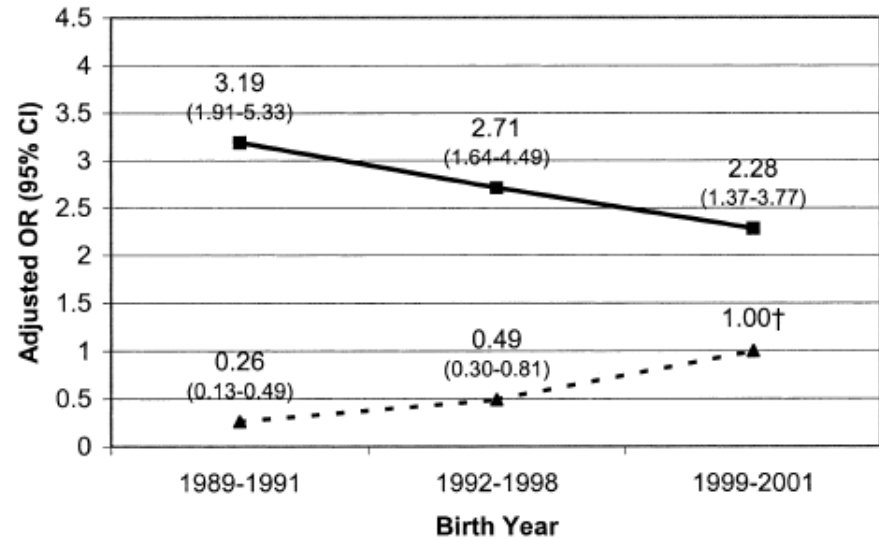
# Má být gravidita u pacientek s CKD považována za rizikovou?

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**ANO**

- 
- ① vysoké riziko komplikací u všech nemocných s CKD
  - ② riziko komplikací narůstá s pokročilostí CKD
  - ③ vysoké riziko u: proteinurie, hypertenze, DM 1. typu, autoimunitních onemocnění
  - ① **MULTIOBOROVÝ PŘÍSTUP!**

# CKD a riziko maternálních komplikací (multi- (A) vs. nuliparita (B))



Kidney disease as in independent risk factor for adverse fetal and maternal outcome in pregnancy. Am J Kidney Dis 2004, 43(3): 415-23.



# Hlavní komplikace gravidity

Country of Origin	Japan <sup>23</sup>	Brazil <sup>24</sup>	Saudi Arabia <sup>25</sup>	Italy <sup>21</sup>	Canada <sup>15</sup>	
Period, y	1986–2007	1988–2008	1992–2003	2000–2012	2000–2013	
Total pregnancies, n	28	52	12	20	22	
Conception before RRT initiated, n	4	28	5	4	4	
Hours of HD per week	18 ± 4	15 (9–21)	4–6 sessions/wk	24 ± 5	43 ± 6	
Live birth rate	64%	87%	58%	NR	86%	
Gestational age, wk ± SD or (range)	28.3 ± 9	32.7 ± 3.1	31.5 (27–36)	31.6 ± 3.6	36 (32–37)	<b>OR 5.7</b>
Birth weight, g ± SD or (range)	1414 ± 759	1554 ± 663	1700 (1115–2300)	1401 ± 512	2118 ± 857	
Preterm delivery (<37 wk)	92%	85%	100%	89%	53%	
Transfusions	32%	25%	0	NR	0%	
Hypertension	39%	70%	NR	53%	18%	
Preeclampsia/HELLP	NR	19%	67%	21%/5%	5%	<b>OR 10.4</b>
Polyhydramnios	39%	40%	42%	NR	5%	
Low birth weight (<2500 g)	94%	NR	100%	100%	44%	<b>OR 4.95</b>
Very low birth weight (<1500 g)	33%	NR	29%	70%	6%	
Incompetent cervix	14%	NR	NR	NR	18%	
Caesarean delivery	38%	65%	57%	95%	9%	<b>OR 2.7</b>

HD = hemodialysis; HELLP = hemolysis, elevated liver enzymes, low platelet count; NR = not reported; RRT = renal replacement therapy; SD = standard deviation.

**CAVE: SLE, autoimmunity, DM (+VVV)**

## Výsledky gravidity v závislosti na CKD

Renal status (dysfunction)	SCr (mg/dl) ( $\mu\text{mol/L}$ )	Problems in pregnancy (%)	Successful obstetric outcome (%)	Compared with prepregnancy a permanent PP loss of kidney function (>25% increment in SCr) (%)	ESRF within 1 yr PP (%)
Mild	$\leq 1.4$ ( $\leq 125$ )	26	96	<2	—
Moderate	$\geq 1.4$ ( $\geq 125$ )	50	90	25	3
Severe	$\geq 2.8$ ( $\geq 250$ )	86	74	55	40
Mild	$\leq 1.4$ ( $\leq 125$ )	26	96	<2	—
Moderate	$\geq 1.4$ ( $\geq 125$ )	42	95	15	1
Severe	$\geq 2.0$ ( $\geq 180$ )	79	78	50	38

ESRF, end stage renal failure; PP, post-partum; SCr, serum creatinine.

Estimates are on the basis of a 26-year literature review (1984–2010) of pregnancies that attained  $\geq 24$  weeks' gestation.

<sup>a</sup>Fetal growth restriction, preeclampsia, preterm delivery, and significant kidney function loss in pregnancy (>25% SCr increment), obstetric outcome, and loss of kidney function: the effect of altering the cutoff between moderate and severe dysfunction from 2.8 mg/dl ( $\geq 250 \mu\text{mol/L}$ ) to 2.0 mg/dl ( $\geq 180 \mu\text{mol/L}$ ), respectively.

# Fetomaternální výsledky

Effect of CKD on maternal and fetal outcome.

Outcome	Overall frequency (n = 80)	Early stage (1) (N = 46)	Late stage(2) (N = 34)	p value (1 vs 2)	Power of study (%)
Preeclampsia, n (%)	44(55)	18(39.1)	26(76.5)	0.001 (s)	89
Anemia, n (%)	50(62.5)	26(56.5)	24(70.6)	0.199	–
Moderate–severe anemia (%)	40(50)	16(34.8)	24(70.6)	0.002 (s)	85.4
Caesarean section, n (%)	54(67.5)	30(65.2)	24(70.6)	0.596	–
ICU admission, n (%)	6(7.5)	2(4.3)	4(11.8)	0.393	–
SGA, n (%)	28(35)	8(17.4)	20(58.8)	0.001 (s)	96
Oligoamnios, n (%)	24(30)	10(21.7)	14(41.2)	0.061	–
Abnormal Doppler, n (%)	26(32.5)	10(21.7)	16(47.1)	0.017 (s)	58
Prematurity(<37 weeks), n (%)	46 (57.5)	20 (43.4)	26 (76.5)	0.577	–
Early preterm (<34 weeks)	14(17.5)	6 (13.04)	8 (23.53)	0.222	–
Late preterm (34 – <37 weeks)	32(40)	14(30.43)	18(52.94)	0.042 (s)	44
Extremely preterm (<28 weeks)	2(2.5)	0(0)	2 (5.88)	0.178	–
Low apgar, n (%)	10(12.5)	0	10(29.4)	0.001 (s)	94
Mean birth weight (kg)	1.95 ± 0.75	2.2 ± 0.68	1.61 ± 0.71	0.001 (s)	96
NICU admission, n(%)	32(40)	12(26.1)	20(58.8)	0.037 (s)	78.6

s: significant.

Effect of pregnancy on renal parameters.

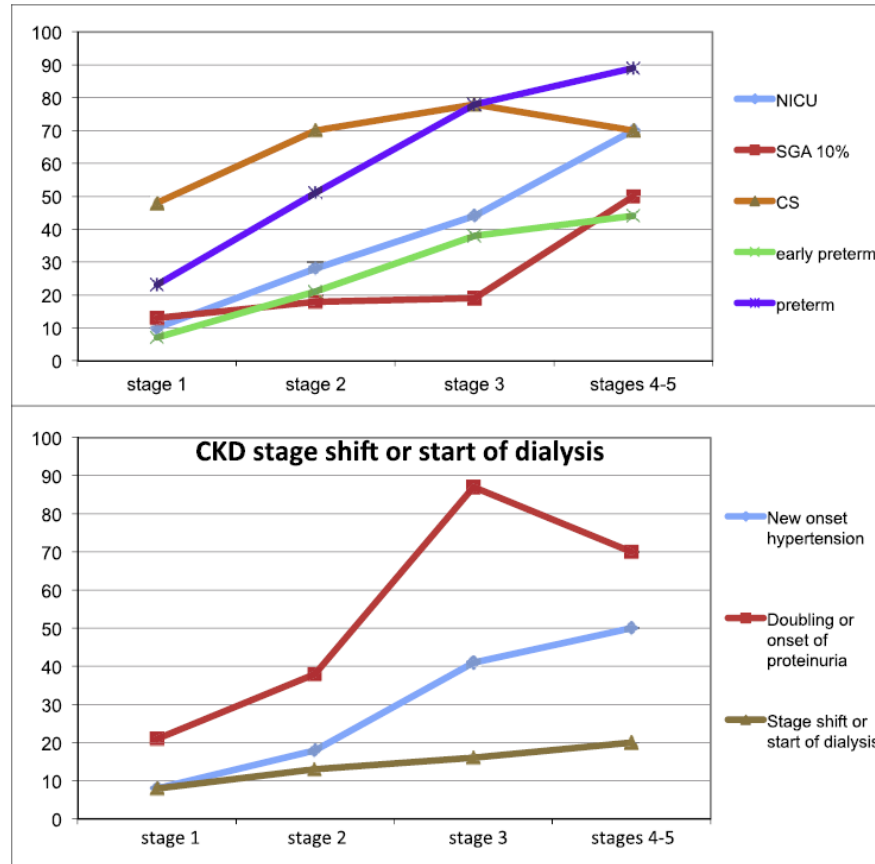
Parameter	Stage group	Baseline (A)	Pre delivery (B)	Postpartum (C)	p value (A vs B)	p value (B vs C)	p value (A vs C)
Mean GFR (ml/min/1.73 m <sup>2</sup> )	Early stage	114 ± 31	85.6 ± 32.6	99.9 ± 38.1	0.001(s)	0.004 (s)	0.005(s)
	Late stage	33.5 ± 14	27.1 ± 13.2	32.0 ± 19.3	0.001(s)	0.013 (s)	0.4
S. Creatinine (mg/dl)	Early stage	0.7 ± 0.24	0.93 ± 0.30	0.86 ± 0.33	0.001(s)	0.045 (s)	0.002(s)
	Late stage	2.22 ± 1.3	3 ± 2.1	2.6 ± 1.8	0.001(s)	0.048 (s)	0.008(s)
B.urea (mg/dl)	Early stage	20.8 ± 6.3	31.5 ± 19	31.2 ± 17.8	0.001(s)	0.886	0.001(s)
	Late stage	53.7 ± 30.1	79.4 ± 47.8	63 ± 32	0.001(s)	0.002 (s)	0.072
24h u.alb (g/24h)	Early stage	1.0 ± 1.3	1.04 ± 1.3	NA	0.802	–	NA
	Late stage	0.96 ± 1.2	1.3 ± 1.3	NA	0.010(s)	–	NA

s: significant.

# Fetomaternální výsledky- studie TOCOS

(Torino Cagliari Cohort study, 504 gravidit s FU)

Main maternal- fetal outcomes across the CKD stages: The TOCOS cohort



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

## Riziko progresse CKD

Progression of CKD stage at the end of 6 weeks postpartum.

Baseline CKD stage	CKD stage at 6 weeks postpartum, n (%)				
	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
Stage 1 (n= 36)	24(66.7)	6 (16.7)	6 (16.7)	0	0
Stage 2 (n= 10)	–	10(100)	0	0	0
Stage 3 (n= 20)	–	–	12 (60)	8 (40)	0
Stage 4 (n= 12)	–	–	–	6 (50)	6 (50)
Stage 5 (n= 2)	–	–	–	–	2 (100)

RF progresse CKD (do 12M po porodu):

- ✓ hypertenze
- ✓ proteinurie
- ✓ úroveň kreatininémie
- ✓ flare zákl. onemocnění

## Přístup k nemocné v PDL ve fertilním věku

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### ANTIKONCEPCE??

#### ANO

- ✓ Bariérová antikoncepce
- ✓ HAT- bezpečná
- ✓ IUD- vyšší riziko krvácení

### GRAVIDITA??

- ✓ individuální posouzení
- ✓ informovanost!!
- ✓ prekoncepční příprava

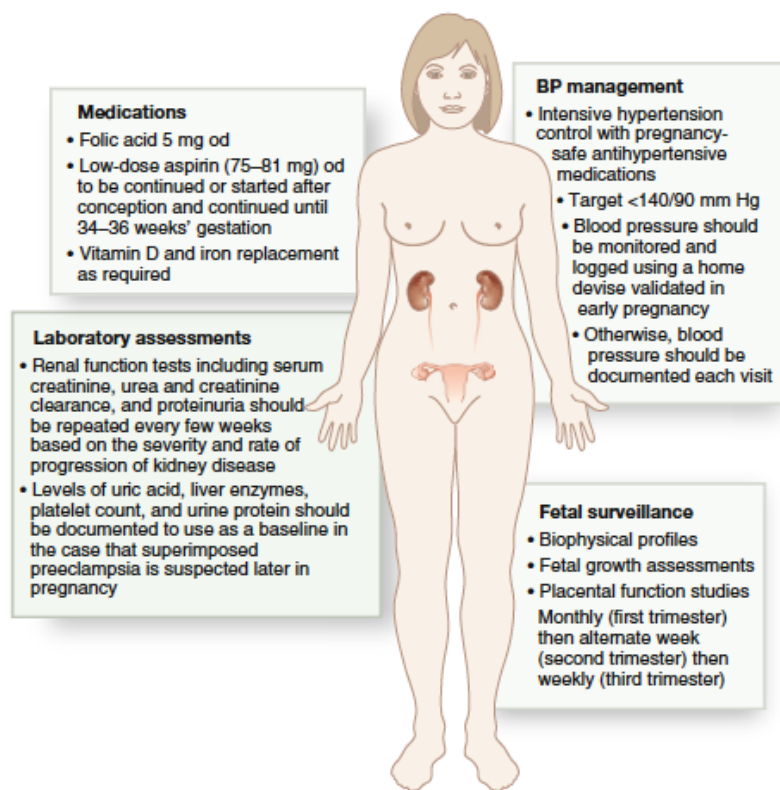


### TRANSPLANTACE

# Antenatální péče u nemocné s CKD

## Cíl= identifikace a korekce RF, optimalizace celkového stavu pacientky

- ✓ stabilizace základního onemocnění
  - ✓ korekce hypertenze
  - ✓ redukce proteinurie
  - ✓ korekce anémie
  - ✓ korekce koagulopatie
  - ✓ korekce hypogonádimu
- (substituce estrogenu/progesteronu)
- ✓ optimalizace vnitřního prostředí
- (intenzifikace dialyzačního režimu)
- ✓ úprava medikace



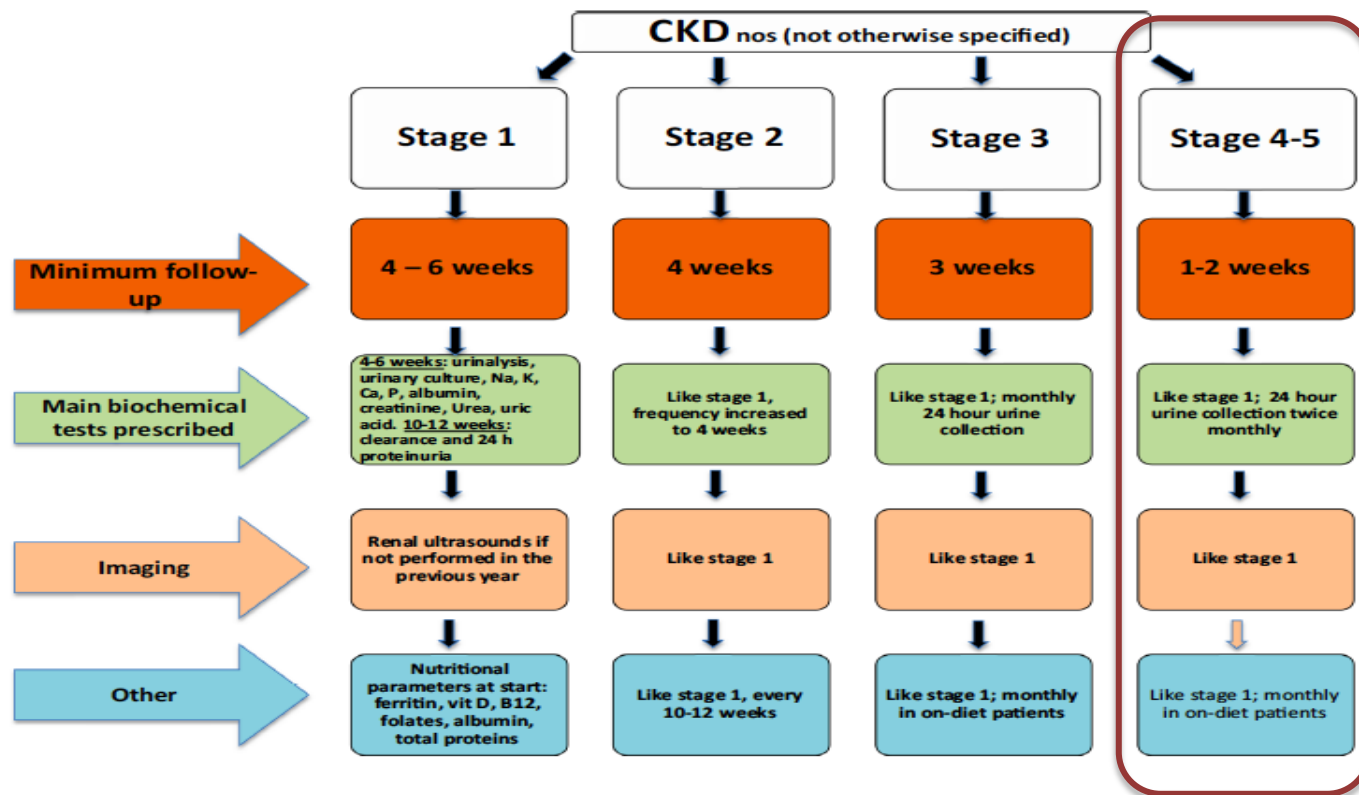
## Stanovení gravidity u dialyzované pacientky

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Incidence gravidity: 0.3-7%



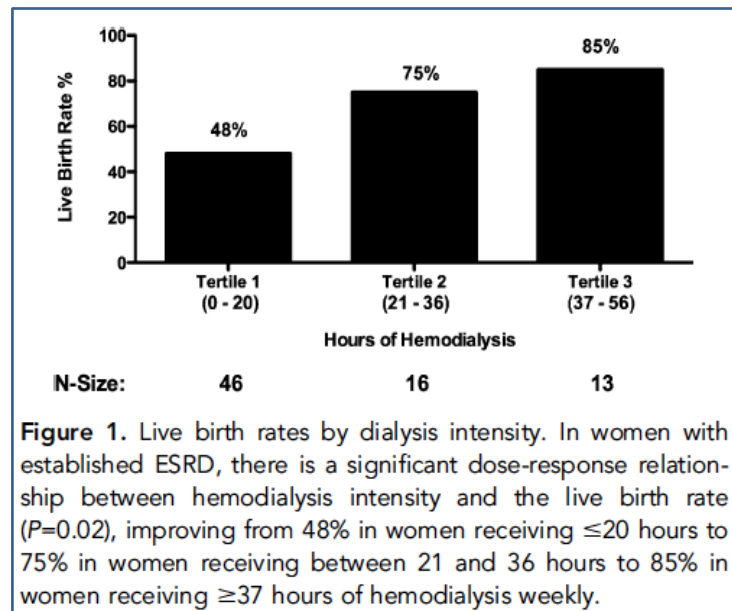
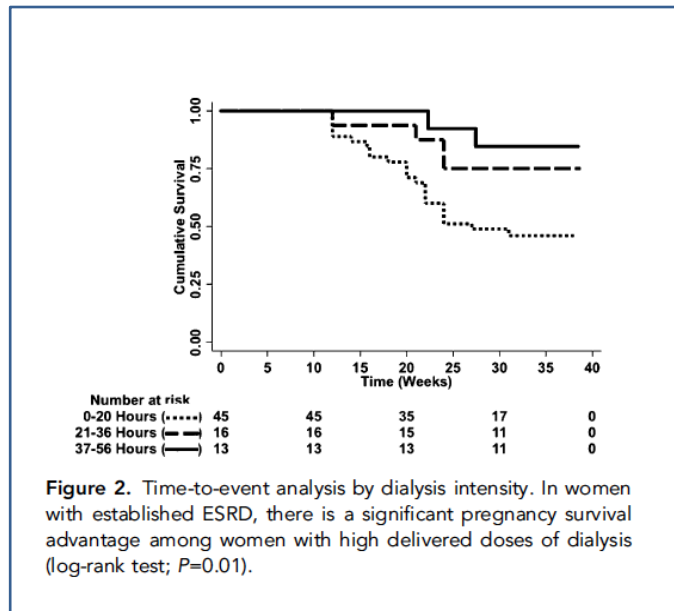
# Péče v těhotenství



# DIALYZAČNÍ TAKTIKA

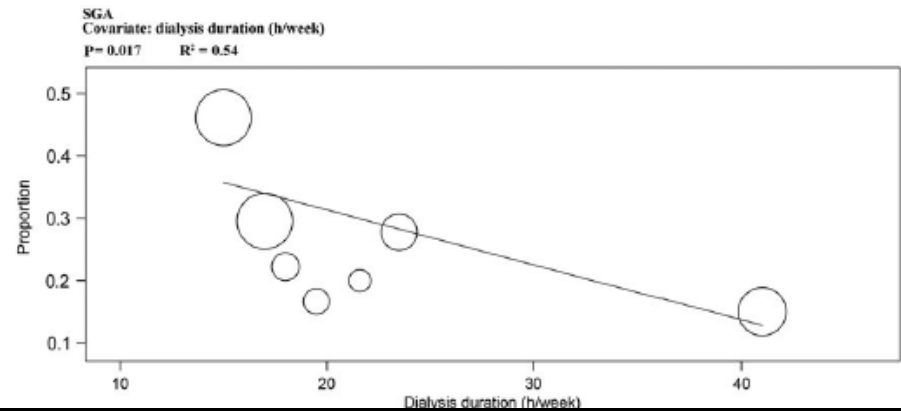
## - HD/PD, frekvence, délka

KDOQI CLINICAL PRACTICE GUIDELINE FOR HEMODIALYSIS ADEQUACY: 2015 UPDATE - Pregnancy  
**2.5 During pregnancy, women with end-stage kidney disease should receive long frequent hemodialysis either in-center or at home, depending on convenience. (Not Graded)**



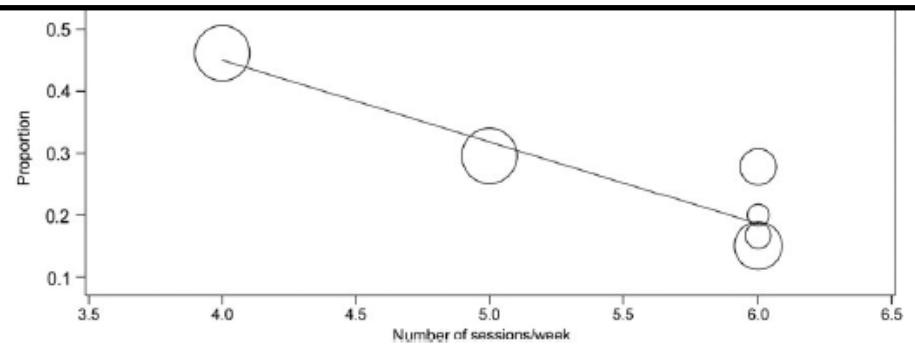
## PD vs. HD

	SGA %		P-value
	Yes	No	
PD	66.7	33.3	<b>0.015</b>
HD all cases	31.0	69.0	
HD: conception before HD start	20.0	80.0	0.130
HD: conception on HD	39.5	60.5	
HD: conception on HD <6 days	29.4	70.6	0.239



**Frekvence a délka dialýzy koreluje s prematuritou a předčasným porodem SGA plodu (IUGR)**

<20 h/w	28.6	71.4	0.249
≥20 h/w	35.7	64.3	
HD all cases			
<20 h/w	26.1	73.9	0.863
≥20 h/w	27.5	72.5	
HD all cases			
<6 days	24.1	75.9	0.871
≥6 days	28.9	70.1	



### Cíl:

- ✓ prodloužení dialyzační procedury >36h/týden, od 16.-20.g.t. procedury denně
- ✓ verze PD na HD není indikována (srovnatelné výsledky)

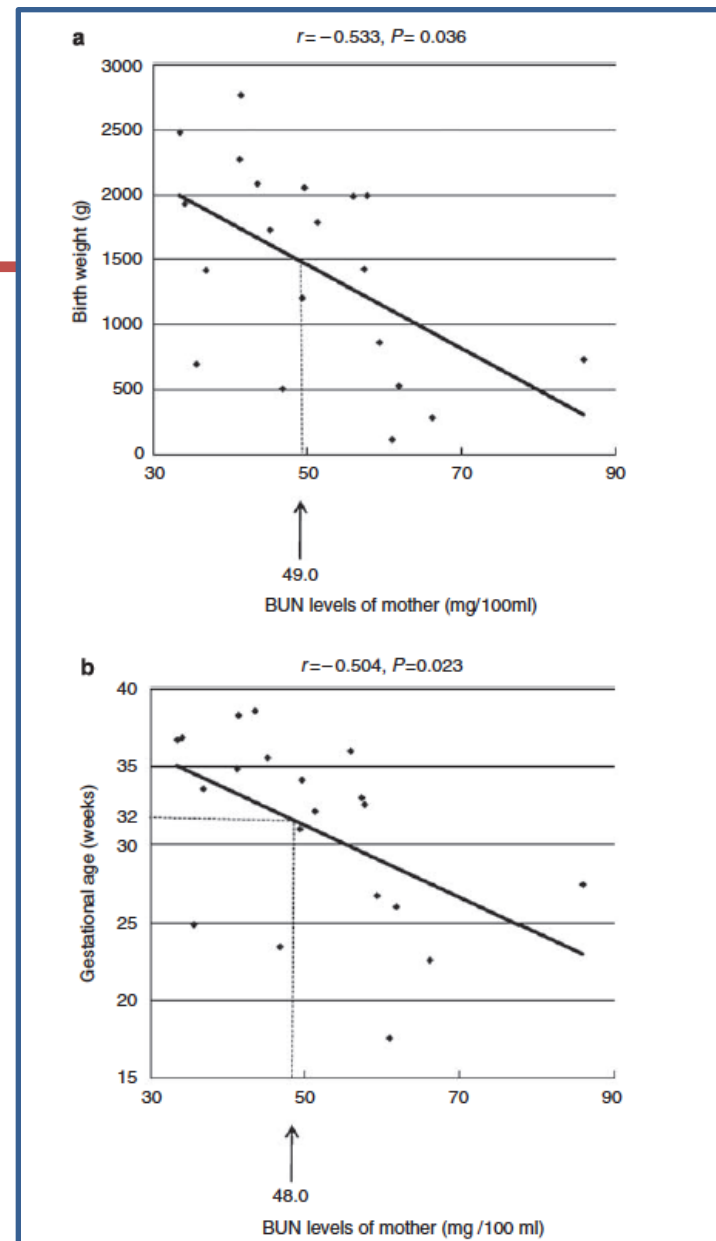
# DIALYZAČNÍ TAKTIKA

## - urea (účinnost)

- ✓ Hladina urey koreluje negativně se:
  1. zralostí/prematuritou
  2. porodní hmotností/SGA-IUGR
  
- ✓ korekce hladiny urey:
  1. snižuje výskyt polyhydramnionu (ureou indukovaná osmotická diuréza plodu)
  2. přispívá k lepší kontrole hypertenze
  3. zvyšuje porodní hmotnost
  4. zvyšuje gestační věk
  5. zlepšuje nutriční stav matky



**Cíl: udržení hladiny urey pod 17umol/l,  
optimálně pod 16umol/l**



# DIALYZAČNÍ TAKTIKA

## - elektrolyty

### Prevent metabolic acidosis

#### Intensity dialysis treatment

Increase the frequency of dialysis sessions (5–7 per week)

Maintain a predialysis BUN <16–18 mmol/L

Increase in maternal weight of 1–1.5 kg in the first trimester; thus 0.45–1 kg per week in the last trimester

Use the minimum possible dose of heparin

Use biocompatible membranes

#### Calcium/phosphorous metabolism

Avoid hypocalcaemia and hyperphosphataemia

Provide calcium supplementation of 1.5–2 g daily, dietary calcium of 800 mg daily and dialysate calcium of 1.5 mmol/L

If necessary, use calcium chelating agents and vitamin D. Avoid post-dialysis hypercalcaemia

Potassium levels in the dialysate must be increased to 3–3.5 mmol/L in order to avoid hypokalaemia. Electrolyte serum levels must be checked weekly [2, 20]. Low bicar-

### Cíl:

- ✓ snížit bikarbonát v dialyzátu (na 25mEq/l) → udržet S-bik 18-22mmol/l (rel. RAL v graviditě)
- ✓ suplementace Ca (1,5-2g/den)+navýšení Ca v dialyzátu (1,5..1,75 →2,5mmol/l)
- ✓ suplementace vit.D (1000-2000IU/den)
- ✓ monitorace elektrolytů+každý trimestr i vit. D a PTH

# DIALYZAČNÍ TAKTIKA

## - LMWH, ASA

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Acetyl salicylate	Low doses during pregnancy needed for the treatment of diverse medical conditions have not been shown to cause foetal harm; may be protective against pre-eclampsia, favoring placentation (see text); discontinuation before delivery is recommended [161–163, 223, 224]
LMWH	Low molecular-weight heparin (LMWH) does not cross the placenta and is safe for the foetus, although bleeding at the utero-placental junction cannot be ruled out. Individualized doses of LMWH are well tolerated and safe for prophylaxis and treatment of thromboembolic complications during pregnancy, and post-partum [355]. Twice-daily heparin should be discontinued prior to induction of labour or planned cesarean delivery and can be resumed after delivery [355, 356]

### Cíl:

- ✓ **ASA v dávce 75-100mg/den jako prevence preeklampsie a perinatálního úmrtí**
- ✓ **heparinizace LMWH během procedur+jako prevence TEN**

# DIALYZAČNÍ TAKTIKA

## - krevní průtok, kapilára

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High biocompatibility dialysers are recommended in pregnant patients [26]. It is best to use membranes with a lower surface area combined with increased time on dialysis in order to avoid excessive fluid losses with consequent episodes of hypotension and sudden changes in osmolarity [20].

### Cíl:

- ✓ postupné navýšení průtoku během prvních 30min procedury ze 180ml/min na 300ml/min
- ✓ velikost kapiláry do 1.7m<sup>2</sup>
- ✓ intradialyzační TK- NE < 120/80
- ✓ postdialyzační TK do 140/90

# DIALYZAČNÍ TAKTIKA

## - monitorace SV

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Maternal dry weight and weight gain should be regularly evaluated and adjusted according to the estimated weight of the fetus. In the first trimester, the mother should gain a minimum of 1–1.5 kg. Thus, a weight increase of 0.45–1 kg per week should be achieved. In the third trimester, fetal haemodynamics, weight and growth can also be directly evaluated using ultrasound and this monitoring might induce changes in dialysis prescription accordingly [17].

Maternal blood pressure and heart rate must be closely monitored before, during and after each dialysis session [17] Ultrafiltration doses should be administered on an individual basis in order to avoid episodes of arterial hypotension, hypovolaemia and arrhythmia. Maternal blood volume expansion and weight gain should be proportional to the gestation stage. Severe maternal weight loss due to rapid and excessive ultrafiltration can reduce the fetal-placental blood flow, which could be very harmful for the fetus. As such, these factors must be considered in ultrafiltration prescription [26]. These considerations underline the importance of intradialytic fetal monitoring in order to change dialysis prescriptions.

## Nutrice a suplementa

### Nutrition

Provide protein intake of 1.2–1.4 g/kg pre-pregnancy weight/day + 20 g/day

Provide calories intake of 25–35 kcal/kg/pregnant weight/day

Provide water-soluble vitamins supplementation

### Cíl:

- ✓ **Bílkoviny: 1.8g/kg/den CAVE: restrikce pod 1.2-1.4g/kg/den**
- ✓ **Kalorický příjem: HD- 35kcal/kg, PD-25kcal/kg**
- ✓ **Kys. Listová: 1mg/den, při denních HD 5mg/den**
- ✓ **Vitamíny: vit.C, riboflavin, niacin, vit. B6**

**Tabulka 1.** Doporučený denní příjem vitaminů pro těhotné a kojící ženy v ČR podle (2)

Vitamin (jednotka)	Těhotné ženy – do 4. měsíce	Těhotné ženy – od 4. měsíce	Kojící ženy
Vitamin A (mg)	neuvádí se	1,1	1,5
Thiamin (mg)	1,2	1,2	1,4
Riboflavin (mg)	1,2	1,5	1,6
Vitamin B <sub>6</sub> (mg)	1,2	1,9	1,9
Vitamin B <sub>12</sub> (μg)	6	6	6
Kyselina pantotenová (mg)	6	6	6
Vitamin C (mg)	100	110	150
Vitamin D (μg)	5	5	5
Vitamin E (mg)	13	13	17
Vitamin K (μg)	60	60	60
Biotin (μg)	30–60	30–60	30–60
Kyselina listová (μg)	400	600	600
Niacin (mg)	15	15	17

## Korekce anémie

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### Anaemia

Provide iron (10–15 mg/day) and folic acid (1 mg/day) supplementations  
Increase of 50–100% EPO dosage  
Maintain haemoglobin at 10–11 g/dL, haematocrit at 30–35% and serum ferritin of 200–300 µg/mL

### Cíl:

- ✓ navýšení dávek ESA k dosažení doporučených hodnot (2-3násobek pregestační potřeby)
- ✓ rEPO neprostupuje placentární bariérou
- ✓ ferrosustituce (i.v.)- potřeba matka+plod 800-1000mg

# Hypertenze

Drug	Main features	FDA
<i>Usually considered FIRST CHOICE drugs [141, 142, 340, 368]</i>		
Alpha-methyl dopa	Widely used in pregnancy, with no reported negative effects on the foetus or on its subsequent development. May not be able to correct severe hypertension in CKD	B
Nifedipine	The long acting drug most commonly used in hypertension in pregnancy. The increase in peripheral oedema may be a relevant side effect in CKD patients	C
Labetalole	Usually well tolerated, should be avoided in subjects with asthma. In a RCT it was shown to be comparable to alphas-methyl dopa [143, 149]	C
<i>Usually considered SECOND CHOICE drugs [141, 340]</i>		
Beta blockers	The main drawback in older studies was foetal growth restriction, possibly as an effect of overzealous correction [142]. Beta selective beta blockers (atenolole) are more often involved. Beta blockers may be more effective than alpha-methyl dopa in severe hypertension, alone or in combined therapy. At delivery they may induce hypoglycaemia, hypotension and bradycardia (usually mild and transient)	D atenolole B pindolole C metoprolol
Clonidine	The effect is similar to alpha-methyl dopa; side effects may be more common and hypertensive rebounds at discontinuation are common; slowing foetal growth is occasionally reported [144]	C
Alpha blockers	Other drugs should be preferred as controlled studies are missing	C
Diuretics	They are usually avoided in pregnancy except when there are nephrological or cardiological indications. Thiazides may be continued in patients previously on treatment [145, 158]. In selected cases with Gitelman syndrome, amiloride may be employed	B hydrochloro-thiazide amiloride
<i>To be avoided [141, 340]</i>		
Short acting nifedipine	Contraindicated by the FDA, RCOG and AIPE due to the risk of severe sudden hypotension with detrimental effects on placental flows	D
ACE-i ARB and related drugs	Both drugs are contraindicated in all phases of pregnancy because of the risk of several major malformations, including cardiovascular, central nervous system, renal and bone malformations [153–155]	C 1st D 2nd 3rd trimester

**Cíl TK: 110-140/80-90mmHg (max. 160/110mmHg pokud nejsou komorbidity)**

**CAVE: akcelerace/nekorigovatelná hypertenze- PREEKLAMPSIE**

## UTI

↑riziko preeklampsie (prematurity)  
a PN (30-40%)

Drug	Characteristics	FDA
<i>Usually considered as safe, when needed</i> [278–280, 304, 340, 350–354]		
Semi-synthetic penicillin	Ampicillin and Amoxicillin are the first-choice antibiotics	B
Clavulanic acid	Bacterial beta-lactamase inhibitor, used in combination with Amoxicillin. The association with beta-lactamase inhibitors is indicated when therapy with only Penicillins and Cephalosporins is not effective	
1st and 2nd generation Cephalosporins	In general, the data available on the use of Cephalosporins, in particular of first and second generation, during pregnancy, does not indicate an increase, over the expectation, of congenital abnormalities on exposed new-borns	
3rd generation Cephalosporins	Indicated for acute pyelonephritis when parenteral administration is necessary. Cefepime and Ceftriaxone: animal studies do not show teratogenic effects. Ceftriaxone should be avoided during the days before delivery because of the possibility of kernicterus (it competes with bilirubin for the binding with albumin)	B
Carbapenems	Meropenem should be the first choice in cases of notable severity, according to sensitivity. Animal studies, in fact, showed adverse effects on the foetus with Imipenem-cilastatin	B
Aztreonam	Valid alternative in the case of allergy to beta-lactams when parenteral administration is necessary	B
Macrolides	Erythromycin represents a valid alternative in the case of allergy to beta-lactams. Clarithromycin and Azithromycin are a second choice but they could be used according to clinical conditions [302]	B
Phosphomycin	Indicated for uncomplicated urinary tract-infections [297, 298, 303]	B
Nitrofurantoin	Contraindicated in G6PDH-deficient women. Their use during the first trimester should be limited to those situations in which no alternative therapies are available. Contraindicated at the end of the pregnancy (38th–40th week) and during delivery because of the risk of haemolytic anaemia in the new-born [26, 305]	B
<i>To be avoided</i>		
Aminoglycosides	They have been associated with ototoxicity. Their use must be avoided	D
Fluoroquinolones	Preclinical animal studies demonstrated abnormalities in the development of cartilages. Ciprofloxacin is not a first-choice drug during pregnancy; its administration should be limited to those cases in which the benefits are greater than the risk connected to the therapy [307]	C
Tetracycline	Their use must be avoided	D
Sulphonamides	Trimethoprim sulfamethoxazole must be avoided during the first trimester (it is a folic acid—antagonist) and at the end of the pregnancy for the risk of kernicterus	D
FDA Classification [340]: A, controlled human studies show no risk; B, no evidence of risk in studies; C, risk cannot be ruled out; D, positive evidence of risk; X, contraindicated in pregnancy		

- Cíl:**
- ✓ léčit I asympt. IMC 3-7 dní dle kultivace (1.trimestr: amoxicilin, cefalexin, cefuroxim, fosfomycin; 2.+3. trimestr (vyjma posledních 2 týdnů: nitrofurantoin, biseptol)
  - ✓ ATB profylaxe- pokud 2x poz. kultivační nález

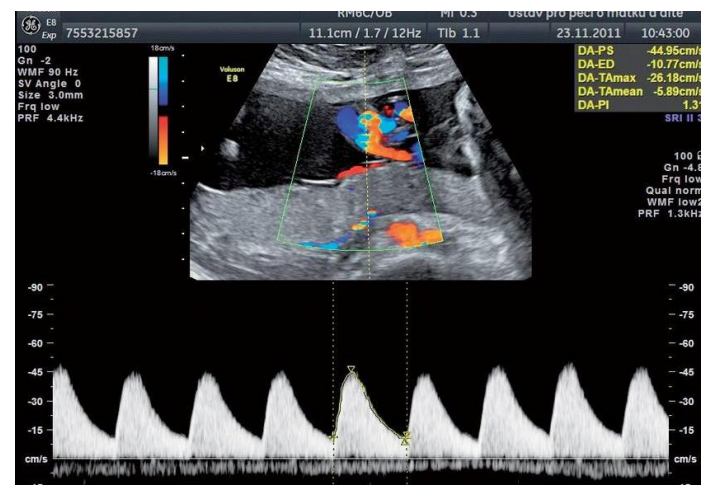
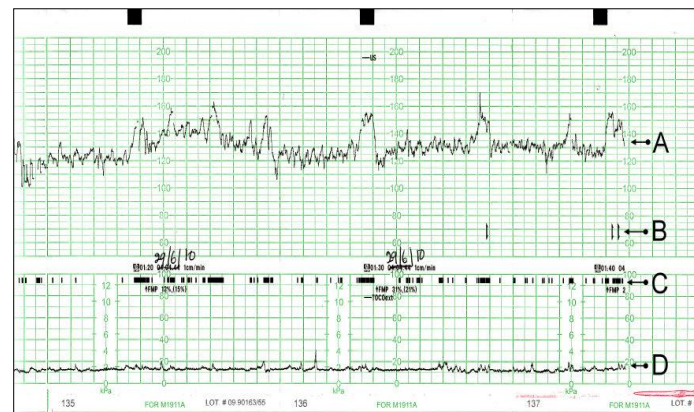
# Monitorace plodu

careful uterine and fetal monitoring during dialysis, such as assessment of the fetal heart rate, combined with measures aimed at preventing dialysis-induced hypotension should be performed. Maternal haemodynamic instability may compromise the uteroplacental circulation and may be associated with the induction of uterine contractions.

it was already clear that the dialysis technique did not influence the infant survival rate

## Cíl:

- ✓ standární biochem.+UZ skrínink (I.+II. trimestr)
- ✓ monitorace děložní aktivity a CTG během HD procedury
- ✓ od 26. g.t. fetální UZ, placentární průtoky, biofyz. profil týdně
- ✓ není indikace k verzi PD/HD, pokud je účinnost dostatečná  
růst plodu proporcionální



# Porod&kojení



## *Delivery*

- Plan induction at or just after 37 wk to ensure all necessary staff and resources are available
- Provide heparin-free dialysis prior to delivery to allow the use of an epidural and limit postpartum bleeding
- Obstetric team will determine mode of delivery; however, vaginal delivery is preferred

## *Neonatal Care*

- Assessment and follow-up by neonatal ICU team in a center equipped to manage preterm babies
- Promote breastfeeding; however, attention should be paid to all medications prescribed to nursing mothers
  - Provide lactation-safe antihypertensive agents as required. Options include methyldopa, labetalol, or long-acting nifedipine. ACEIs, including captopril, quinalapril, and enalapril, are secreted in low amounts and may be used as necessary. Overly aggressive ultrafiltration may reduce milk supply
  - Avoid heparin containing the preservative benzyl alcohol, as it is potentially toxic to premature and low-birth-weight infants

# TAKE HOME MESSAGE

## úspěšná gravidita v PDL

<i>Factor</i>	<i>Recommendations</i>
Anemia	
Hemoglobin	10-11 g/dL; requires increase in erythropoietin dose by 50%-100%
Iron saturation	maintenance intravenously iron to keep iron saturation >30%; administer in small doses
Folate	1 mg/d
Hypertension/hemodynamics	Avoid maternal hypotension or volume depletion; increase EIW by about 0.5 kg Per week; requires close clinical follow-up and frequent assessments 2nd-3 <sup>rd</sup> trimester
Hemodialysis prescription dialysate	Nonreuse, biocompatible, smaller surface area dialyzer to reduce ultrafiltration rate per treatment To avoid metabolic alkalosis use 25 mEq/L HCO <sub>3</sub> bath; To avoid hypokalemia use 3-4 mEq/L potassium bath Add phosphorus to dialysate as needed to keep predialysis phosphorus 4-5 mg/dL
Predialysis BUN	keep less than 45-50 mg/dL
Frequency of treatments	5-6 a week; daily nocturnal hemodialysis and hemodiafiltration also possible
Nutrition	
Protein intake	1.5 g/kg/d in HD; 1.8 g/kg/d in PD
Caloric intake/fluid intake	30-35 kcal/kg/d/750-1,500 mL/d
Calcium	1,500 mg d; usually achieved with 2.5 mEq/L calcium dialysate; measure and Supplement 25OH vitamin D every trimester
Phosphorus	oral, or may add to dialysate
Vitamins	Vitamin C, thiamine, riboflavin, niacin, vitamin B6, folate
Preterm labor	Consider progesterone for prevention; tocolysis with indomethacin (short term), Magnesium, keep serum level <5 mg/dL, or calcium- channel blocker
Obstetric/fetal monitoring	nonstress testing, ultrasounds, close obstetric, and neonatal care

# TRANSPLANTACE

---

Sexual dysfunction is common in men and women KTRs.  
Many patients will not spontaneously report sexual dysfunction.  
Modification of medications may alleviate sexual dysfunction.  
Therapies are available, although less are available for women than men.  
Sexual dysfunction negatively affects quality of life.  
Contraception can help prevent unwanted pregnancies.  
Safe sex practices can help prevent the acquisition of disease.



## SEXUAL FUNCTION

- 25.1.1: Evaluate adults for sexual dysfunction after kidney transplantation. (Not Graded)**
- 25.1.2: Include discussion of sexual activity and counseling about contraception and safe sex practices in follow-up of adult KTRs. (Not Graded)**

# Fertilita mužů po transplantaci

---

Male fertility improves in most KTRs, and may become normal.

Outcomes of pregnancies fathered by KTRs are similar to those of the general population.

Rapamycin is associated with low sperm counts. The abnormality is reversible with discontinuation of rapamycin.

## MALE FERTILITY

**25.3.1: We suggest that male KTRs and their partners be advised that:**

- male fertility may improve after kidney transplantation (2D);
- pregnancies fathered by KTRs appear to have no more complications than those in the general population. (2D)

**25.3.2: We recommend that adult male KTRs be informed of the possible risks of infertility from mTORi. (1C)**

**25.3.2.1: We suggest that adult male KTRs who wish to maintain fertility should consider avoiding mTORi, or banking sperm prior to mTORi use. (2C)**

## Fertilita žen po transplantaci

---

Fertility is increased in KTRs compared to CKD stage 5 before transplantation. Pregnancy and childbirth in KTRs have a high incidence of complications to mother and child. Complications of pregnancy and childbirth can be minimized by the use of lower-risk immunosuppressive agents and multidisciplinary care that includes an obstetrician with expertise in managing high-risk pregnancies.

### FEMALE FERTILITY

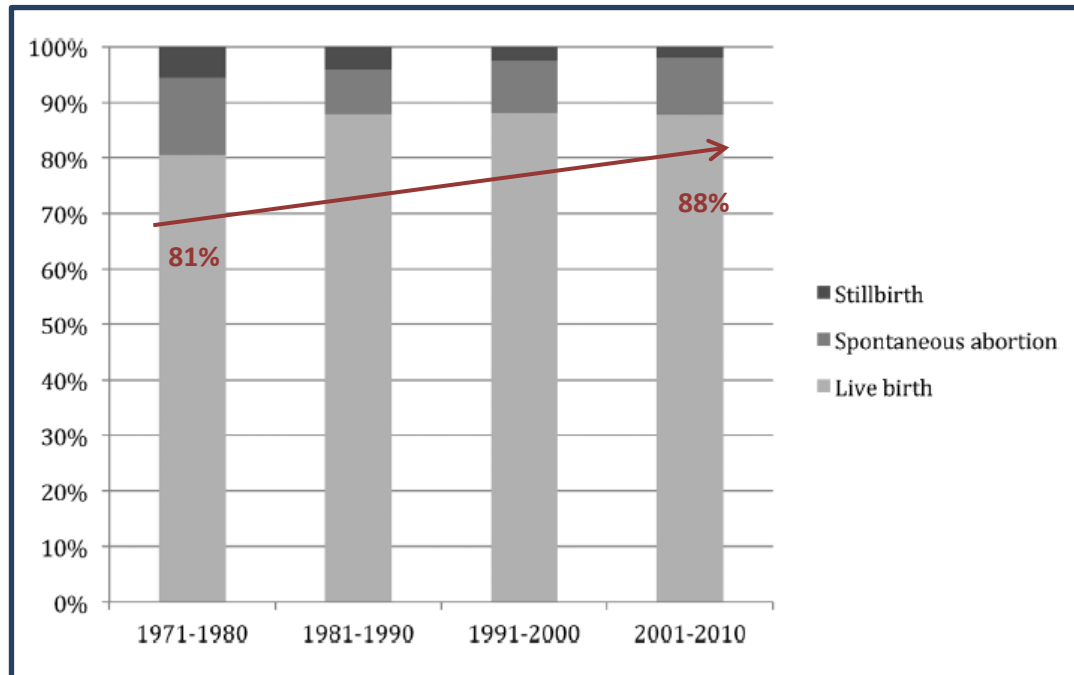
- 25.2.1:** We suggest waiting for at least 1 year after transplantation before becoming pregnant, and only attempting pregnancy when kidney function is stable with  $<1$  g/day proteinuria. *(2C)*
- 25.2.2:** We recommend that MMF and EC-MPS be discontinued or replaced with azathioprine before pregnancy is attempted. *(1A)*
- 25.2.3:** We suggest that mTORi be discontinued or replaced before pregnancy is attempted. *(2D)*
- 25.2.4:** Counsel female KTRs with child-bearing potential and their partners about fertility and pregnancy as soon as possible after transplantation. *(Not Graded)*
- 25.2.5:** Counsel pregnant KTRs and their partners about the risks and benefits of breastfeeding. *(Not Graded)*
- 25.2.6:** Refer pregnant patients to an obstetrician with expertise in managing high-risk pregnancies. *(Not Graded)*

## Výsledky gravidit po SOT

National Transplantation Pregnancy Registry Maternal and Neonatal Outcome Data According to Transplanted Organ Type

	Kidney (%)	Liver (%)	Kidney/ Pancreas (%)	Heart (%)	Lung (%)
<b>Maternal Complications</b>					
Hypertension	53-64	17-40	41-95	28-51	52
Preeclampsia	30-32	20-24	22-32	10-25	5
Diabetes	5-12	2-13	0-5	0-4	26
Rejection	1-2	2-11	0-14	3-21	16
Graft loss within 2 y	6-9	2-8	10-17	0-4	14
<b>Pregnancy Outcomes</b>					
Spontaneous abortion	12-25	15-20	8-31	19-44	27
Live birth	71-77	72-82	64-79	48-70	58
Prematurity (< 37 wk)	52-53	30-48	65-84	8-54	63
Mean gestational age (wk)	35.3-35.9	36-37.3	33.7-34.8	36.1-37.8	33.9
Cesarean delivery	43-57	29-45	61-69	30-57	32

## Úspěšnost těhotenství se v čase zlepšuje (ANZDATA)



## Fetomaternální komplikace po TxL a OTJ

Maternal and Neonatal Complications in Kidney and Liver Transplant Recipients		
	Liver (N = 450)	Kidney (N = 4002)
<b>Pregnancy Outcome</b>		
Live birth (%)	76.9 (72.7-80.7)	73.5 (72.1-74.9)
Miscarriage (%)	15.6 (12.3-19.2)	14.0 (12.9-15.1)
Termination (%)	6.2 (4.2-8.9)	9.5 (8.6-10.4)
Stillbirth (%)	0.9 (0.2-2.3)	2.5 (2.0-3.0)
Ectopic pregnancy (%)	0.4 (0.1-1.6)	0.6 (0.4-0.9)
<b>Obstetric Complication</b>		
	<b>Liver</b>	<b>Kidney</b>
Hypertension (%)	27.2 (22.9-31.9)	54.2 (52.0-56.4)
Preeclampsia (%)	21.9 (17.7-26.4)	27.0 (25.2-28.9)
Gestational diabetes (%)	5.1 (3.0-8.0)	8.0 (6.7-9.4)
<b>Delivery Outcome</b>		
	<b>Liver</b>	<b>Kidney</b>
Cesarean delivery (%)	44.6 (39.2-50.1)	56.9 (54.9-58.9)
Preterm birth (%; < 37 wk)	39.4 (33.1-46.0)	45.6 (43.7-47.5)
Gestational age (wk)	36.5	35.6
Birth weight (g)	2677	2420

## Prekoncepční poradenství - adekvátní informovanost!

---

1. Discuss the effect of pregnancy on transplant organ function
2. Discuss risks of maternal complications: hypertension, preeclampsia, diabetes, rejection, and graft loss
3. Obtain good control of prepregnancy hypertension and diabetes
4. Discuss risks of neonatal complications: prematurity and low birth weight
5. Modification of immunosuppressive regimen if necessary
6. Test for cytomegalovirus and other potential infections

## Specifika antenatální péče – optimalizace celkového stavu

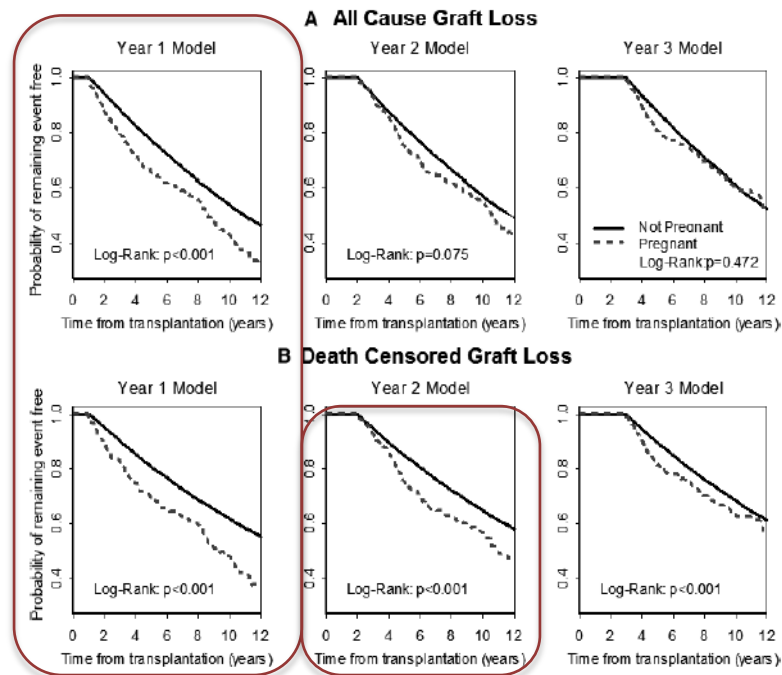
- ✓ korekce RF jako u nemocných s CKD
- ✓ úprava medikace (vysazení potenc. teratogenních léků)
- ✓ nutriční intervence (protein 1g/kg/den, suplementace Ca, vit. D)
- ✓ **+ úprava konkomitantní imunosuprese**

Drug	Main features	FDA
<i>Usually considered as relatively safe, when absolutely needed [341–349]</i>		
Azathioprine	This is the most widely used immunosuppressive drug. It is teratogenic in animal models, but not in humans, possibly because the foetal liver is not able to activate the drug. KDIGO and European Best Practice Guidelines suggest switching from Mycophenolate to Azathioprine before pregnancy [341–343]	D
Cyclosporine A	This Calcineurin inhibitor has not been associated with increased teratogenicity; however, small for gestational age babies and preterm delivery have been reported, possibly due to the maternal disease and not specifically to the drug; levels may vary in pregnancy and the hypertensive, hyperglycaemic and nephrotoxic effects should be mentioned [344]	C
Tacrolimus	The drug has similar effects and side effects as Cyclosporine A; since it is a relatively new drug, experience is more limited than with the previous drug [345]	C
Steroids	Together with azathioprine these are the most often employed and best known drugs. The most frequently used short-acting corticosteroids include prednisone, methylprednisolone and prednisolone, while betamethasone and dexamethasone are among the long-acting drugs. No major malformations have been reported, and the issue of labio-palatoschisis is debated. A higher risk of premature rupture of membranes has been reported. Other relevant side effects include infectious risk, and the increased risk of gestational diabetes [346]	C
Hydroxy-chloroquine	This synthetic anti-malaric agent crosses the placenta but was not found to be associated with foetal toxicity [217–219]	B
<i>To be avoided [341–349]</i>		
Cyclophosphamide	This alkylating agent is contraindicated in pregnancy; a few reports suggest that pregnancy termination is common in the case of inadvertent use or need for life saving therapy. A few positive reports, mainly in women with SLE are also available [68]	D
Mycophenolate	Severe foetal malformations are reported, mainly involving cardiovascular and cranial malformations. Discontinuation for at least 6 months, to stabilize kidney function, is usually indicated after kidney transplantation [347, 348]	D
Rituximab	There are no data on whether rituximab can cause foetal harm. Rituximab was detected postnatally in the serum of infants exposed in utero: B-cell lymphocytopenia generally lasting less than 6 months can occur in infants. The manufacturer recommends contraception for up to 12 months following therapy [369, 370]	C
m-Tor inhibitors	Very few studies have considered their use in pregnancy. They are teratogenic in animals and discontinuation in humans is a matter of debate; KDIGO guidelines suggest discontinuation in anticipation of pregnancy [347, 349]	C

# Timing gravidity- doporučení

## Cíl:

- ✓ min. odstup od Tx 1R (optimálně 2R)
- ✓ dobře kompenzovaná hypertenze
- ✓ min. PU (do 0.5g/den)
- ✓ stabilní funkce štěpu
- ✓ úroveň CKD (S-krea 125umol/l)
- ✓ stabilní IS
- ✓ absence rejekcí



**Figure 3:** Kaplan-Meier curves showing association of pregnancy with allograft failure from any cause (A) and death censored graft loss (B) by timing of pregnancy after kidney transplantation.

# IS a gravidita

	2-year graft loss (n = 380)		p-value	5-year graft loss (n = 380)		p-value
	Yes	No		Yes	No	
Pregnancy number						
1	13 (6.1)	199 (93.9)	0.853	23 (10.8)	189 (89.2)	0.948
2	1 (1.2)	81 (98.8)		8 (9.8)	74 (90.2)	
3	1 (2.1)	46 (97.9)		5 (10.6)	42 (89.4)	
4	0	17 (100)		0	17 (100)	
5-12	0	22 (100)		0	22 (100)	
Missing (0)						
Cyclosporine	4 (4.7)	82 (95.3)	0.947	13 (15.1)	73 (84.9)	0.068
Missing (0)						
Tacrolimus	11 (3.9)	272 (96.1)	1.000	23 (8.1)	260 (91.9)	0.184
Missing (0)						
Sirolimus	3 (30.0)	7 (70.0)	0.001	4 (40.0)	6 (60.0)	0.005
Missing (0)						
Azathioprine	5 (2.5)	197 (97.5)	0.192	13 (6.4)	189 (93.6)	0.048
Missing (0)						
Preeclampsia	4 (4.9)	77 (95.1)	1.000	7 (8.6)	74 (91.4)	0.448
Missing (6)						
Cesarean section	7 (4.9)	137 (95.1)	1.000	16 (11.1)	128 (88.9)	1.000
Missing (1)						
MPA discontinuation_1						
>6 WPtP	4 (1.8)	216 (98.2)	0.038	9 (4.1)	211 (95.9)	<0.001
<6 WPtP	3 (12)	22 (88)		7 (28.0)	18 (72.0)	
First trimester	4 (6.6)	57 (93.4)		11 (18.0)	50 (82.0)	
Second trimester/ never discontinued	4 (5.4)	70 (94.6)		9 (12.2)	65 (87.8)	
Missing (0)						
MPA discontinuation_2						
>6 WPtP	4 (1.8)	216 (98.2)	0.026	9 (4.1)	211 (95.9)	<0.001
Anytime <6 WPtP	11 (6.9)	149 (93.1)		27 (16.9)	133 (83.1)	
Missing (0)						
MPA discontinuation_3						
Before conception	7 (2.9)	238 (97.1)	0.232	16 (6.5)	229 (93.5)	0.014
After conception	8 (5.9)	127 (94.1)		20 (14.8)	115 (85.2)	
Missing (0)						
Low gestational age	12 (4.9)	233 (95.1)	0.340	27 (11.0)	218 (89.0)	0.169
Missing (6)						
Low birth weight (<2500 g)	9 (8.9)	92 (91.1)	0.010	18 (17.8)	83 (82.2)	0.010
Missing (6)						
Birth weight (g)	n = 11	241	<0.001	n = 28	224	0.001
Mean ± SD	1710 ± 796	2614 ± 724		2129 ± 853	2630 ± 718	

Cíl:

✓ plán. vysazení MMF min. 6 týdnů před koncepcí se stabilní funkcí štěpu → ↓ riziko ztráty štěpu po 5R FU

# Imunosupresivní režim

mTORi- gonadotoxicita, teratogenicita

MMF- teratogenicita

Při vysazení min. 6týdnů před

konceptí → ↓ kong. defekty (výskyt 4-5% ≈ obecná populace)

## Cíl:

✓ Vysadit MMF/mTORi před plán. konceptí

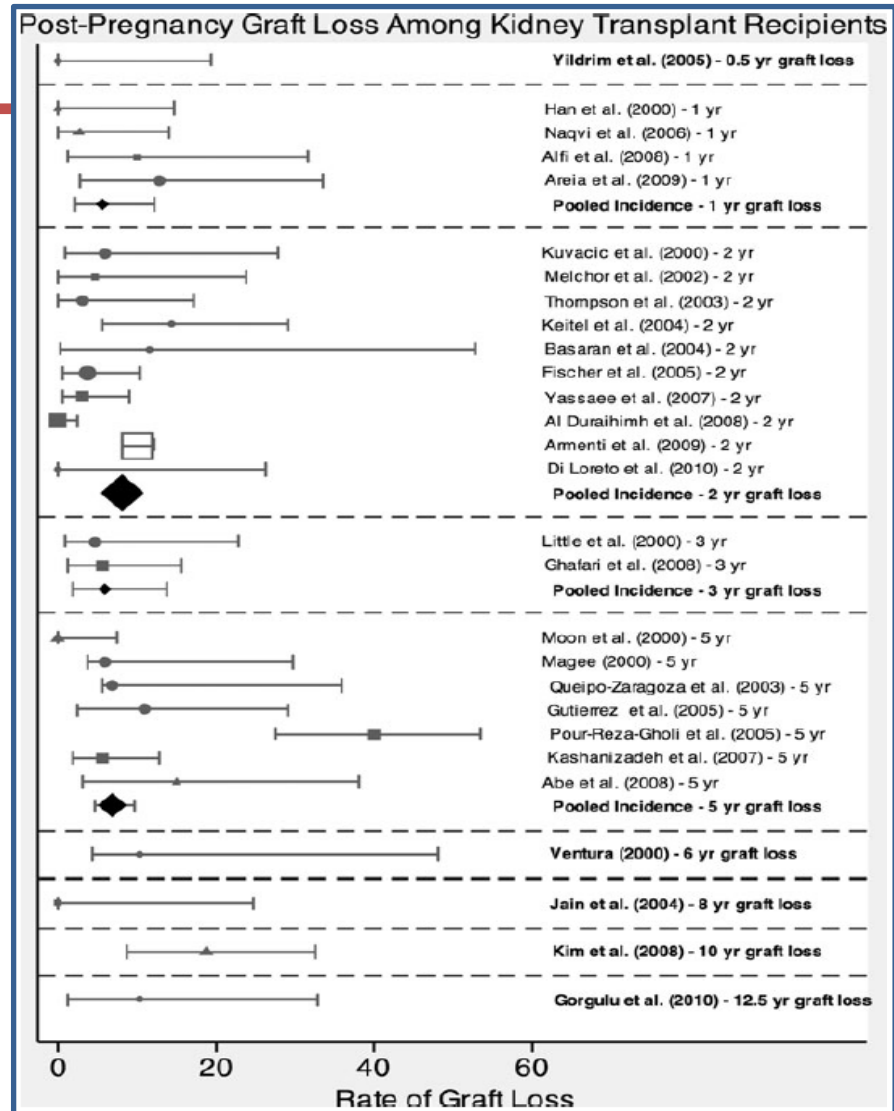
✓ min. 3-6M stabilní fce štěpu- cílená koncepte

✓ Vysadit MMF/mTORi optimálně 6týdnů před plán. konceptí (do 2.trimestru nejpozději! /kong. Defekty 32%/)

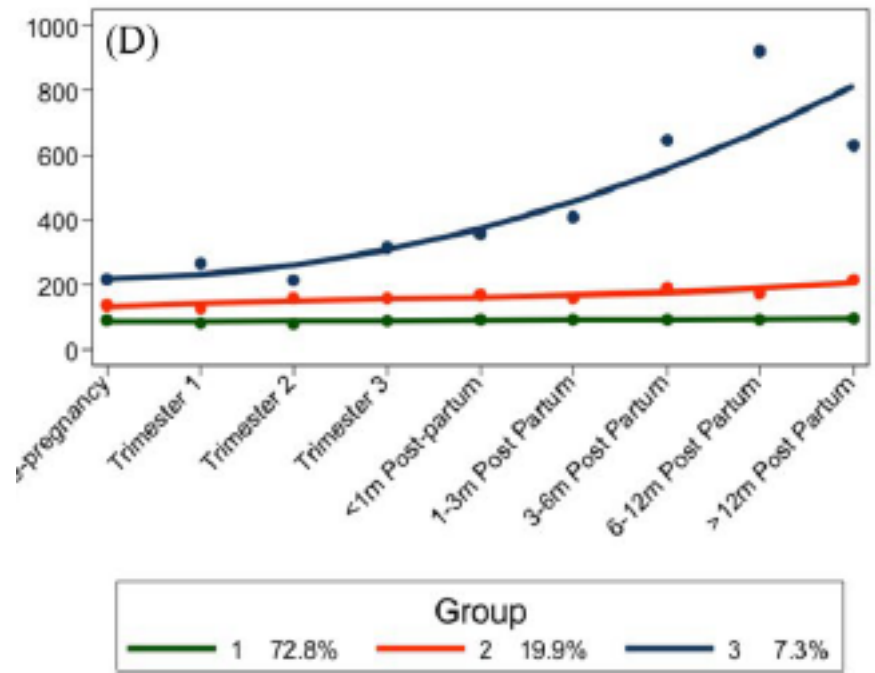
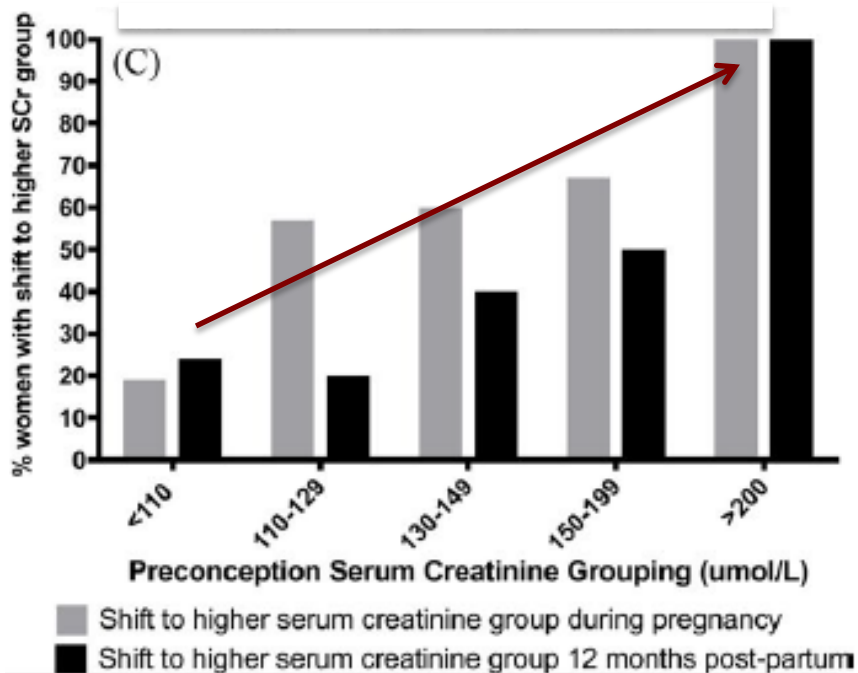
Variable	Miscarriages (n = 382)		p-value	Birth defects (n = 256)		p-value
	Yes	No		Yes	No	
Cyclosporine Missing (0)	30 (34.9)	56 (65.1)	0.335	2 (3.6)	53 (96.4)	0.194
Tacrolimus Missing (0)	81 (28.5)	203 (71.5)	0.307	19 (9.8)	175 (90.2)	0.585
Sirolimus Missing (0)	2 (20.0)	8 (80.0)	0.721	1 (12.5)	7 (87.5)	1.000
Azathioprine Missing (0)	39 (19.3)	163 (80.7)	<0.001	13 (8.2)	146 (91.8)	0.724
Twins						
Single birth	115 (30.8)	258 (69.2)	0.140	23 (9.3)	224 (90.7)	0.714
Twin	0	9 (100)		0	9 (100)	
Missing (0)						
Preeclampsia Missing (6)	1 (1.2)	80 (98.8)	0.747	7 (8.9)	72 (91.1)	1.000
Cesarean section Missing (1)				9 (6.3)	133 (93.7)	0.208
MPA discontinuation_1						
>6 WPtP	44 (19.9)	177 (80.1)	<0.001	12 (7.1)	158 (92.9)	0.005
<6 WPtP	5 (20.0)	20 (80.0)		1 (5.0)	19 (95.0)	
First trimester	13 (21.3)	48 (78.7)		4 (8.5)	43 (91.5)	
Second trimester/ never discontinued	53 (70.7)	22 (29.3)		6 (31.6)	13 (68.4)	
Missing (0)						
MPA discontinuation_2						
>6 WPtP	44 (19.9)	177 (80.1)	<0.001	12 (7.1)	158 (92.9)	0.199
Anytime <6 WPtP	71 (44.1)	90 (55.9)		11 (12.8)	75 (87.2)	
Missing (0)						
MPA discontinuation_3						
Before conception	49 (19.9)	197 (80.1)	<0.001	13 (6.8)	177 (93.2)	0.074
After conception	66 (48.5)	70 (51.5)		10 (15.2)	56 (84.8)	

# Postpartální riziko ztráty štěpu

FU 0.5R	0%
1R	6%
2R	8%
3R	6%
5R	7%
6R	10%
10R	19%
12.5R	11%



# Riziko selhání štěpu koreluje s úrovní CKD před těhotenstvím

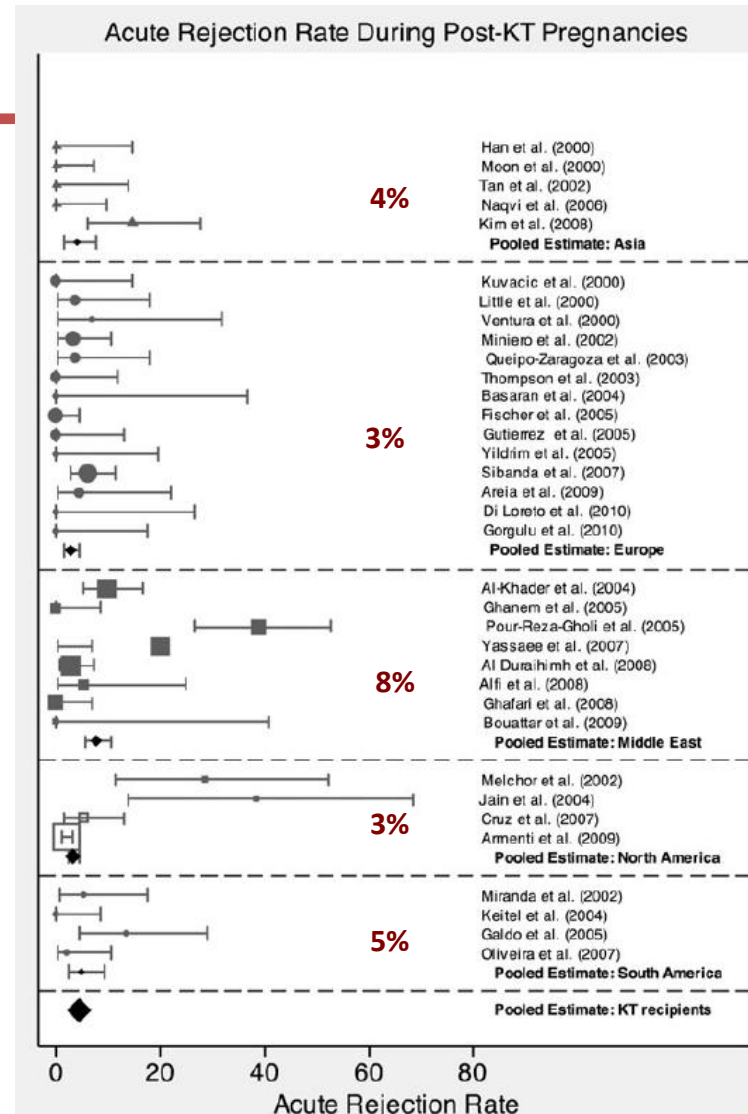


# Akutní rejekce

Biopsie- proveditelná do 32.g.t.

Celulární rejekce→KS

Humorální rejekce→KS+IVIG (PF KI v pozdní graviditě)



# IS: rejekce, ztráta štěpu po SOT

Organ Transplant Subgroup	Pregnant women with an organ transplant			Non-pregnant women with organ transplant		
	N	Rejection during pregnancy	Graft loss within 2 y of delivery	N	Rejection within 1 y of transplant	Graft loss within 2 y of transplant
<b>Kidney*</b>						
CsA	517	1%	9%	17,379	11%	11%
CsA mod	241	2%	6%			
Tacrolimus	278	2%	6%			
<b>Liver</b>						
CsA	100	11%	8%	2,891	19%	23%
CsA modified	64	2%	3%			
Tacrolimus	140	5%	5%			
<b>Pancreas-Kidney</b>						
CsA	23	14%	13%	1,855	10%	12%
CsA modified	23	0%	17%			
Tacrolimus	42	5%	10%			
<b>Heart</b>						
CsA	43	21%	0%	1,259	31%	21%
CsA modified	25	4%	4%			
Tacrolimus	35	3%	3%			
<b>Lung</b>	31	16%	14%	1,257	32%	28%

N, number of pregnancies or number of non-pregnant women. Data was obtained from the NTPR (2011 Annual Report)<sup>18</sup> and the Organ Procurement and Transplantation Network on May 24, 2013. The non-pregnant women were 18–39 y old and received their transplant between 2000–2010. CsA, Sandimmune® brand cyclosporine A; CsA modified, newer formulation of CsA became available in 1994 with improved absorption over CsA. \*The NTPR data on rejection in kidney transplants during pregnancy is acute, biopsy-proven rejection. Rejection for other organ transplants represents both acute and chronic rejection and is not always biopsy-proven.

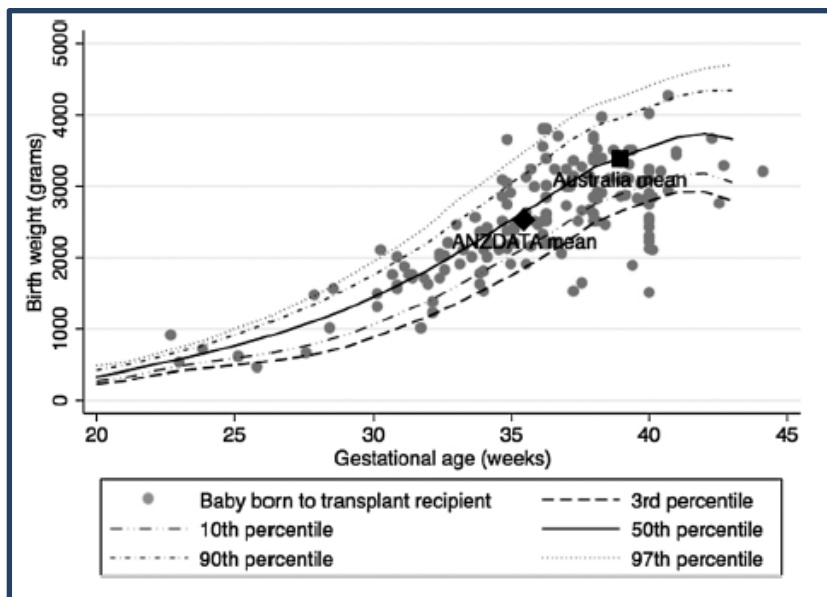
## Management těhotné pacientky po Tx

- ✓ přesné stanovení gravidity
- ✓ frekventní monitorace funkce štěpu a hladin imunosupresiv
- ✓ infekční surveilance (UTI, HSV, CMV)
- ✓ frekventní monitorace plodu (růst, VVV)
- ✓ surveillance matky
  - hypertenze
  - gestační diabetes
  - preeklampsie
  - gynekologicko-porodnická péče na specializovaném pracovišti



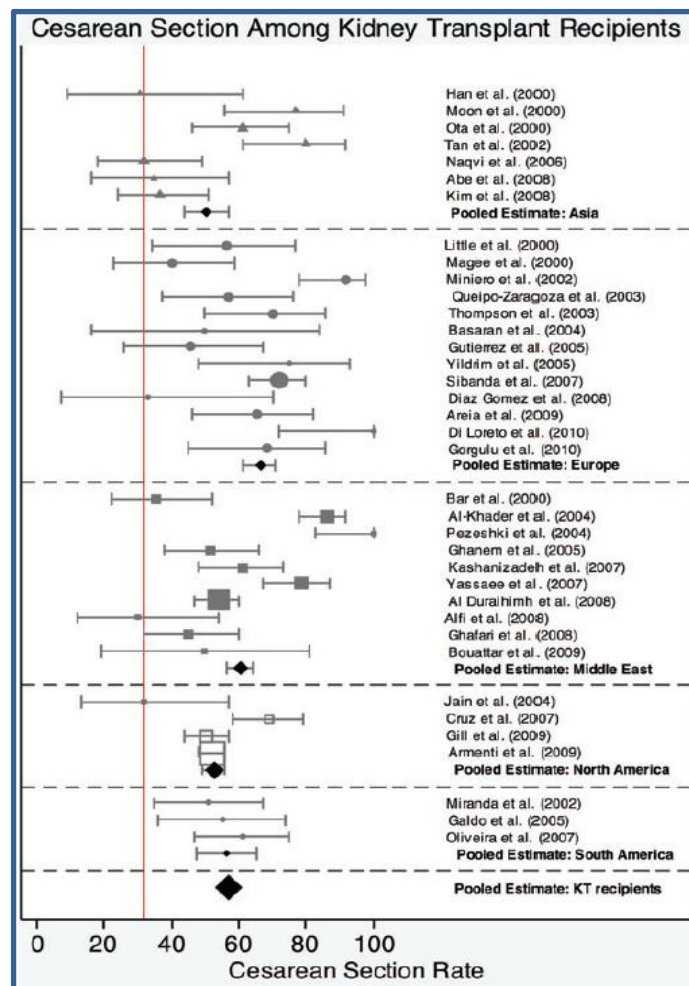
Preeclampsia	Preeclampsia is diagnosed in the setting of hypertension in association with thrombocytopenia, impaired liver function tests, the new development of renal insufficiency, pulmonary edema, or new-onset cerebral or visual disturbances
Chronic hypertension	Antihypertensive requirement before pregnancy or hypertension beginning before the 20th week of pregnancy or hypertension continuing for >12 weeks after delivery
Chronic hypertension with superimposed preeclampsia	Combination of the two
Gestational hypertension	Blood pressure elevation after 20 weeks of gestation in the absence of proteinuria, thrombocytopenia, impaired liver function, new onset of kidney dysfunction, pulmonary edema, or new cerebral or visual disturbances

# Porod



## Cíl:

- ✓ porod v termínu
- ✓ vaginální vedení porodu



## Kojení s IS?

---

### Kontraindikovány:

- ✓ CPA
- ✓ MTX
- ✓ MMF

### Možné:

- ✓ AZA
- ✓ CyA – nutná monitorace toxicity
- ✓ KS
- ✓ hydroxychlorochin

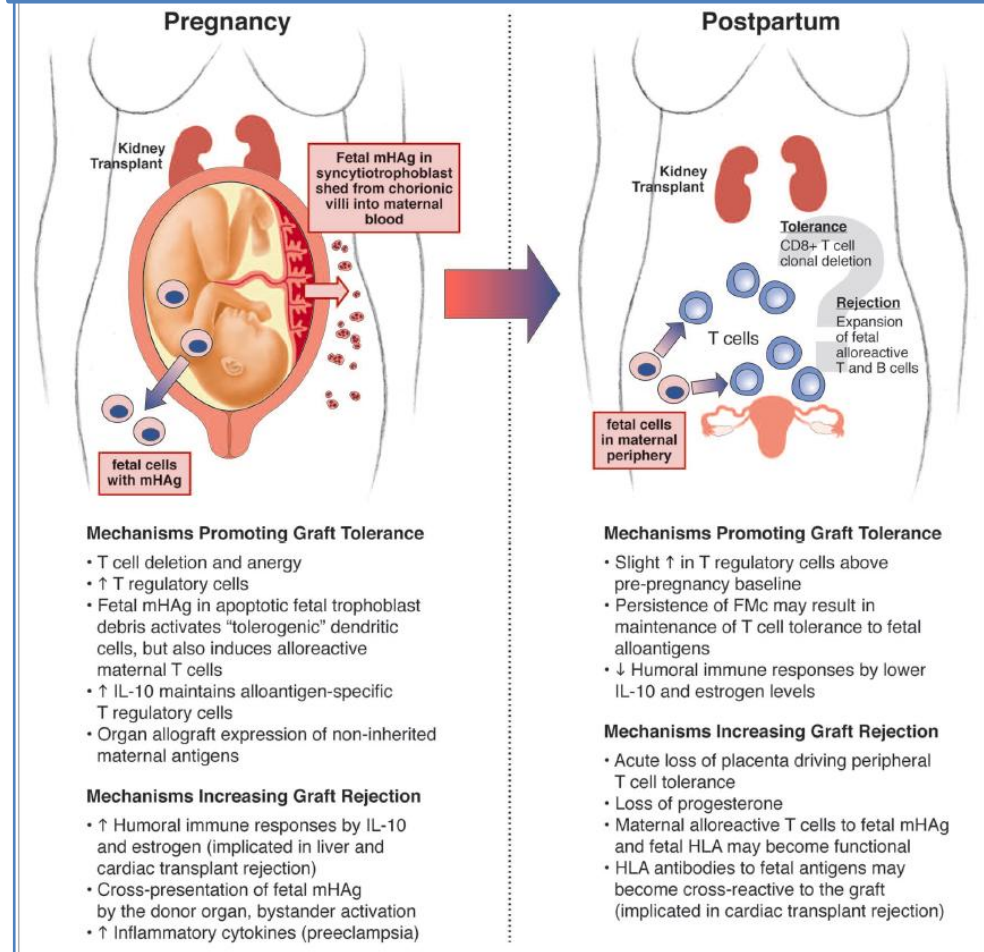
### Málo dat:

- ✓ TAK
- ✓ anti TNF
- ✓ RTX
- ✓ anti-IL6
- ✓ CLA4-Ig (abatacept)



# Senzitizace, alloreaktivita

Possible mechanisms for solid organ transplant rejection or tolerance during pregnancy and postpartum.



# TAKE HOME MESSAGE

## pro Tx

---

### After Transplantation

1. Delay conception for at least 1 year with adequate contraception
2. Assess and monitor graft function
3. Maintain immunosuppressive regimen
4. Manage comorbid conditions

### Preconception Counseling

1. Discuss the effect of pregnancy on transplant organ function
2. Discuss risks of maternal complications: hypertension, preeclampsia, diabetes, rejection, and graft loss
3. Obtain good control of prepregnancy hypertension and diabetes
4. Discuss risks of neonatal complications: prematurity and low birth weight
5. Modification of immunosuppressive regimen if necessary
6. Test for cytomegalovirus and other potential infections

### Early Pregnancy

1. Accurate and early diagnosis and dating of pregnancy
2. Close monitoring of graft function and immunosuppressive drug levels
3. Surveillance for bacterial infection [urine culture and viral infection (cytomegalovirus and herpes simplex virus)]
4. Fetal surveillance for malformation, fetal growth, and well-being
5. Maternal surveillance for hypertension, gestational diabetes, and preeclampsia
6. Anesthesia evaluation/consult for heart/lung transplant patients

### Labor and Delivery

1. Aim to deliver at term
2. Perform cesarean delivery only for appropriate obstetric reasons
3. For heart, lung, and heart-lung recipients: continuous cardiac monitoring, judicious use of intravenous fluids, early involvement with anesthesiology

### Postpartum

1. Monitor immunosuppressive drug levels and alter doses and regimen as necessary
2. Begin contraception when appropriate
3. The documented benefits of breastfeeding may outweigh the potential risks of infant immunosuppressive exposure
4. Mental health counseling if needed for postpartum depression