Case presentation
TCMR after successful kidney transplantation

Gvantsa Metskhvarishvili MD

Case presentation

- 29 yo female
- January 2019 -CKD st.5,RRT (HD)

(Primary kidney diagnosis unknown)

- March 2019- Tx , Living donor – Mother, ECD
- 110 mismtach, not sensitized

➢**Induction therapy**:Basiliximab

➢**Maintenance immunosuppression**: MP, Tac, MMF

Crea- 1.0-1.4 mg/dl (eGfr 73- 55 **mL/min**)

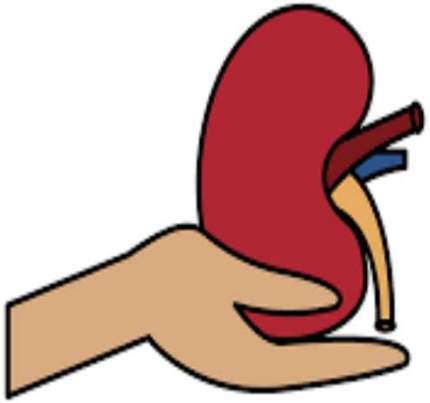
Case presentation

- 2019 Patient got married
- 2 years later pregnancy was planned

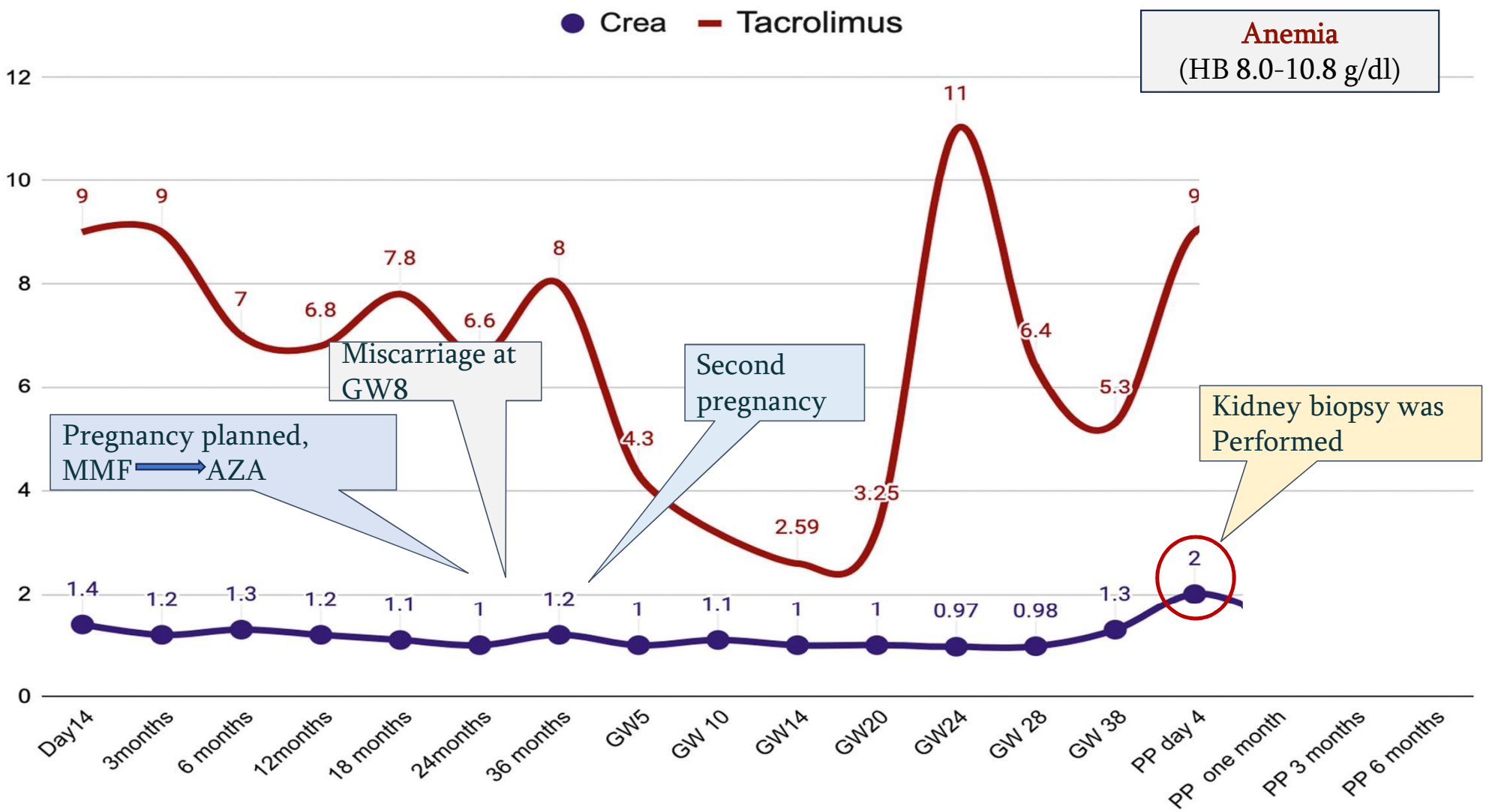
➢ MMF 500 mg b.i.d. ⟶ AZA 150 a day

➢ Dec 2021 –misscariage at GW8

➢ March 2022- second pregnancy



No proteinuria or HTN, Crea- 1. 2 mg/dl


Crea
Tacrolimus
Anemia
(HB 8.0-10.8 g/dl)
Pregnancy planned,
MMF ⟹ AZA
Miscarriage at
GW8
Second
pregnancy
Kidney biopsy was
Performed
12
10
8
6
4
2
0
9
9
7
6.8
7.8
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8
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9
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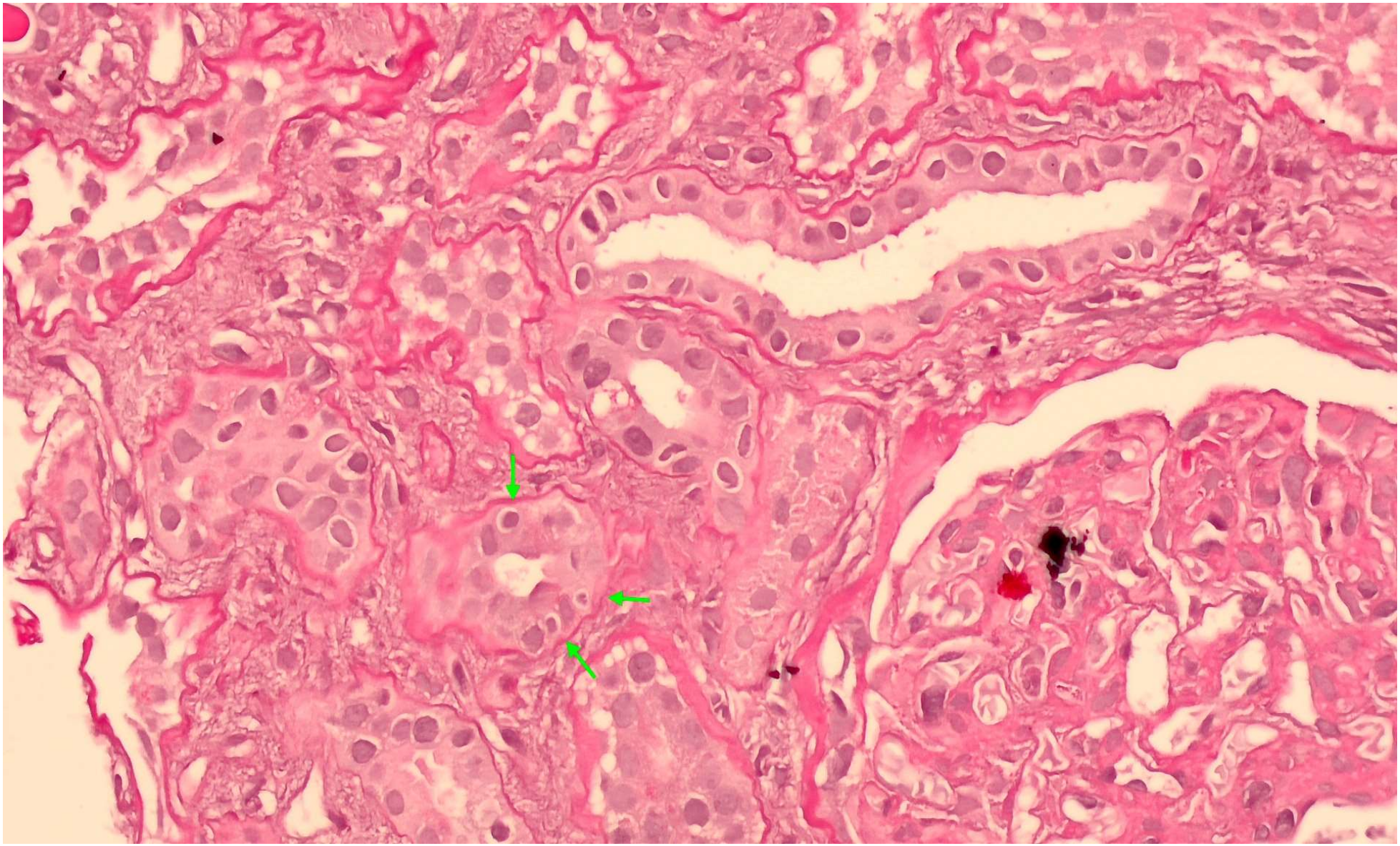
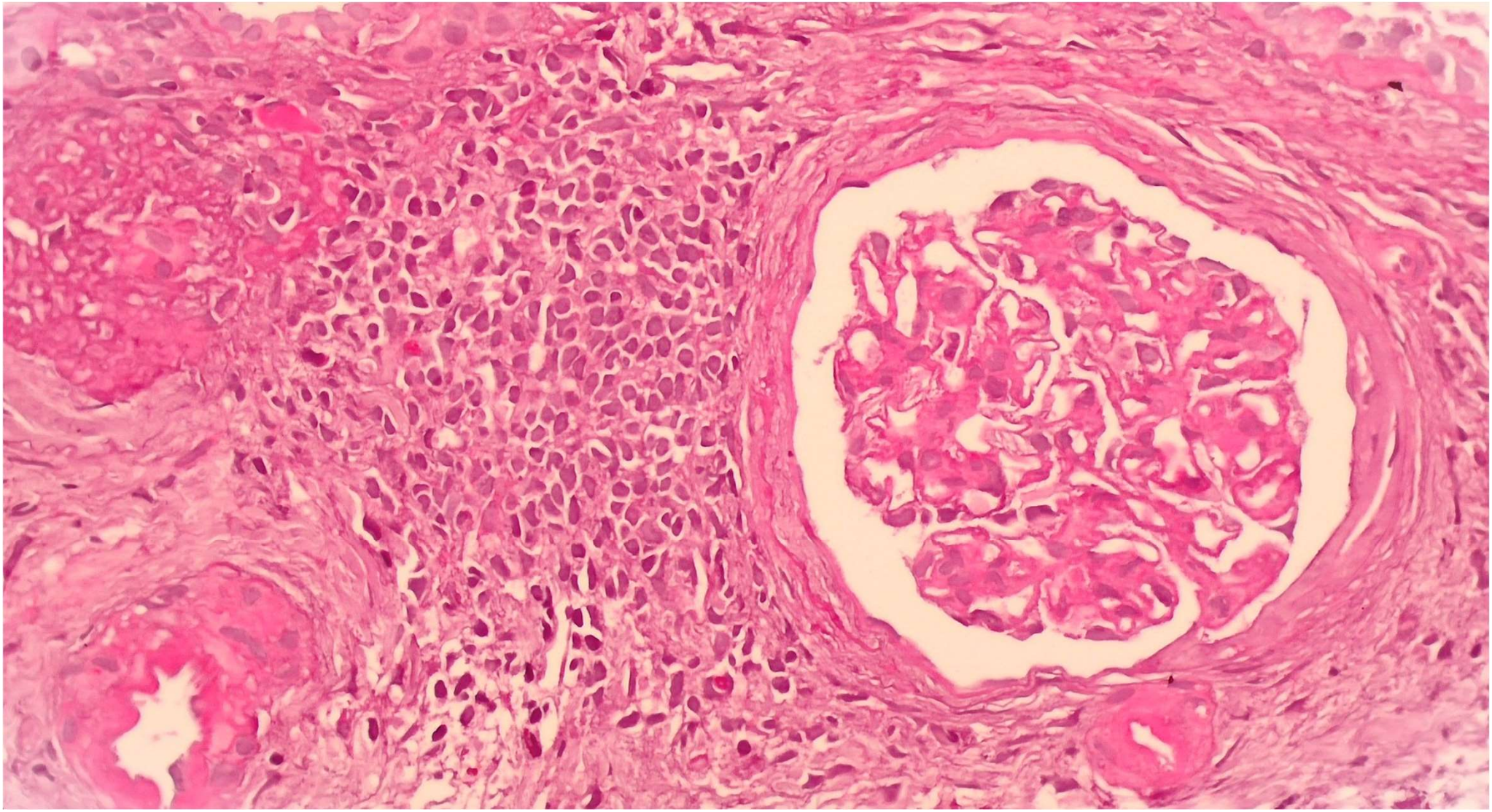
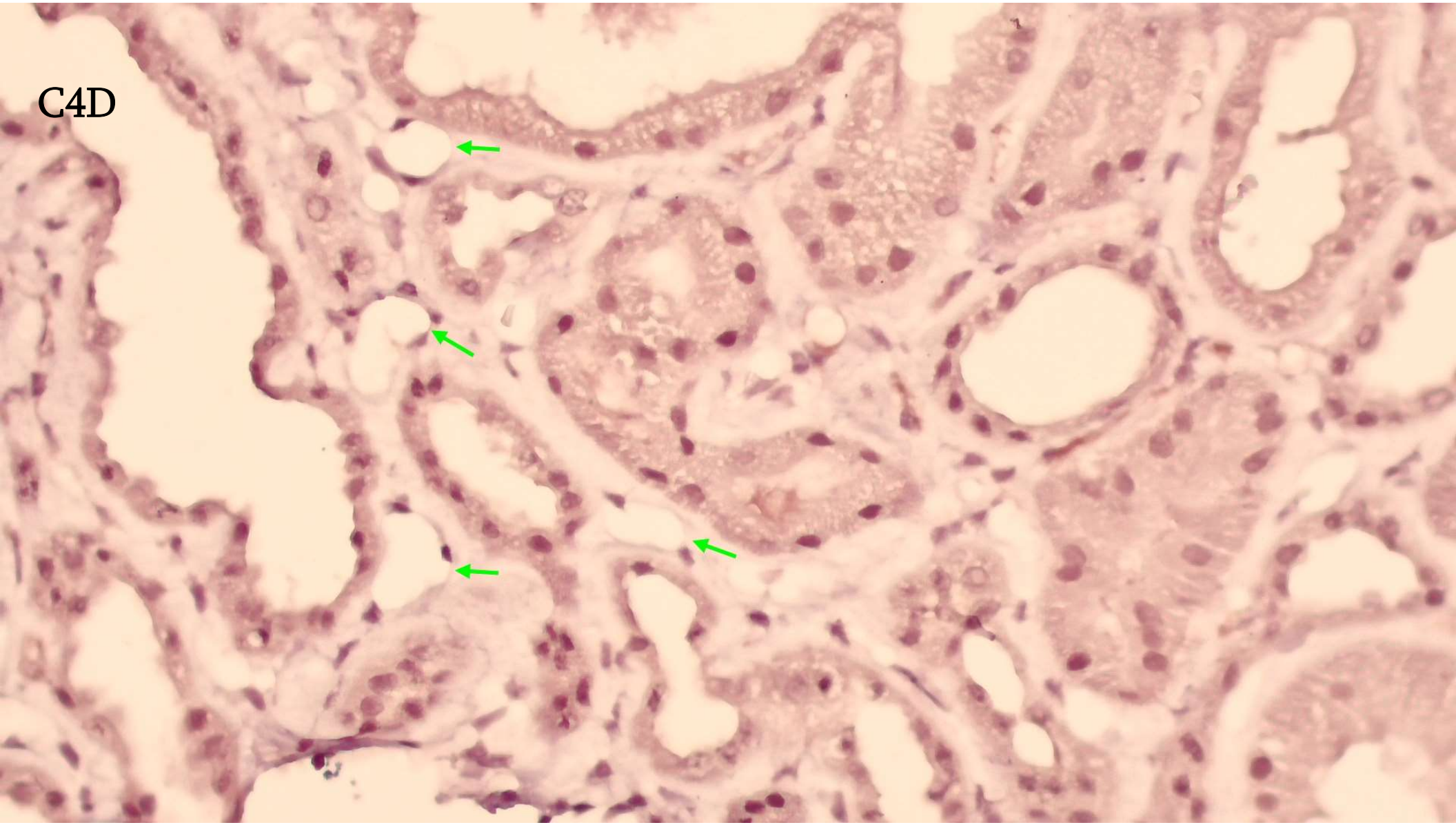
1
1.2
1
1.1
1
1
0.97
0.98
1.3
2
Day14
3months
6 months
12months
18 months
24months
36 months
GW5
GW 10
GW14
GW20
GW24
GW 28
GW 38
PP day 4
PP one month
PP 3 months
PP 6 months





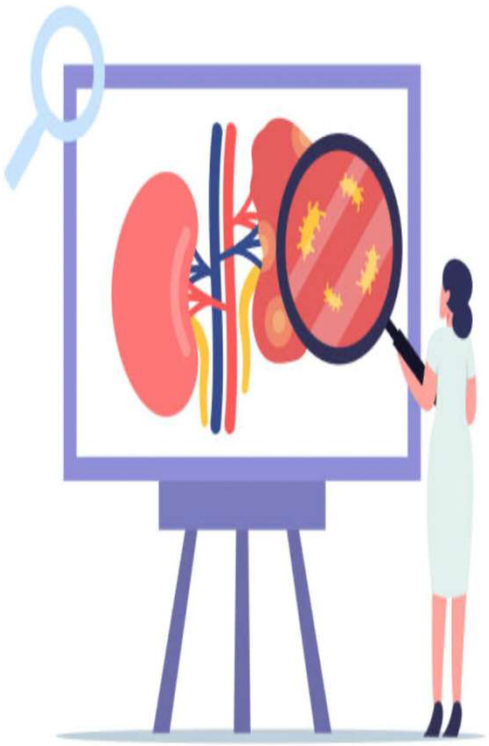

C4D

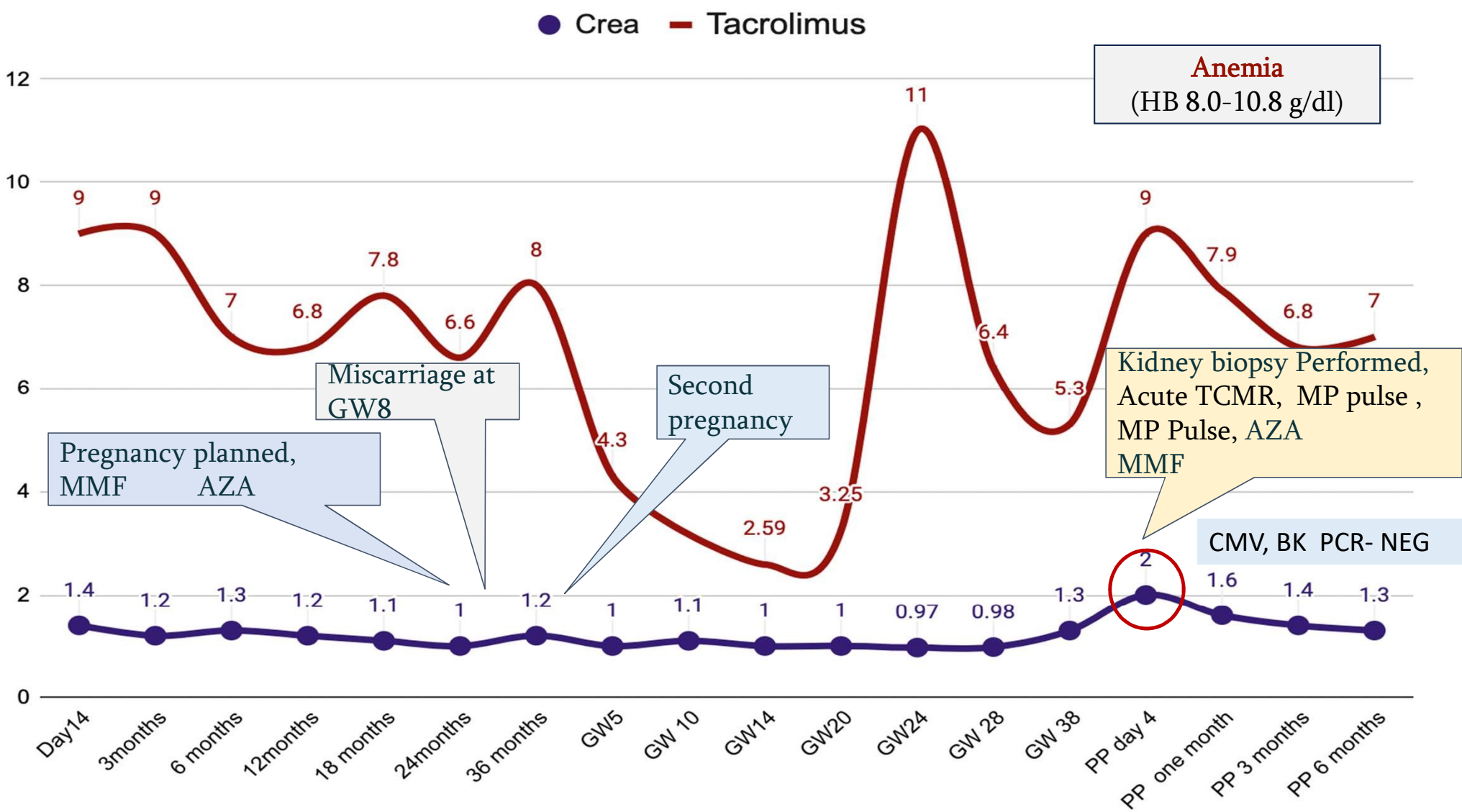
Microvasculature		Tubulointertitial changes	
Glomerulitis(g)	0	Inflammation (i)	1
Peritubular capillaritis (ptc)	0	Tubulitis (t)	1
C4d in peritubular capillaries (C4d)	0	Fibrosis (ci)	2
GBM duplication(cg)	0	Atrophy (ct)	2
Mesangial matrix(mm)	1	SV40	
PTC			
Arteries		Arterioles	
Arteriitis (v)	0	Hialinosis (ah)	2
Arterial intimal fibrosis (cv)	2		

Case presentation

- Diagnosis: Borderline Acute TCMR
- DSA- neg

- MP pulse 500 mg i.v 5 days with subsequent tapering
- AZA 150 mg a day → MMF 500 mg b.i.d.

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Pregnancy planned,
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Second
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Kidney biopsy Performed,
Acute TCMR, MP pulse ,
MP Pulse, AZA
MMF
CMV, BK PCR- NEG
12
10
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0.98
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1.6
1.4
1.3
Day14
3months
6 months
12months
18 months
24months
36 months
GW5
GW 10
GW14
GW20
GW24
GW 28
GW 38
PP day 4
PP one month
PP 3 months
PP 6 months

The first pregnancy in a transplant recipient occurred 67 years ago

Edith Helm, a 21-year-old woman with kidney failure received a living-donor kidney transplant from her identical twin on May 24, 1956

How high are the risks?

Mother

Baby

Graft

Pregnancy outcomes in kidney transplant recipients

Outcome	TPR (4)	Deshpande *et al.* (5)	Shah *et al.* (6)	United States Population[a]
Live births	75%	73.5% (95% CI, 72.1 to 74.9)	72.9% (95% CI, 70.0 to 75.6)	62%
Miscarriages	18%	14.0% (95% CI, 12.9 to 15.1)	15.4% (95% CI, 13.8 to 17.2)	17.1%
Neonatal deaths	1.4%	Not reported	3.8% (95% CI, 2.8 to 5.2)	0.4%
Still births	2%	2.5% (95% CI, 2.0 to 3.0)	5.1% (95% CI, 4.0 to 6.5)	0.6%
Hypertension in pregnancy	48%	54.2% (95% CI, 52.0 to 56.4)	24.2% (95% CI, 18.1 to 31.5), only pregnancy-induced hypertension reported	Not reported
Preeclampsia	31%	27.0% (95% CI, 25.2 to 28.9)	21.5% (95% CI, 18.5 to 24.9)	3.8%
Gestational diabetes mellitus	8%	8.0% (95% CI, 6.7 to 9.4)	5.7% (95% CI, 3.7 to 8.9)	9.2%
Cesarean-section	52%	56.9% (95% CI, 54.9 to 58.9)	62.6% (95% CI, 57.6 to 67.3)	31.9%
Preterm (before 37 wk)	51%	45.6% (95% CI, 43.7 to 47.5)	43.1% (95% CI, 38.7 to 47.6)	12.5%
Mean gestational age (wk)	35.9±3.4	35.6 (95% CI, 35.5 to 35.7)	34.9 (95% CI not available)	38.7
Mean birth weight (g)	2571±762	2420 (95% CI, 2395 to 2445)	2470 (95% CI not available)	3389
Acute rejection rate during pregnancy	1%	4.2%	9.4% (95% CI, 6.4 to 13.7)	Not applicable
Postpartum rejection	1.3%	Not reported	Not reported	Not applicable
Postpregnancy graft loss within 2 yr	5.6%	8.1%	9.2%	Not applicable
Birth defects	4.5%	Not reported	Not reported	Not reported

Pregnancy outcomes in kidney transplant recipients. TPR, Transplant Pregnancy Registry International; 95% CI, 95% confidence interval.
[a]From Deshpande *et al.* (5) and Shah *et al.* (6).

Song C. Ong and Vineeta Kumar, CJASN 15: 120–122, 2020

Shah *et al. BMC Nephrology* (2019) 20:24
https://doi.org/10.1186/s12882-019-1213-5

BMC Nephrology

RESEARCH ARTICLE Open Access

Pregnancy outcomes in women with kidney transplant: Metaanalysis and systematic review

Silvi Shah[1*], Renganathan Lalgudi Venkatesan[2], Ayank Gupta[2], Maitrik K. Sanghavi[2], Jeffrey Welge[3], Richard Johansen[2], Emily B. Kean[2], Taranpreet Kaur[1], Anu Gupta[4], Tiffany J. Grant[2] and Prasoon Verma[5]

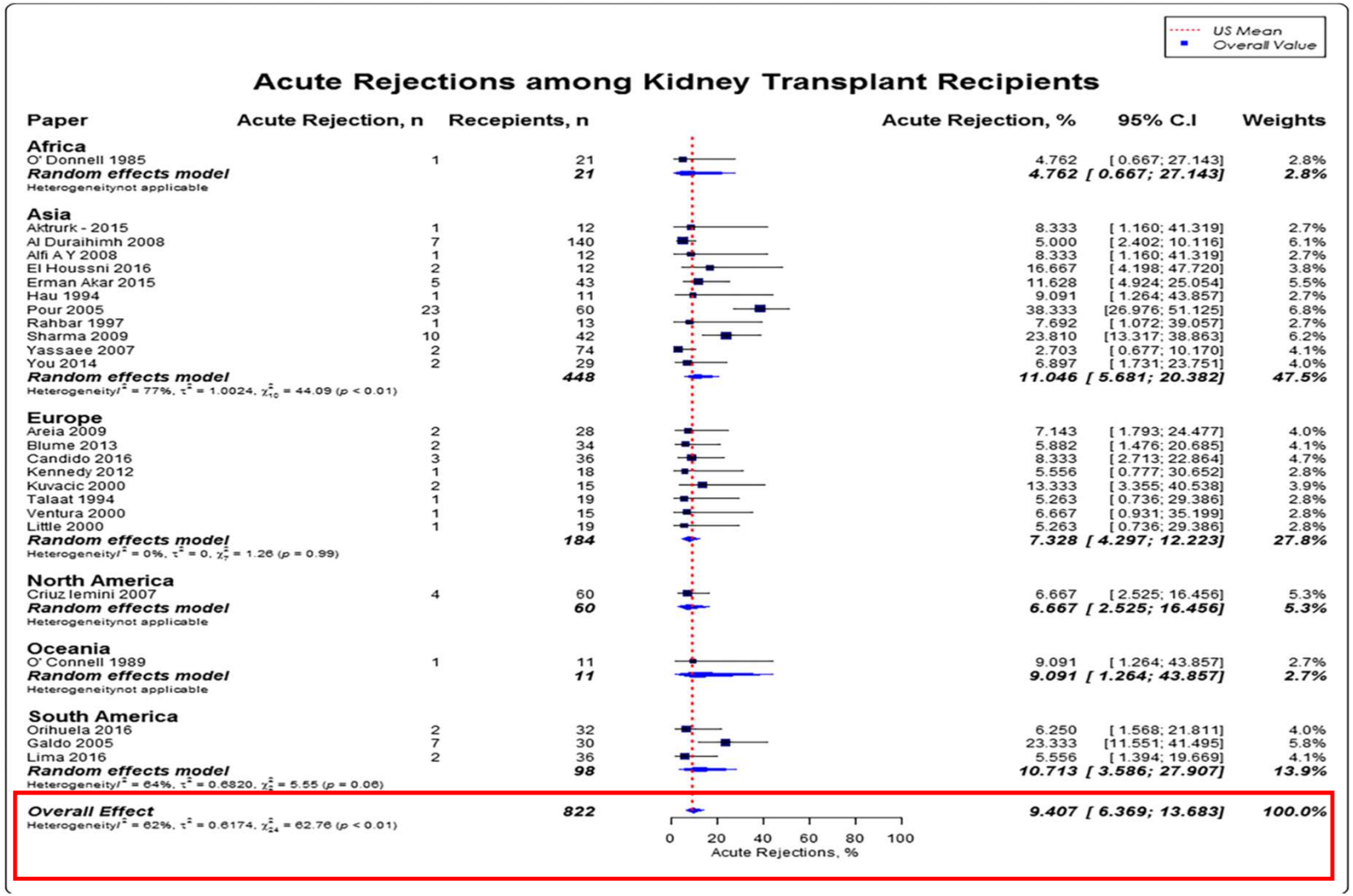

US Mean
Overall Value
Acute Rejections among Kidney Transplant Recipients
Paper
Acute Rejection, n
Recepients, n
Acute Rejection, %
95% C.I
Weights
Africa
O' Donnell 1985 1 21 4.762 [0.667; 27.143] 2.8%
Random effects model 21 4.762 [0.667; 27.143] 2.8%
Heterogeneitynot applicable
Asia
Aktrurk - 2015 1 12 8.333 [1.160; 41.319] 2.7%
Al Duraihimh 2008 7 140 5.000 [2.402; 10.116] 6.1%
Alfi A Y 2008 1 12 8.333 [1.160; 41.319] 2.7%
El Houssni 2016 2 12 16.667 [4.198; 47.720] 3.8%
Erman Akar 2015 5 43 11.628 [4.924; 25.054] 5.5%
Hau 1994 1 11 9.091 [1.264; 43.857] 2.7%
Pour 2005 23 60 38.333 [26.976; 51.125] 6.8%
Rahbar 1997 1 13 7.692 [1.072; 39.057] 2.7%
Sharma 2009 10 42 23.810 [13.317; 38.863] 6.2%
Yassaee 2007 2 74 2.703 [0.677; 10.170] 4.1%
You 2014 2 29 6.897 [1.731; 23.751] 4.0%
Random effects model 448 11.046 [5.681; 20.382] 47.5%
Heterogeneity I^2 = 77%, τ^2 = 1.0024, χ^2_{10} = 44.09 (p < 0.01)
Europe
Areia 2009 2 28 7.143 [1.793; 24.477] 4.0%
Blume 2013 2 34 5.882 [1.476; 20.685] 4.1%
Candido 2016 3 36 8.333 [2.713; 22.864] 4.7%
Kennedy 2012 1 18 5.556 [0.777; 30.652] 2.8%
Kuvacic 2000 2 15 13.333 [3.355; 40.538] 3.9%
Talaat 1994 1 19 5.263 [0.736; 29.386] 2.8%
Ventura 2000 1 15 6.667 [0.931; 35.199] 2.8%
Little 2000 1 19 5.263 [0.736; 29.386] 2.8%
Random effects model 184 7.328 [4.297; 12.223] 27.8%
Heterogeneity I^2 = 0%, τ^2 = 0, χ^2_7 = 1.26 (p = 0.99)
North America
Criuz Iemini 2007 4 60 6.667 [2.525; 16.456] 5.3%
Random effects model 60 6.667 [2.525; 16.456] 5.3%
Heterogeneitynot applicable
Oceania
O' Connell 1989 1 11 9.091 [1.264; 43.857] 2.7%
Random effects model 11 9.091 [1.264; 43.857] 2.7%
Heterogeneitynot applicable
South America
Orihuela 2016 2 32 6.250 [1.568; 21.811] 4.0%
Galdo 2005 7 30 23.333 [11.551; 41.495] 5.8%
Lima 2016 2 36 5.556 [1.394; 19.669] 4.1%
Random effects model 98 10.713 [3.586; 27.907] 13.9%
Heterogeneity I^2 = 64%, τ^2 = 0.6820, χ^2_5 = 5.55 (p = 0.06)
Overall Effect 822 9.407 [6.369; 13.683] 100.0%
Heterogeneity I^2 = 62%, τ^2 = 0.6174, χ^2_{24} = 62.76 (p < 0.01)
0 20 40 60 80 100
Acute Rejections, %

Table 4: Cause of allograft failure among women who did or did not become pregnant in the first 3 posttransplant years (percentages shown)

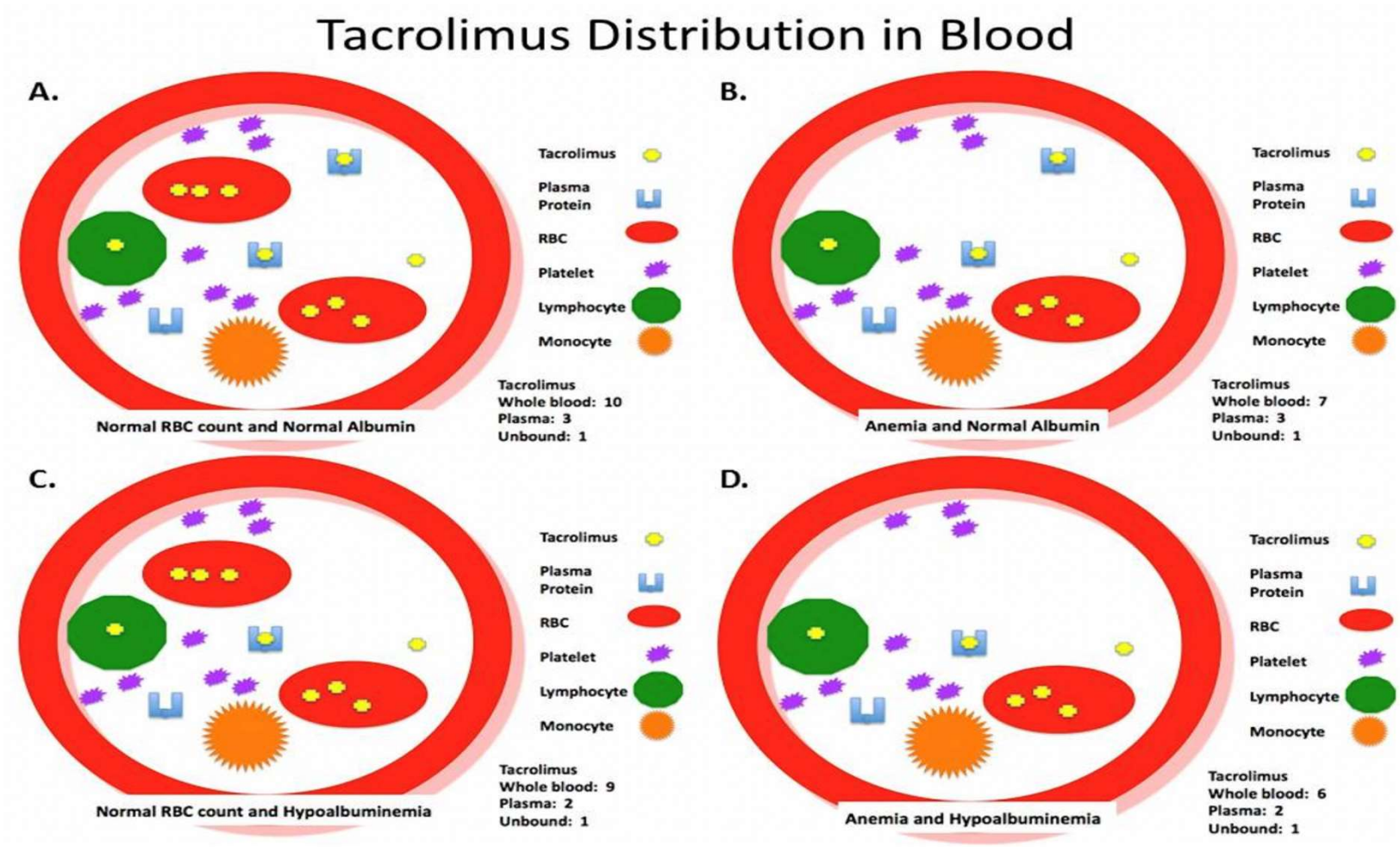
	Women who become pregnant in the first 3 posttransplant years N = 424/729 (58%) allograft failures[1]	Women who did not become pregnant in the first 3 posttransplant years N = 10 638/21 085 (50%) allograft failures
Death with function	40 (12.5)	22 385 (29.5)
Acute rejection	50 (15.5)	841 (10.4)
Chronic rejection	165 (51.1)	3347 (41.4)
Recurrent disease	14 (4.1)	307 (3.8)
Infection	2 (0.6)	65 (0.8)
Other	52 (16.2)	1140 (14.1)

C.Rose at al, American Journal of Transplantation 2016

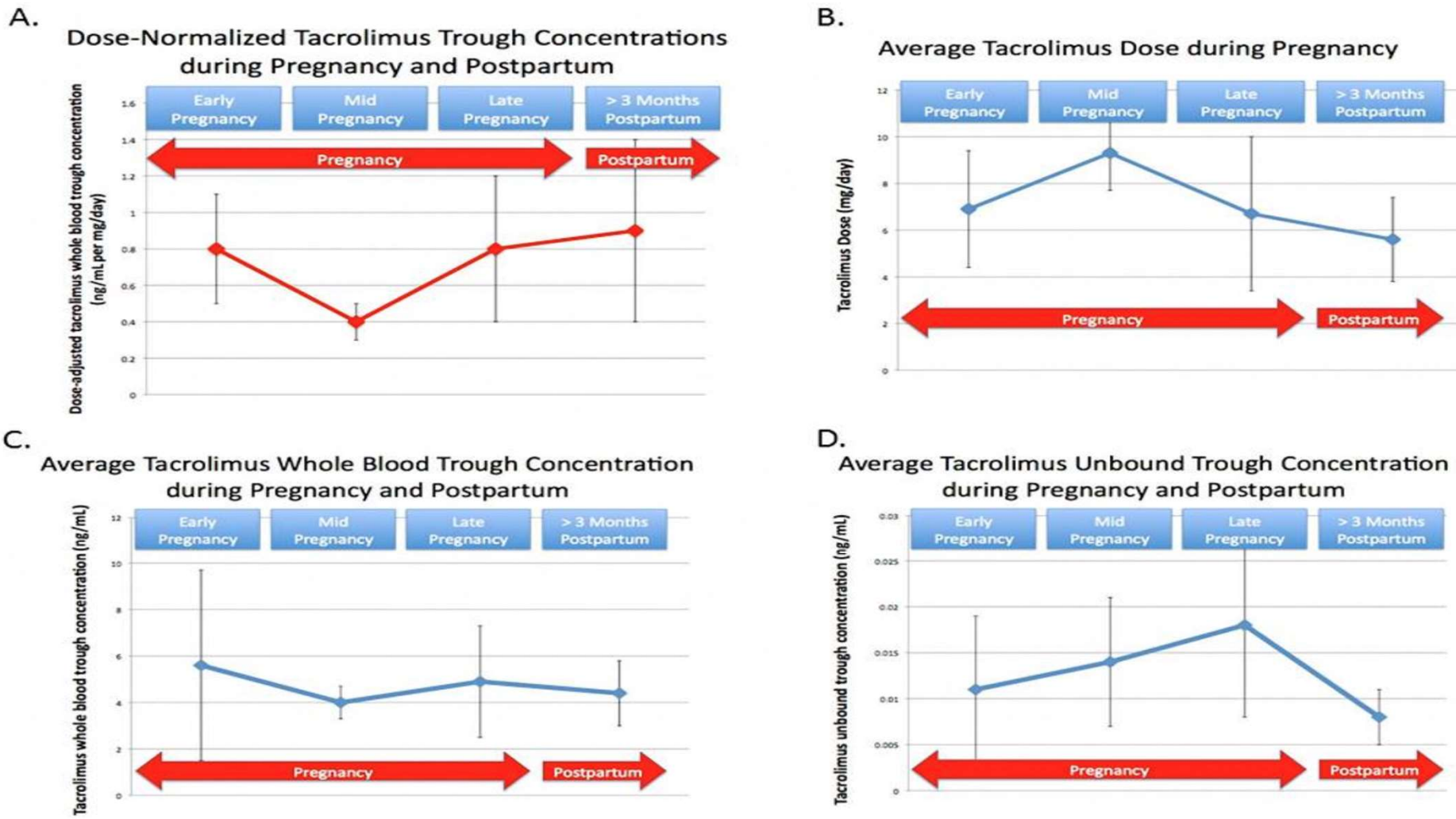
Drug level fluctuations due to changes in Gfr and drug metabolism during pregnancy

Close moniitoring of Tacrolimus trough levels- every 2-4 weeks

is neccesary to maintain Tacrolimus trough levels



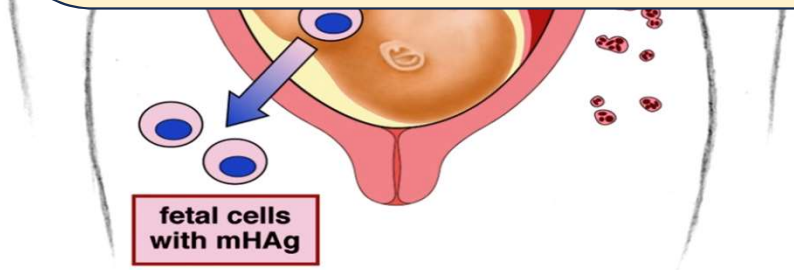
Mary F. Hebert et al , Transplantation 2013



Mary F. Hebert et al , Transplantation 2013

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

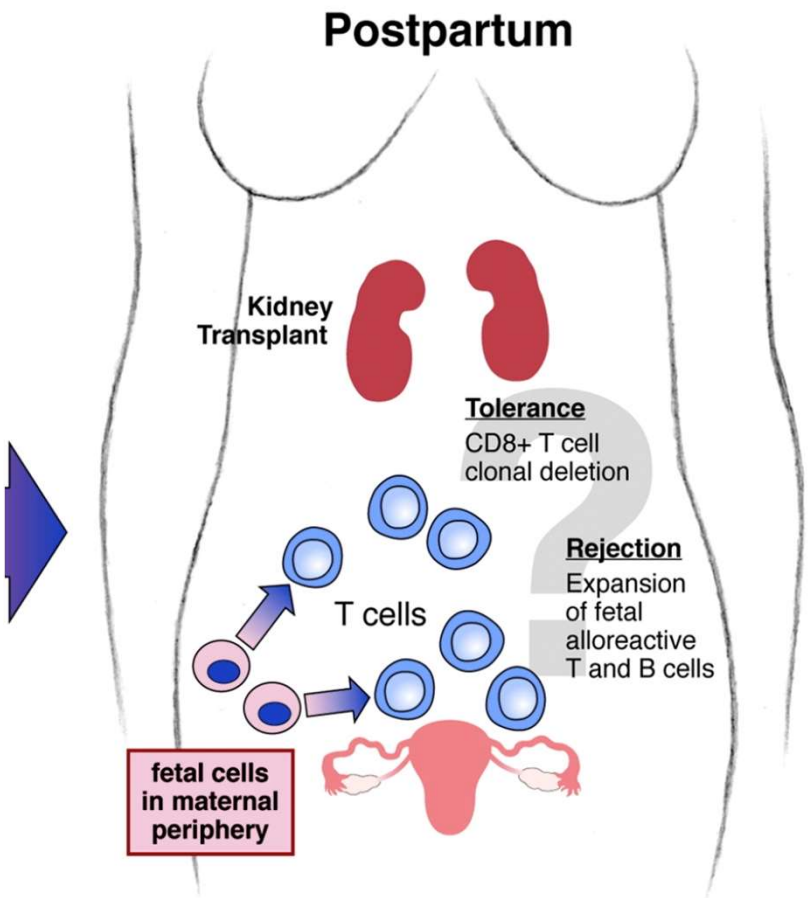
- Hemodynamic stress on the graft associated with a 30–50%increase in cardiac output during pregnancy and peripartum fluid shifts.
- Both of these factors may contribute to endothelial dysfunction or oxidative stress within the graft.



- ↑ Humoral immune responses by IL-10 and estrogen (implicated in liver and cardiac transplant rejection)
- Cross-presentation of fetal mHAg by the donor organ, bystander activation
- ↑ Inflammatory cytokines (preeclampsia)

Kimberly K. Ma, Margaret G. Et al, Complex chimerism, Chimerism, 4:3, Aug 2013

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



Mechanisms Promoting Graft Tolerance

- Slight ↑ in T regulatory cells above pre-pregnancy baseline
- Persistence of FMc may result in maintenance of T cell tolerance to fetal alloantigens
- ↓ Humoral immune responses by lower IL-10 and estrogen levels

Mechanisms Increasing Graft Rejection

- Acute loss of placenta driving peripheral T cell tolerance
- Loss of progesterone
- Maternal alloreactive T cells to fetal mHAg and fetal HLA may become functional
- HLA antibodies to fetal antigens may become cross-reactive to the graft (implicated in cardiac transplant rejection)

Kimberly K. Ma, Margaret G. Et al, Complex chimerism, Chimerism, 4:3, Aug 2013

Drug	Teratogenicity	Fetal/Neonatal Effects	Recommendations in Pregnancy	Recommendations in Breast-Feeding
Treatment for acute rejection and induction				
Methylprednisolone	None	Rare, cataract, adrenal insufficiency, and infection	Yes	Yes
Intravenous immunoglobulin	None	None reported	Yes	Yes
Alemtuzumab	Unknown	Unknown	Manufacturer recommends avoiding pregnancy for at least 6 months after exposure	Unknown, but possible transfer into milk, neonate gastrointestinal digestion
Basiliximab	Unknown	No toxicity or teratogenicity in monkeys	Manu av lea exposure	but possible into milk, neonate testinal digestion
Belatacept	Unknown	Unknown	Do not administer in pregnancy	Unknown, but transfer into breast milk unlikely as Fc fragment of IgG1
Antithymocyte globulin	Unknown	Unknown	Do not administer in pregnancy	Unknown, but possible transfer into milk, neonate gastrointestinal digestion

Plasma exchange – Yes

Kate Bramham, Seminars in Nephrology 2017

Predictors of graft loss or renal function deterioration after pregnancy

	Negative association		No association	
Risk factors	**Unit**	**Author**	**Unit**	**Author**
Hypertension	>140/90 mm Hg	Queipo Zaragoza (2003)	Pre-existing hypertension	Stoumpos (2016)
Before or at the beginning of pregnancy	Drug-treated hypertension	Sibanda (2007), Abe (2008), Kato (2012)	Chronic hypertension Chronic hypertension	Svetitsky (2018) Vannevel (2018)
Proteinuria	>1 g/d	Queipo Zaragoza (2003)	>0.3 g/d >0.5 g/d	Thompson (2003) Rocha (2013)
Pre-eclampsia	Borderline effect (OR, 1.09; 95% CI [0.92-1.34], $P = 0.09$).	Svetitsky (2018)	–2.69 (–14.54 to 9.15), $P = 0.65$	Vannevel (2018)
Prepregnancy SCr	>1.47–1.50 mg/dL >1.69–1.75 mg/dL >2.10 mg/dL Worse graft function (OR 1.71; 95% CI [CI 1.15-3.45], $P = 0.04$)	O'Reilly (2001), Alfi (2008) Thompson (2003), Keitel (2004) Kim (2008), Crowe (1999), Queipo Zaragoza (2003) Aivazoglou (2010) Svetitsky (2018)	<2.26 mg/dL <1.3 mg/dL Worse graft function (OR –011; 95% CI [–0.44 to 0.23], $P = 0.52$)	Hooi (2003) Rocha (2013) Vannevel (2018)
Age at transplantation	Older age (OR 1.13; 95% CI [1.03-1.21], $P = 0.03$)	Svetitsky (2018)		
Transplant to conception interval	<1 y	Alfi et al (2008)	General <1 y <2 y >5 y Mo (OR, 0.05; 95% CI [-0.07 to 0.18], $P = 0.42$)	Stoumpos (2016) Fischer (2005) Pour-Reza-Gholi (2005) Gaughan (1996) Vannevel (2018)

CI, confidence interval; SCr, serum creatinine.

TRANSPLANTATION

Transplantation104(8):1675-1685, August 2020. Van Buren, Marleen C.; Schellekens, et. al

Long-term Graft Survival and Graft Function Following Pregnancy in Kidney Transplant Recipients: A Systematic Review and Meta-analysis

Counselling

Lower Risk

- Stable and good kidney function
- Stable immunosuppression, no past rejection
- Well-controlled blood pressure, none or not much urine protein
- No other health problems
- Expected pregnancy after preconception counseling

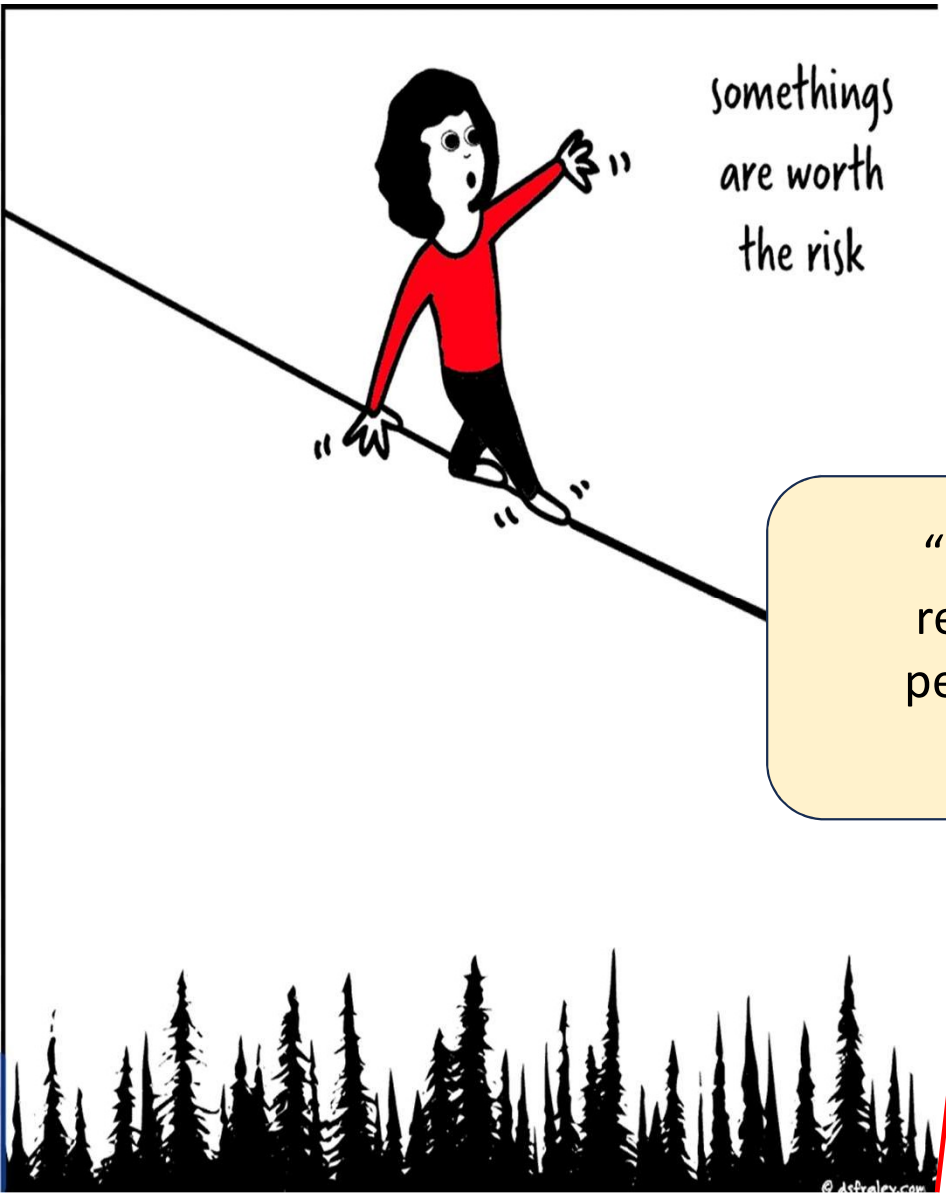
Moderate Risk

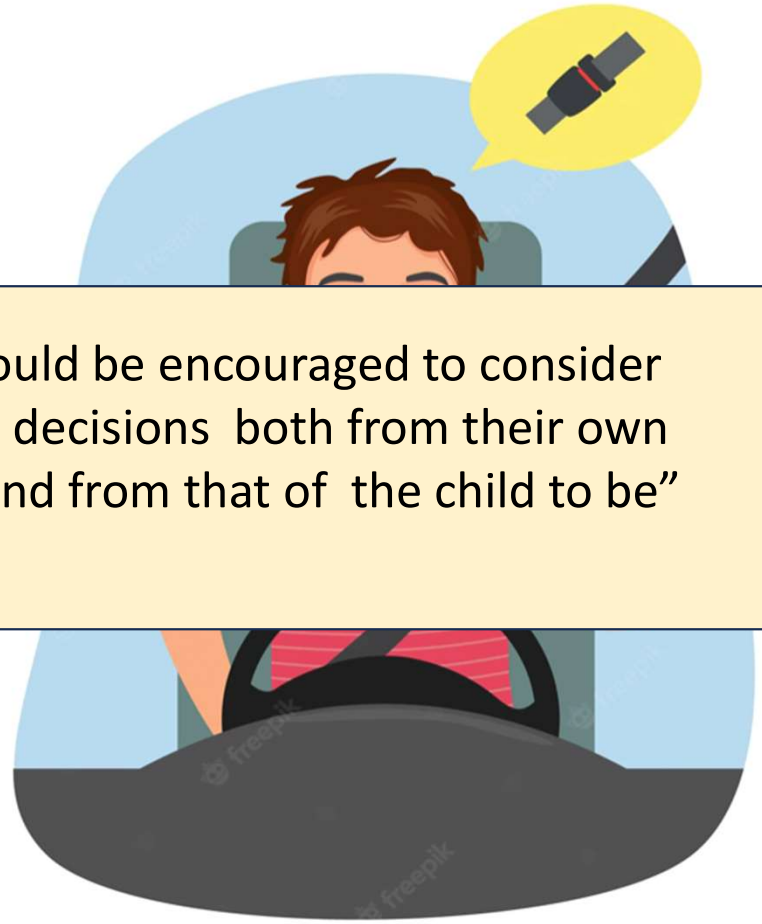
- Unstable or reduced kidney transplant function
- Past rejection or immune concerns
- High blood pressure, anemia, urine protein
- Previous infections
- Unexpected pregnancy, no prior planning

High Risk

- Worse kidney transplant function
- Recent or ongoing rejection or immune concerns
- Uncontrolled blood pressure, high urine protein
- Recent or ongoing infections
- Unexpected pregnancy, no prior planning

S Jesudason et al.
Pregnancy Advisory Consumer Group, led by BH and AW , Kidney International Reports (2022)





"Women should be encouraged to consider reproductive decisions both from their own perspective and from that of the child to be"

Summery

- Improvement of reproductive system is one of the main benefits of of kidney Tx
- However … The risks…
- Councelling before Tx and ongoing after Tx is a must
- Decisions should be made on the basis of known risks and the risk tolerance of the **individual**
- Shared desicion- making
- Multidisciplinary team management and support