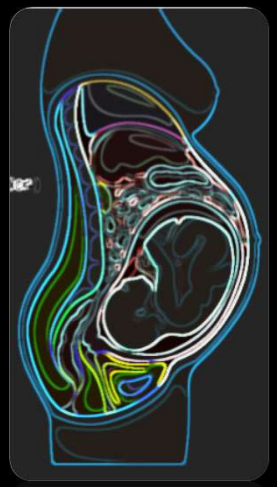


Pregnancy and fertility in the kidney transplant recipient

Steven Van Laecke
Nephrology Dept. Ghent University Hospital
Tbilisi, September 14th 2023

UZ GENT

OUTLINE

1. Fertility after transplantation
2. Implications for the transplanted future father?
3. Implications for the transplanted future mother?
4. Complications in the pregnant KTR
5. The kidney function in KTR
6. Anticonception?
7. Pregnancy and the living donor

NO DISCLOSURES

Fertility: highly relevant for KTR (but not for everyone)

Fertility after kidney transplantation

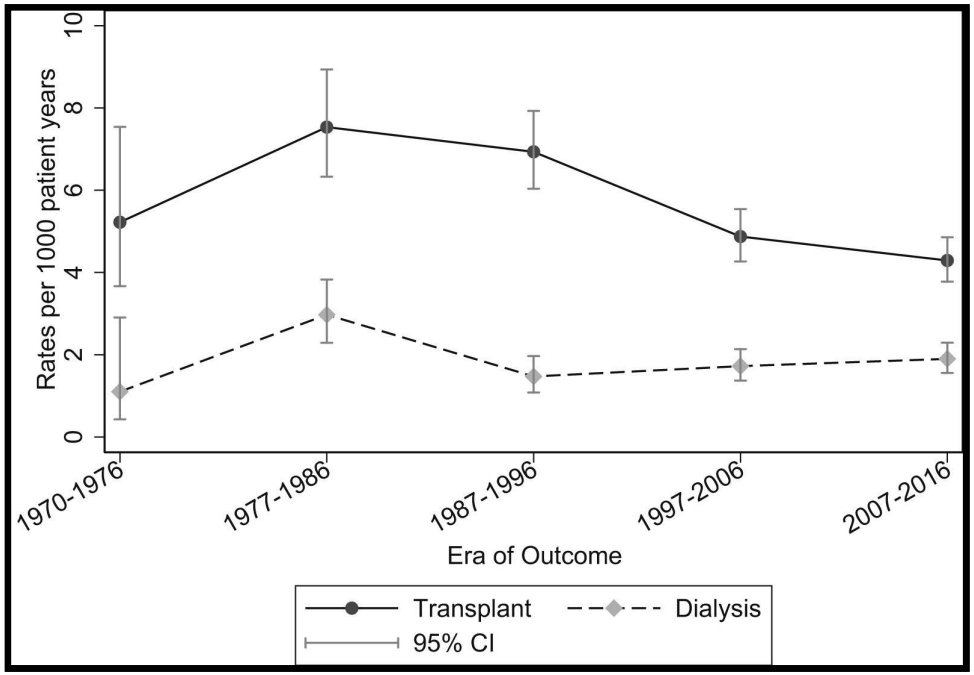
A. Drug	Comment	
CS	No effect	9
CNI	No effect	9
MPA	Rodent studies show no effect on fertility. Very limited data in humans	10
AZA	No effect	9
mTORi	Hypogonadism with high levels of FSH and LH and low levels of testosterone. Rodent studies show inhibition of mTOR mediated P70S6K phosphorylation, leading to reduced spermatogonial proliferation. Consequently, oligospermia after 4 wk and azoospermia after 3 mo exposure. In male KTRs, less motile spermatozoa, lower sperm count, and lower pregnancy rate. Sperm count was reversed after sirolimus discontinuation. Recovery of spermatogenesis after long-term therapy has not been studied to date. In female KTRs, increased prevalence of hypogonadism, dysmenorrhea, ovarian cysts, and infertility	11-1
Belatacept	Rodent study showed no effect on fertility. Very limited data in humans	15
Basiliximab	Very limited data	15
Rituximab	Rodent studies showed no effect on fertility. Very limited data in humans.	10,1
ATG	Very limited data.	15
Antiviral	Possible testicular damage.	17
B. Non-pharmacological	Comment	
Renal dysfunction	Inhibition of the hypothalamic-pituitary-gonadal axis, with high levels of circulating FSH, LH and prolactin and low levels of sex hormones, which leads to infertility and loss of libido in both sexes, erectile dysfunction in male KTRs and reduced vaginal lubrication, inability to achieve orgasm, oligo- or amenorrhea in female KTRs.	7
Uremic toxins	Germinal aplasia and destruction of seminiferous tubules in male KTRs, which may not be completely reversed even if renal function is normalized.	18
Dialysis vintage	Epidydimal calcification and microlithiasis, obscuring the epidydimal phase of spermatogenesis, which leads to persistent azo- or oligospermia and morphological sperm abnormalities in male KTRs.	18
CMV infection	Reduced sperm quality.	19

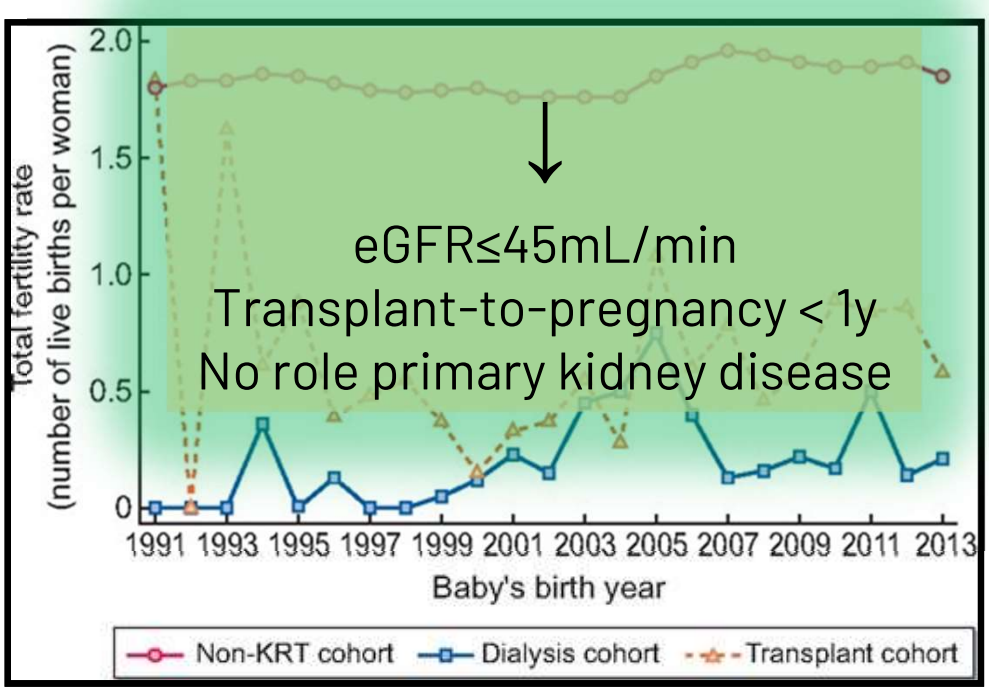
AVOID

References to studies in the right column.
ATG, anti-thymocyte globulin; AZA, azathioprine; CMV, cytomegalovirus; CNI, calcineurin inhibitor; CS, corticosteroids; FSH, follicle-stimulating hormone; KTRs, kidney transplant recipients; LH, luteinizing hormone; MPA, mycophenolic acid; mTORi, mammalian target of rapamycin inhibitor.

Anupam C et al. Transplantation 2019

Fertility after kidney transplantation





Jesudason S et al. AJKD 2020- Hewawasam E et al. NDT 2022

Fatherhood and mycophenolate?

Correspondence

Changing of the Guards: EMA Warning on Paternal Use of Mycophenolate Mofetil: An Unnecessary and Insufficiently Substantiated Precaution

OPEN

Exposure to Mycophenolate and Fatherhood

Karsten Midtvedt, MD, PhD,[1] Stein Bergan, PhD,[2,3] Anna Varberg Reisæter, MD, PhD,[1,4] Bjørn Egil Vikse, MD, PhD,[5,6] and Anders Åsberg, PhD[1,3,4]

TABLE 1.

Birth outcomes between exposed (MPA+) and not exposed (MPA–) groups

	MPA+ N = 155	MPA– N = 195	*P* value
Acute caesarean section	16 (10.3%)	24 (12.3%)	0.39
Normal placenta	121 (78.1%)	118 (60.5%)	0.32
Child weight (g)	3381 ± 681	3429 ± 714	0.53
Gestational age (wk)	38.9 ± 2.5	39.1 ± 2.7	0.30
Child length (cm)	49.6 ± 3.2	49.9 ± 3.0	0.32
Child head circumference (cm)	34.7 ± 2.1	35.1 ± 2.1	[illegible]
APGAR score after 1 min	8.6 ± 1.5	8.6 ± 1.[illegible]	[illegible]
APGAR score after 5 min	9.3 ± 1.3	9.3 ± 1.[illegible]	[illegible]
Stillborn	1 (0.6%)	4 (2.1%)	[illegible]
Born alive, dead within 24 h	0 (0.0%)	1 (0.5%)	[illegible]
Congenital malformations	6 (3.9%)	5 (2.6%)	[illegible]
Respiratory distress syndrome	4 (2.6%)	2 (1.0%)	0.40
Neural tube defects	0 (0.0%)	0 (0.0%)	1.00
Icterus	11 (7.1%)	[illegible] (12%)	0.33
Hip dysplasia	1 (0.6%)	1 (0.5%)	1.00

No different outcome

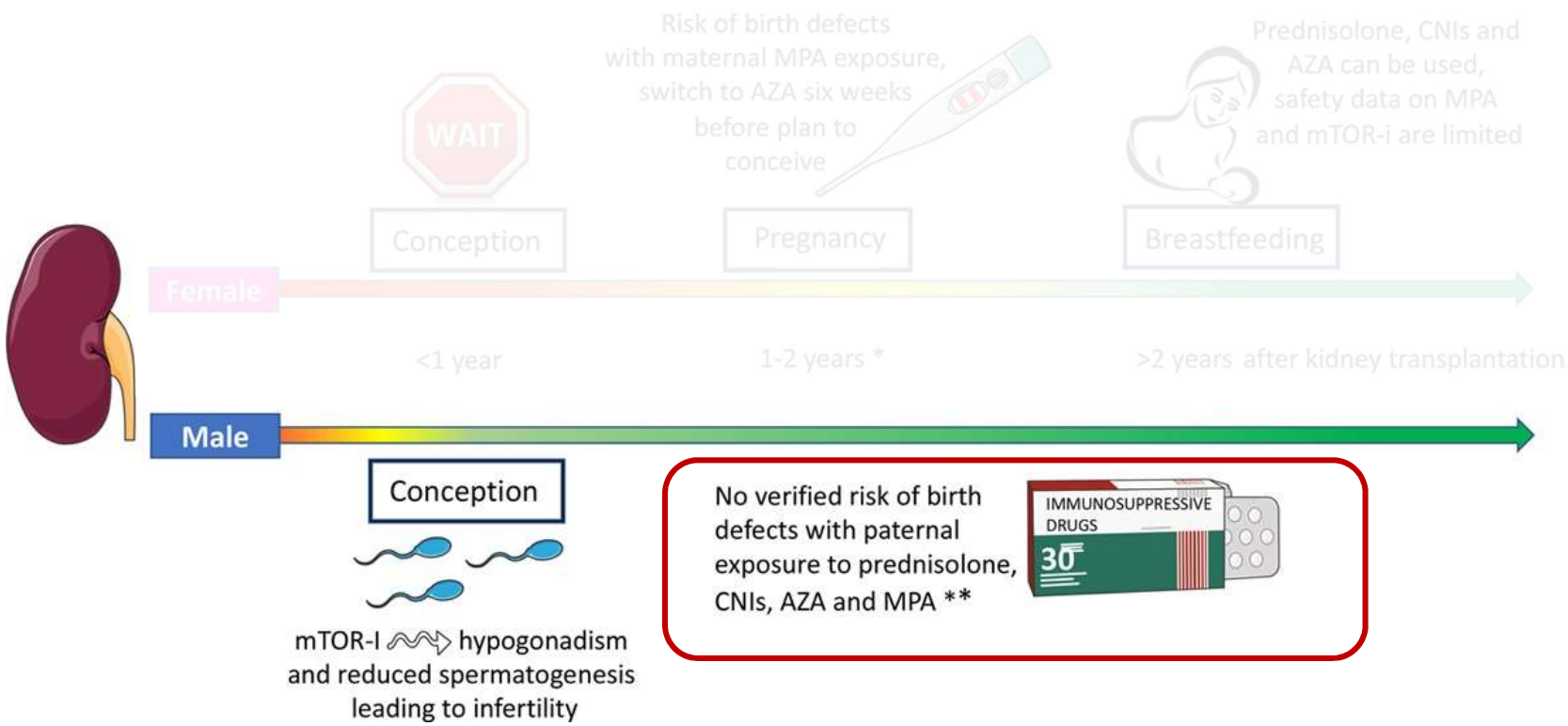
RESEARCH ARTICLE — Open Access

Paternity in male kidney transplant recipients: a French national survey, the PATERNAL study

Annabel Bo[illegible] Lobbedez[1,2,3], Mohamed Ouethrani[1], Angélique Thuillier Lecouf[1], Nicolas Bouvier[1,3], Va[illegible] Hurault de Ligny[1,3] and On behalf of the Spiesser transplant group

	MMF/MPA *n* = 313	CTC *n* = 298	Tacrolimus *n* = 255	Cyclosporine *n* = 152
Number of recipients	195	177	166	94
Age, median (IQR), years	40 (36–45)	43 (37–50)	40 (35–45)	46 (38–52)
Age at conception, median (IQR), years	34 (30–38)	34 (31–38)	35 (31–38)	33 (29–37)
Transplant to conception time[a], median (IQR)	5 (2–9)	5 (3–10)	5 (7–10)	4 (2–7.5)
Pregnancy outcomes				
Live births, including 6 twin pregnancies	268 (86%, [81–89])	257 (86%, [82–90])	219 (86%, [81–90])	136 (89%, [83–94])
Twin pregnancy	6 (2%, [0.7–4])[b]	6 (2%, [0.7–4])[b]	5 (2%, [0.6–5])	2 (1%, [0.2–5])[b]
Spontaneous abortion	32 (10%, [7–14])	29 (10%, [7–14])	23 (9%, [6–13])	12 (8%, [4–13])
Therapeutic abortion	8 (3%, [1–5])	10 (3%, [2–6])	8 (3%, [1–6])	2 (1%, [0.2–5])
Still births	2 (1%, [0.1–2])[c]	2 (0.7%, [0.1–2])[c]	2 (0.8%, [0–3])[c]	0 (0%, [0–2])
Ongoing pregnancy	8 (3%, [1–5])	5 (2%, [0.5–4])	8 (3%, [1–6])	3 (2%, [0.4–6])
Live births, including twins	268	257	219	136
Gestational age in weeks, median (IQR)	41 (39–41)	41 (39–41)	41 (39–41)	41 (39–41)
Pre-term delivery (< 37 weeks)	24 (9%, [6–13])	22 (9%, [5–13])	16 (7%, [4–12])	16 (12%, [7–18])
Birthweight (Kg), median (IQR)	3.3 (3–3.7)	3.4 (3–3.7)	3.4 (3–3.7)	3.3 (2.9–3.7)
Low birthweight (< 2.5 Kg)	18 (7%, [4–10])	10 (4%, [2–7])	12 (5%, [3–9])	9 (7%, [3–12])
Sex (male)	142 (53%, [47–59])	143 (56%, [49–62])	119 (54%, [47–61])	76 (56%, [47–64])
Intellectual disability	1 (0.4%, [0–2])	2 (0.8%, [0–3])	1 (0.5%, [0–3])	1 (0.7%, [0–4])
Congenital malformation	9 (3%, [1–6])	9 (4%, [2–7])	10 (5%, [2–8])	4 (3%, [1–7])

Fertility after kidney transplantation



Anupam C et al. Transplantation 2019

Drug exposure during pregnancy

B. Maternal disease and obstetric complications

CS	Adverse effects on glucose metabolism, hence increased risk of gestational diabetes.
CNI	CsA increases the risk of hypertension and dyslipidemia. Tac increases the risk of hyperglycemia. Both CNIs may impair renal function. Animal studies report intrauterine growth retardation with both CNIs and more preterm births after Tac exposure. In humans, the prevalence of obstetric complications in patients treated with Tac and CsA is similar to other immunosuppressive regimens, including preterm birth rate.
MPA	A multination European prospective study reported a relative risk of miscarriage of 45% after MPA exposure during pregnancy. Furthermore, prevalence of preterm birth was 62% and low birth weight 31% after MPA exposure.
AZA	Prevalence of obstetric complications after AZA therapy is similar to other MPA-free immunosuppressive regimens.
mTORi	Very limited data.
Belatacept	Limited data. Two successful pregnancies on belatacept treatment have been reported.
Basiliximab	Very limited data.
Rituximab	Limited data. A retrospective study of 153 non-transplant pregnancies on rituximab therapy, found a 22% miscarriage rate, 24% preterm births, 12% neonatal hematological abnormalities, two congenital malformations, one neonatal death, and one maternal death. Although there are reports of successful pregnancies on rituximab treatment, available data suggest that conception should be delayed after rituximab exposure.
ATG	Very limited data.

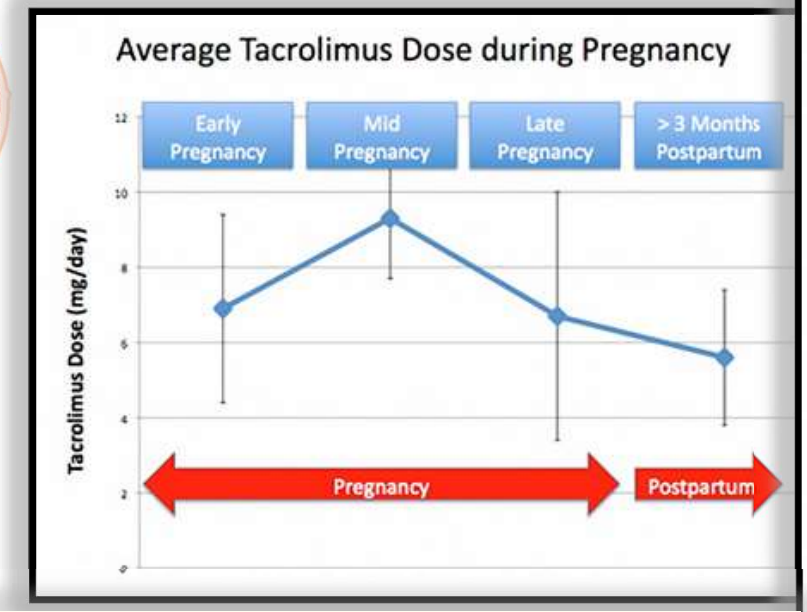
C. Congenital malformations

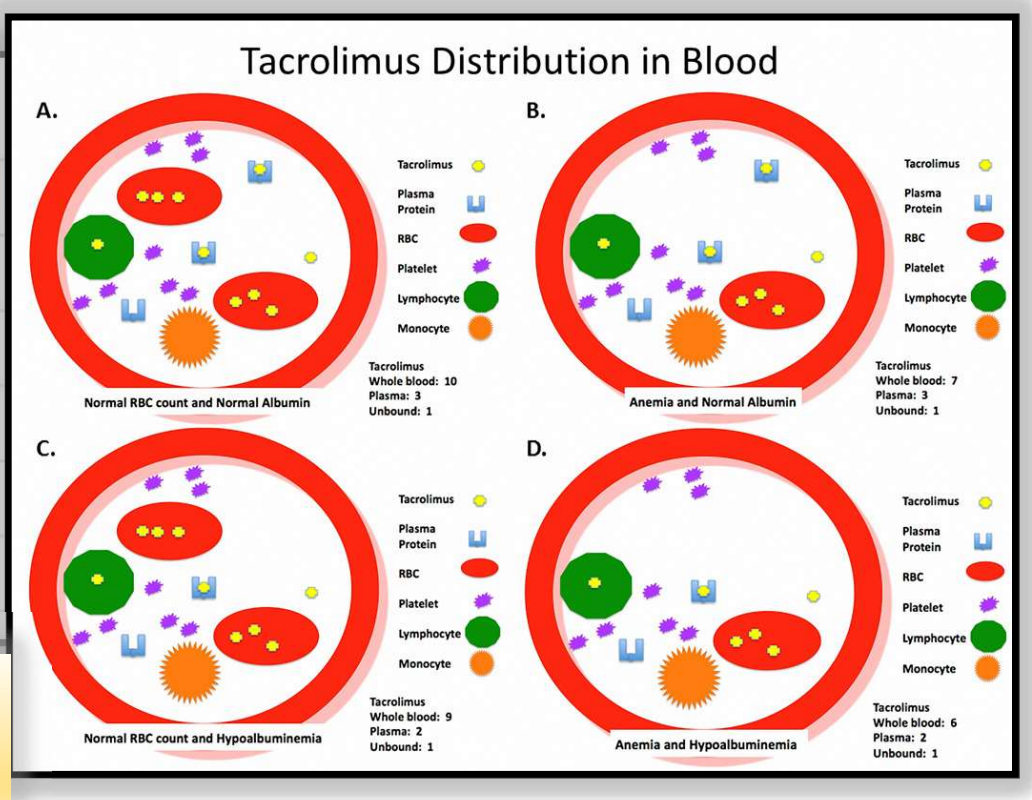
CS	Animal studies report an increased risk of cleft palate with CS use. In humans, there are studies showing a higher prevalence of cleft palate, but most report no association, even at high doses.
CNI	Animal study showed skeletal retardation with CsA exposure. No increased prevalence or pattern of congenital malformations in humans.
MPA	MPA pose a major threat to the fetus with a congenital malformation prevalence of 26%. Structural malformations caused by MPA [illegible] sent. Other structura[illegible] lomeningocele, hydrone[illegible] range of severe teratoge[illegible] age rate.
AZA	Animal stu[illegible] re is low and there are [illegible], hypogammaglobulinemia and atrial and ventricular septal defects, but there is no clear pattern of congenital malformations. Observational studies suggest that AZA is safe in pregnant women.
mTORi	Animal studies report a high risk of intra-uterine growth retardation, impaired skeletal ossification, and miscarriage after mTORi exposure. Safety studies on mTORi in pregnant women are scarce, with no congenital malformations reported.
Belatacept	Very limited data.
Basiliximab	Very limited data.
Rituximab	Very limited data.
ATG	Very limited data.

Animal data do not seem to apply in humans

Anupam C et al. Transplantation 2019

Tacrolimus exposure during pregnancy

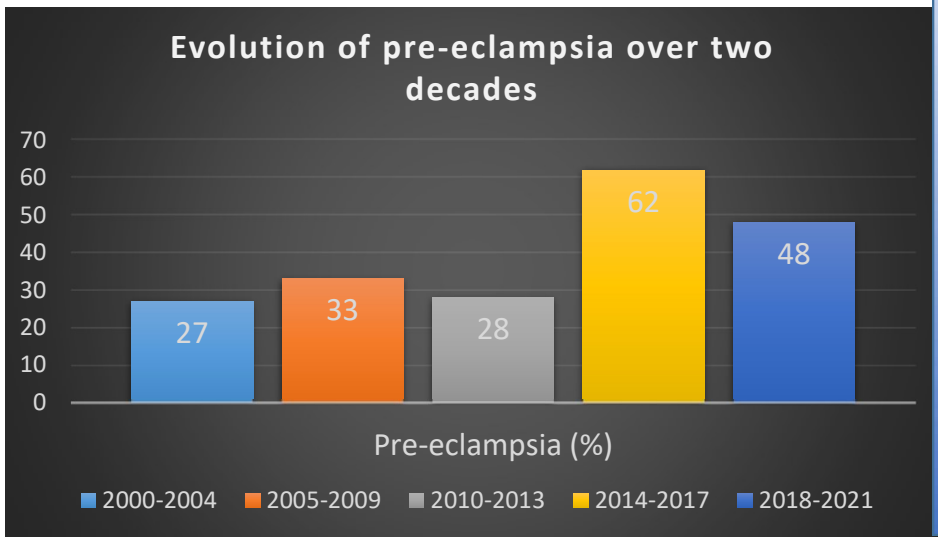




Activity CYP3A +25-100%
Increase in PGP-activity

Herbert MF et al. Transplantation 2013

Pre-eclampsia in KTR



Previous exposure to calcineurin inhibitors

Higher creatinine pre-conception

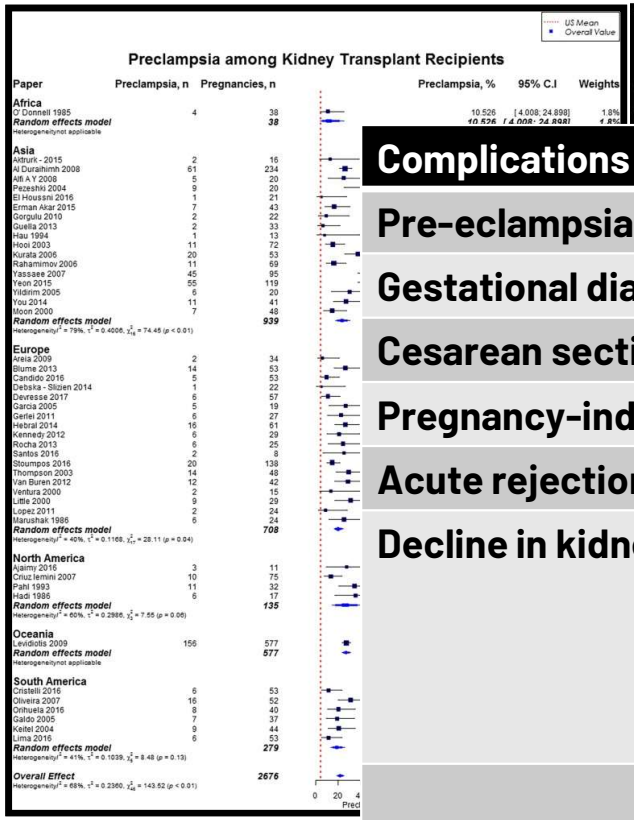
Era of birth event

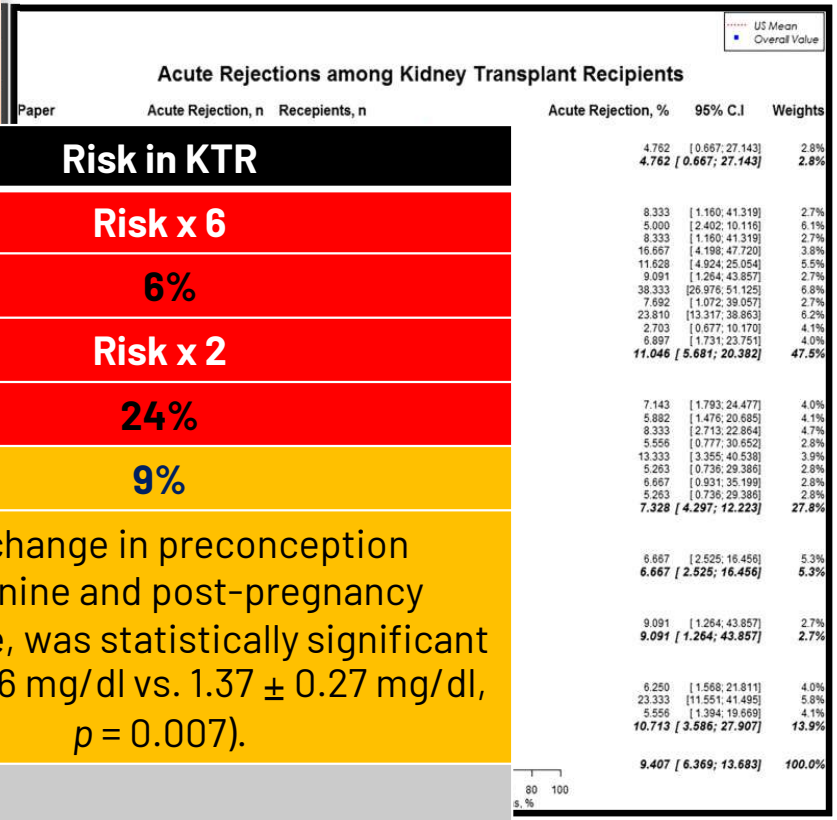
Pre-eclampsia: DCGL
aHR 0.88 (0.52-1.47)

Lu J et al. cJASN 2023

Pregnancy-associated risks in KTR

6712 pregnancies in 4174 KTR (87 studies)
Mean maternal age 29.6 ± 2.4y
Mean gestational age 34.9w

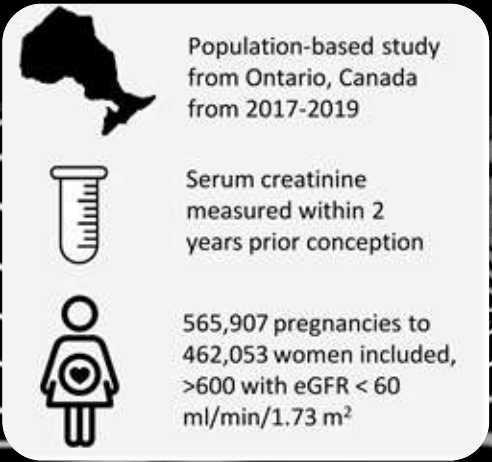


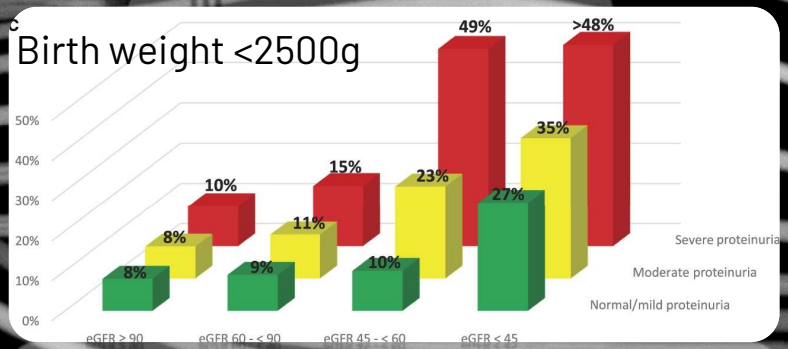


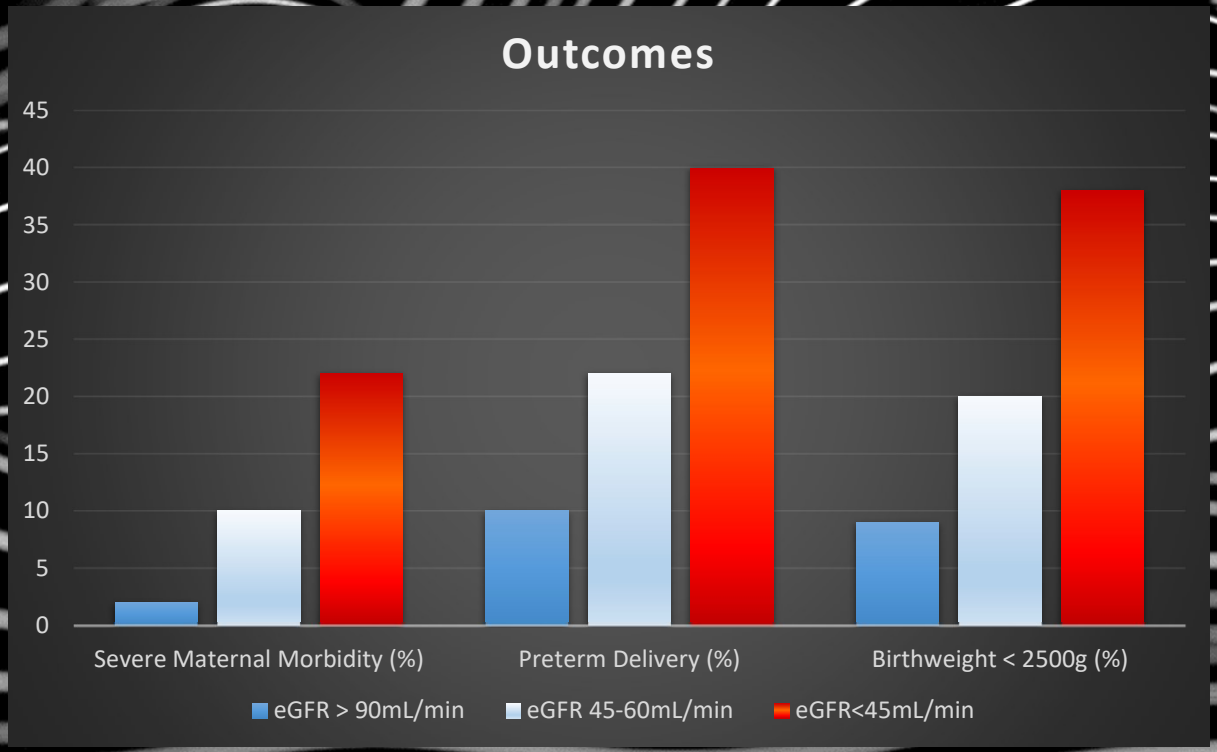
Complications	Risk in KTR
Pre-eclampsia	Risk x 6
Gestational diabetes	6%
Cesarean section	Risk x 2
Pregnancy-induced hypertension	24%
Acute rejection	9%
Decline in kidney function	The change in preconception creatinine and post-pregnancy creatinine, was statistically significant (1.23 ± 0.16 mg/dl vs. 1.37 ± 0.27 mg/dl, $p = 0.007$).

Shah S et al BMC Nephrol 2019

Kidney function and pregnancy outcome

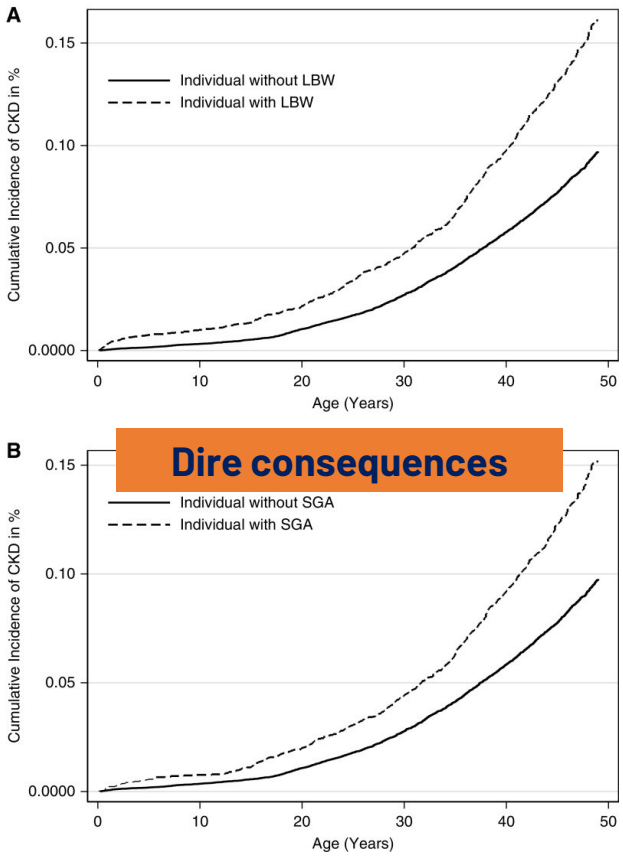




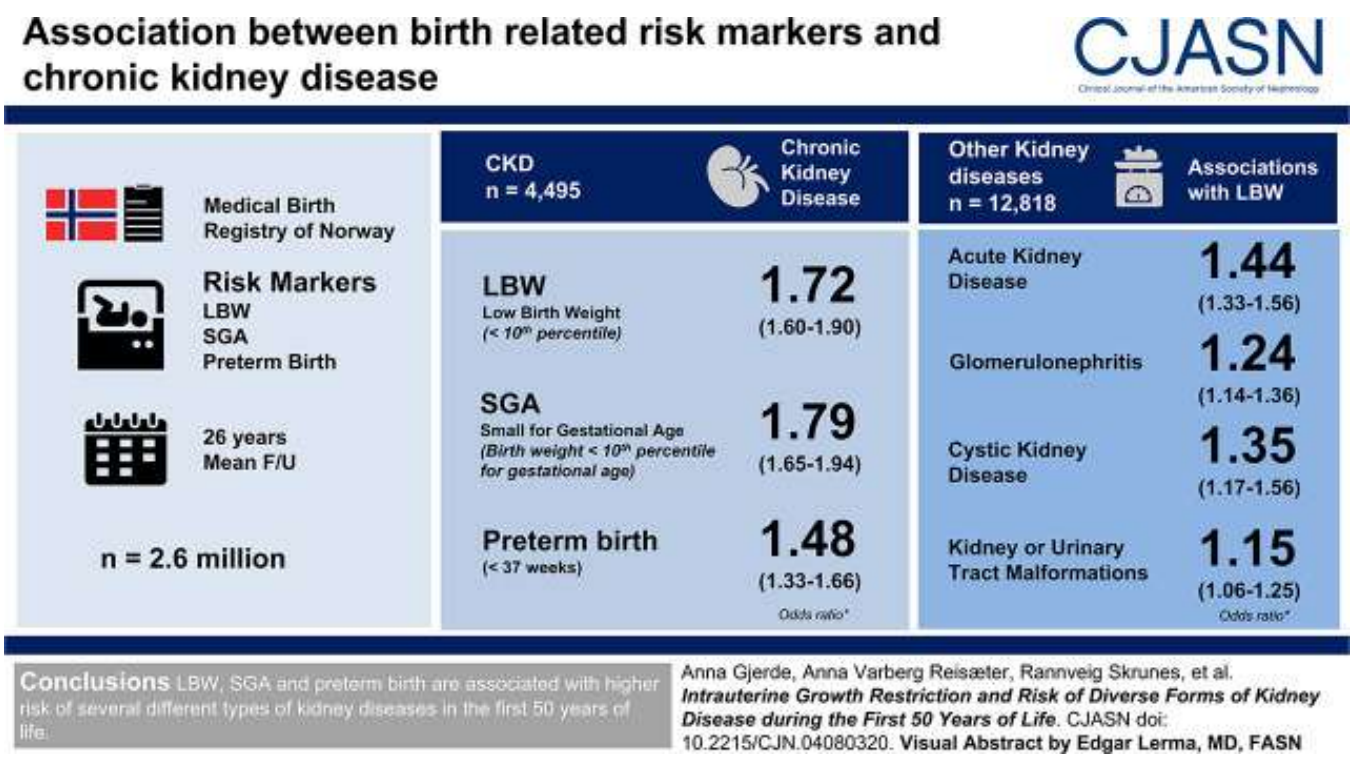


Tangren J et al. JASN 2023

SGA in KTR: future implications?



Dire consequences



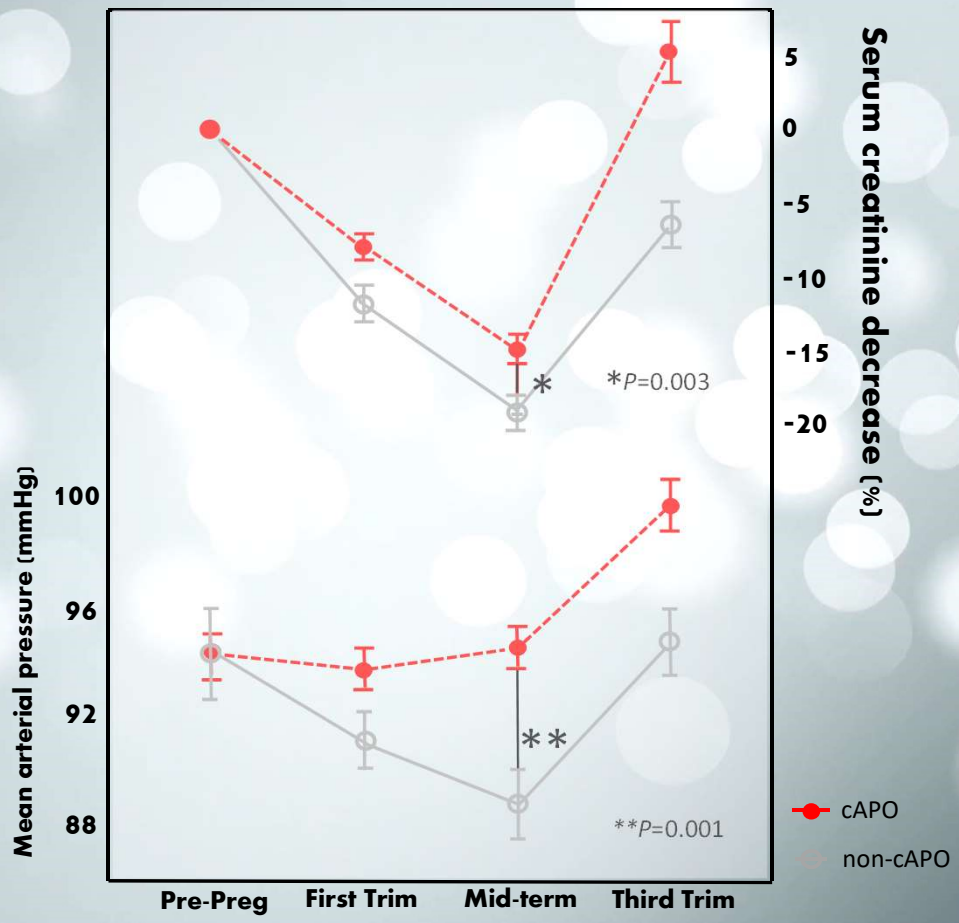
Gjerde A et al cJASN 2020

Hemodynamic adaptation in pregnancy: prognostic!

Netherlands 1971-2017

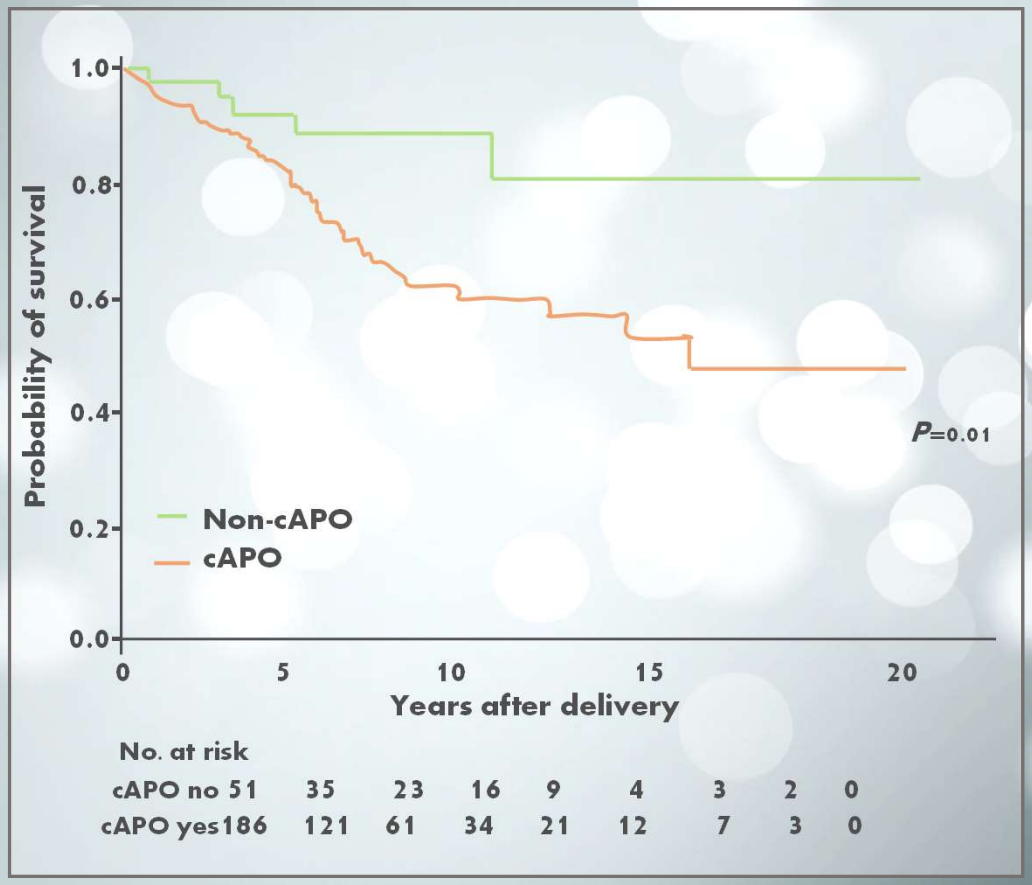
Retrospective cohort KT:
- Pregnancy > 20 weeks
- Analyses per prepregnancy eGFR-CKD-category

Combined adverse pregnancy outcome (cAPO):
- Birthweight <2500 gram
- Preterm birth <37 weeks
- Severe hypertension
- >15% graft deterioration during pregnancy



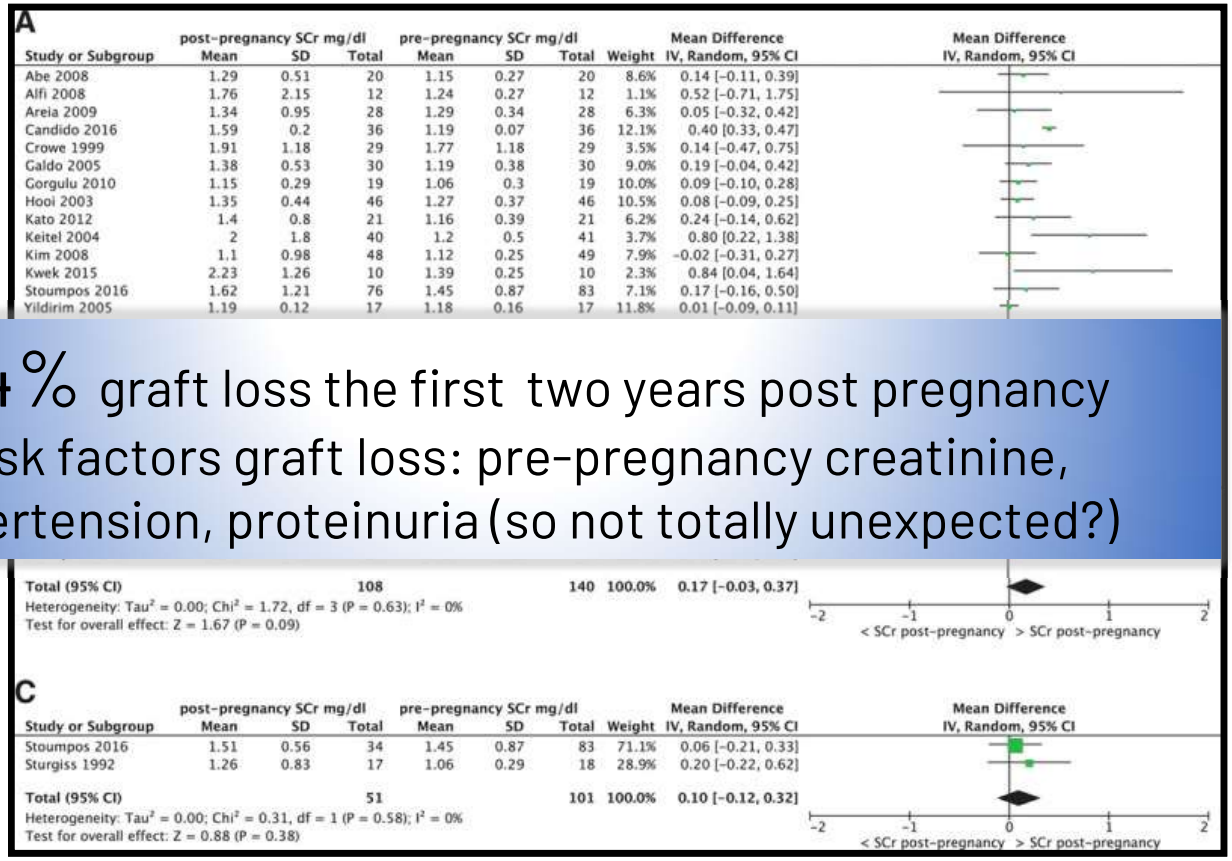
Gosselink et al. Kidney Int 2022

Hemodynamic adaptation in pregnancy: prognostic!



Gosselink et al. Kidney Int 2022

Evolution kidney function post-pregnancy in KTR



A

Study or Subgroup	post-pregnancy SCr mg/dl Mean	SD	Total	pre-pregnancy SCr mg/dl Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Abe 2008	1.29	0.51	20	1.15	0.27	20	8.6%	0.14 [-0.11, 0.39]
Alfi 2008	1.76	2.15	12	1.24	0.27	12	1.1%	0.52 [-0.71, 1.75]
Areia 2009	1.34	0.95	28	1.29	0.34	28	6.3%	0.05 [-0.32, 0.42]
Candido 2016	1.59	0.2	36	1.19	0.07	36	12.1%	0.40 [0.33, 0.47]
Crowe 1999	1.91	1.18	29	1.77	1.18	29	3.5%	0.14 [-0.47, 0.75]
Galdo 2005	1.38	0.53	30	1.19	0.38	30	9.0%	0.19 [-0.04, 0.42]
Gorgulu 2010	1.15	0.29	19	1.06	0.3	19	10.0%	0.09 [-0.10, 0.28]
Hooi 2003	1.35	0.44	46	1.27	0.37	46	10.5%	0.08 [-0.09, 0.25]
Kato 2012	1.4	0.8	21	1.16	0.39	21	6.2%	0.24 [-0.14, 0.62]
Keitel 2004	2	1.8	40	1.2	0.5	41	3.7%	0.80 [0.22, 1.38]
Kim 2008	1.1	0.98	48	1.12	0.25	49	7.9%	-0.02 [-0.31, 0.27]
Kwek 2015	2.23	1.26	10	1.39	0.25	10	2.3%	0.84 [0.04, 1.64]
Stoumpos 2016	1.62	1.21	76	1.45	0.87	83	7.1%	0.17 [-0.16, 0.50]
Yildirim 2005	1.19	0.12	17	1.18	0.16	17	11.8%	0.01 [-0.09, 0.11]
Total (95% CI)			108			140	100.0%	0.17 [-0.03, 0.37]

Heterogeneity: Tau² = 0.00; Chi² = 1.72, df = 3 (P = 0.63); I² = 0%
Test for overall effect: Z = 1.67 (P = 0.09)

Mean Difference IV, Random, 95% CI
-2 -1 0 1 2
< SCr post-pregnancy > SCr post-pregnancy

C

Study or Subgroup	post-pregnancy SCr mg/dl Mean	SD	Total	pre-pregnancy SCr mg/dl Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Stoumpos 2016	1.51	0.56	34	1.45	0.87	83	71.1%	0.06 [-0.21, 0.33]
Sturgiss 1992	1.26	0.83	17	1.06	0.29	18	28.9%	0.20 [-0.22, 0.62]
Total (95% CI)			51			101	100.0%	0.10 [-0.12, 0.32]

Heterogeneity: Tau² = 0.00; Chi² = 0.31, df = 1 (P = 0.58); I² = 0%
Test for overall effect: Z = 0.88 (P = 0.38)

Mean Difference IV, Random, 95% CI
-2 -1 0 1 2
< SCr post-pregnancy > SCr post-pregnancy

9.4% graft loss the first two years post pregnancy
Risk factors graft loss: pre-pregnancy creatinine, hypertension, proteinuria (so not totally unexpected?)

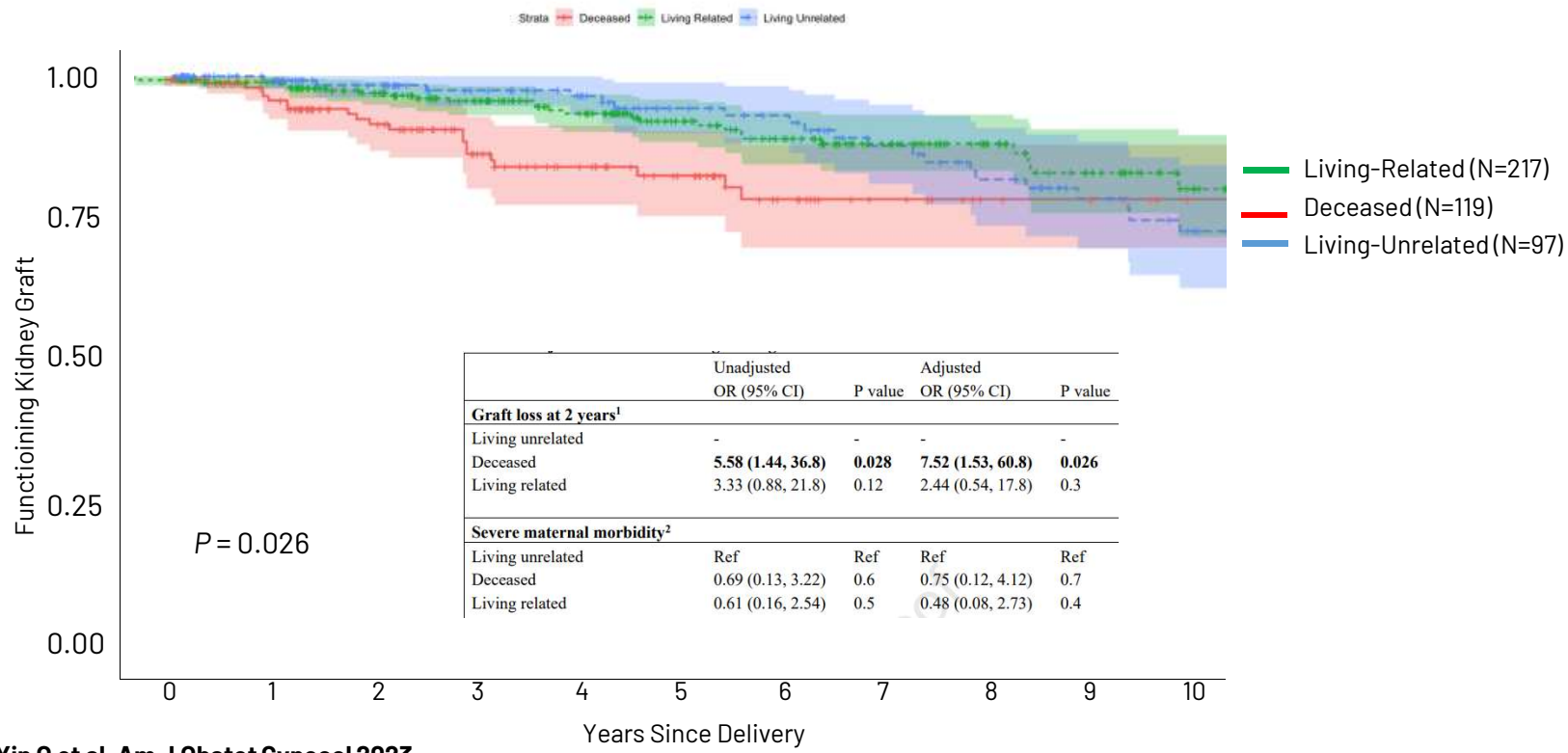
0-2years
Δ 0.2mg/dL

2-5years

>5years

Van Buren MC et al. Transplantation 2020

Graft outcome post pregnancy: better in LD?



	Unadjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Graft loss at 2 years[1]				
Living unrelated	-	-	-	-
Deceased	**5.58 (1.44, 36.8)**	**0.028**	**7.52 (1.53, 60.8)**	**0.026**
Living related	3.33 (0.88, 21.8)	0.12	2.44 (0.54, 17.8)	0.3
Severe maternal morbidity[2]				
Living unrelated	Ref	Ref	Ref	Ref
Deceased	0.69 (0.13, 3.22)	0.6	0.75 (0.12, 4.12)	0.7
Living related	0.61 (0.16, 2.54)	0.5	0.48 (0.08, 2.73)	0.4

Yin O et al. Am J Obstet Gynecol 2023

A rare case of AKI in pregnant KTR

ELSEVIER

Hydronephrosis in a Pregnant Renal Transplant Patient

P.B. Mark, I.V. McCrea, G. Baxter, and M.A. McMillan

Transplant Proceedings 2009

- Few cases reported (not mentioned in systematic reviews pregnancy KTR)
- Diagnosis: no recurrent hydronephrosis-post delivery
- Percutaneous nephrostomy versus silicone stent?

Pregnancy in the sensitized kidney transplant recipient

- Case series 8 sensitized pregant recipients with high risk of adverse maternal complications and of ABMR (3 of 8 patients) in postpartum
- Pregnancy as sensitizing event
- Pre-eclampsia more common in sensitized women?
- Hesitancy to biopsy in third pregnancy trimester?
- DD rejection: pyelonephritis and pre-eclampsia
- Scarcity of data: shared decision making!

Lubetzky AM et al. Clin Transplantation 2016

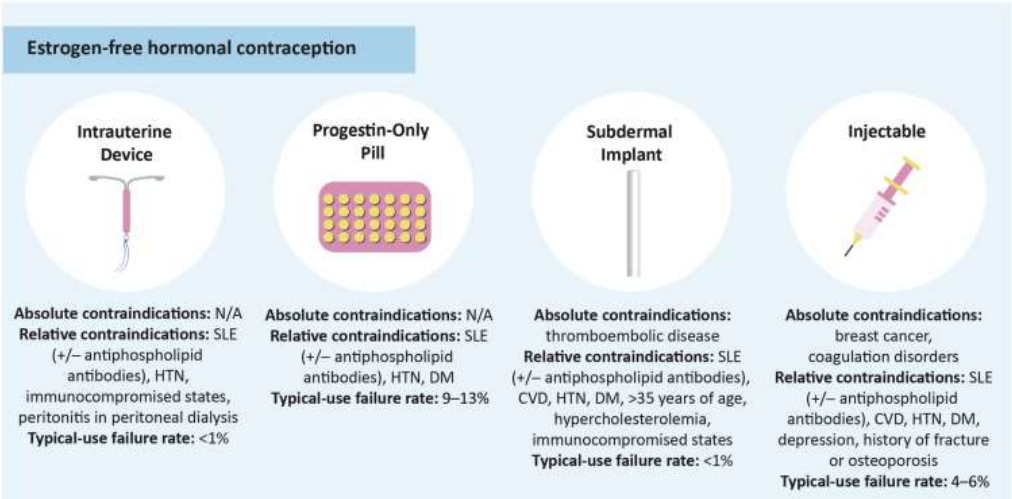
Anticonception and transplantation

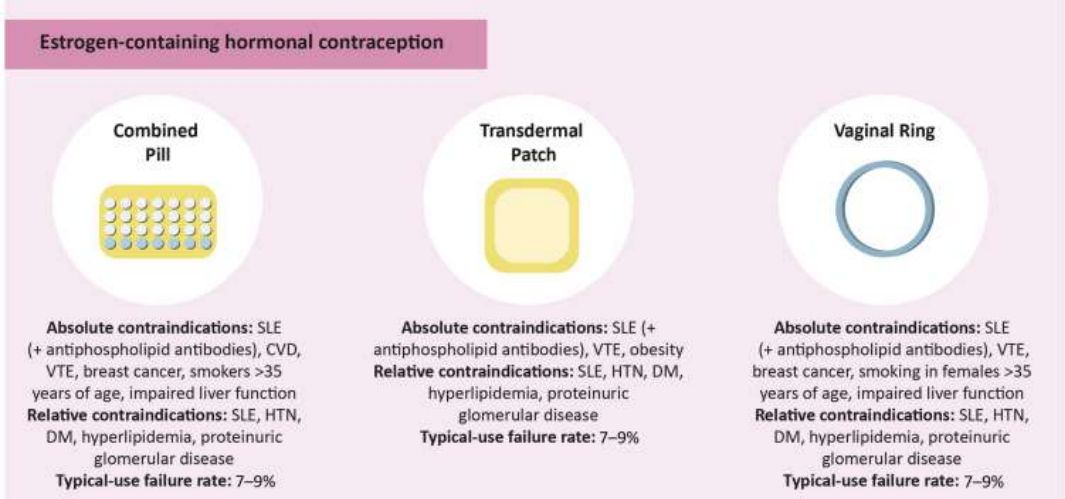
Contraceptive method	Typical use failure rate (%)	Immunosuppressive drug interactions and transplant-related safety measures
Sterilization	0.5	No interaction. Female sterilization surgery might be complicated by previous abdominal surgery (kidney engraftment) and male partner sterilization or a long-acting reversible contraceptive method should be considered.
Progestin subdermal implant	0.05	Very limited safety data in KTRs.
Levonorgestrel IUD	0.2	Historically, KTRs received advice not to use IUDs due to anticipated reduced efficacy with concomitant use of immunosuppressive drugs and case reports of pelvic infections. These concerns have been refuted by later studies. It acts locally with no risk of drug interaction.
Copper IUD	0.8	No interaction. Can increase menstrual bleedings and should not be used in severe anemia or coagulopathy.
DMPA injection	6	No interaction. Increased risk of osteoporosis.
Progestin pill	9	Very limited safety data in KTRs.
CHC pill, patch or ring	9	Interaction with corticosteroids and mycophenolic acid-reducing efficacy. Increased risk of hypertension and venous thromboembolic disease.
Barrier method like condom or diaphragm	18	No interaction. Should only be used in combination with efficient contraceptive method and for protection against sexually transmitted diseases.

Table adapted from Krajewski CM, Geetha D, Gomez-Lobo V. Contraceptive options for women with a history of solid-organ transplantation. *Transplantation*. 2013;95:1183–6 and Trussell J. Contraceptive failure in the United States. *Contraception* 2011;83:397–404.
CHC, combined hormone contraception with estrogen and progestin; DMPA, depot medroxyprogesterone acetate; IUD, intrauterine device; KTR, kidney transplant recipient.

Anupam C et al. Transplantation 2019

Anticonception and transplantation





MIND high failure rates !

Chang D et al. KI reports 2021

Outcome of children of KTR?

53 articles

28 cohort studies

19 case reports

6 cross-sectional

20 up to 4y follow-up

5 >18y follow-up

1664 offspring

78% kidney

17% liver

Results

Growth
- Appears to be normal

Immunology
- No opportunistic/chronic infection
- Normal antibody response to vaccination
- Possible increased risk of hospitalization for infection
- At young age (<9 years) some alterations in numbers of immune cells

Neurobehavioral
- Similar to the general population

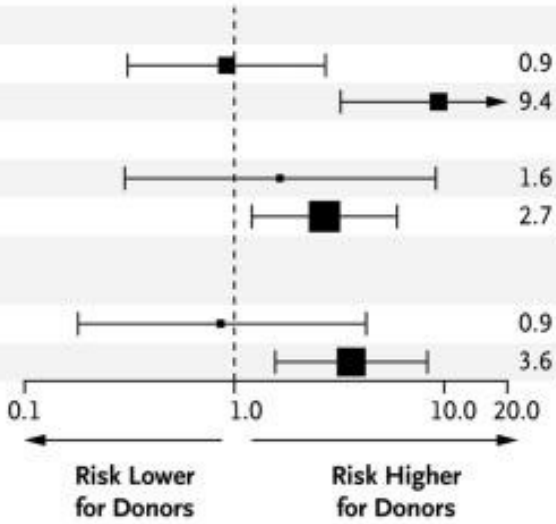
Kidney
- No abnormalities in kidney function reported in 96% (243/252) of the assessed children.

NEED FOR MORE DATA WITH MORE LONG-TERM FOLLOW-UP

Meinders JR et al. Transplant Int 2022

Pregnancy after kidney donation

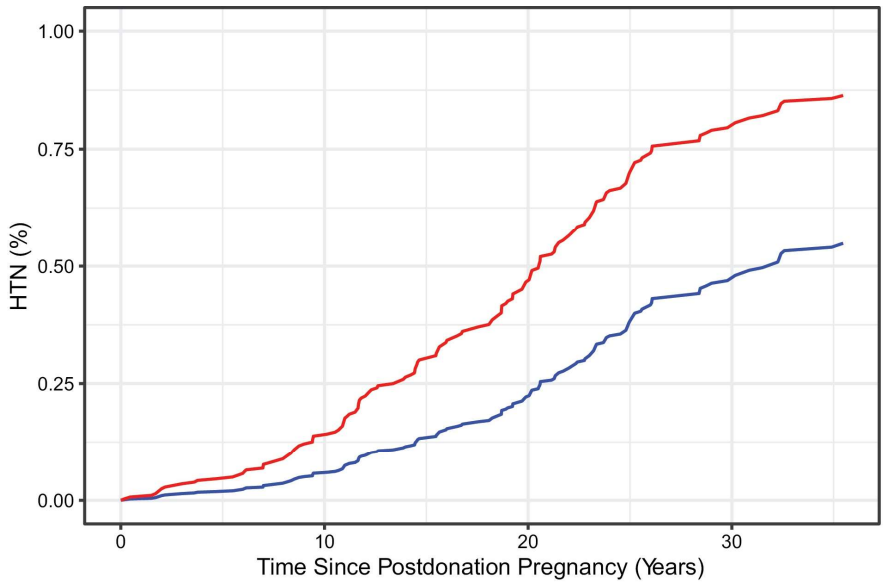
Subgroup	Pregnancies in Donors	Pregnancies in Nondonors	Odds Ratio (95% CI)	P Value for Interaction
	no. of events/no. at risk (%)			
Age at pregnancy				0.004
≤32 yr	≤5/85 (≤6)	30/492 (6)	0.9 (0.3–2.7)	
>32 yr	≥10/46 (≥22)	8/296 (3)	9.4 (3.2–27.5)	
Prior pregnancy				0.61
Yes	≤5/31 (≤16)	7/173 (4)	1.6 (0.3–9.1)	
No	≥10/100 (≥10)	31/615 (5)	2.7 (1.2–6.0)	
Time of pregnancy since cohort entry				0.12
≤2 yr	≤5/46 (≤11)	16/302 (5)	0.9 (0.2–4.3)	
>2 yr	≥10/85 (≥12)	22/486 (5)	3.6 (1.6–8.3)	

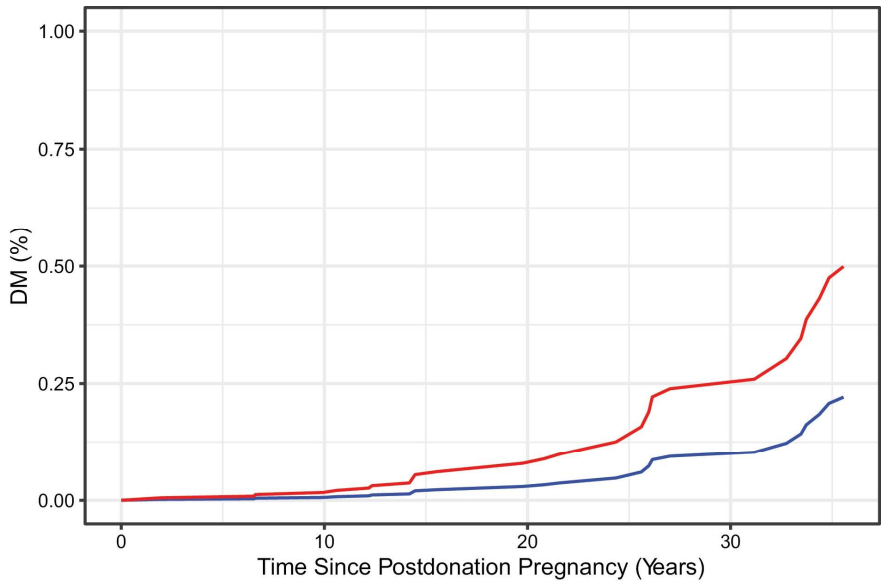


SIGNIFICANT RISE IN PRE-ECLAMSPIA RISK: OR 2.4 (95%CI 1.2-5.0; *P*=0.01)

Garg et al NEJM 2015

Pregnancy after kidney donation





Number at Risk

PE	35	32	24	20	14	8	4	3
No PE	590	540	468	368	272	173	124	82

Number at Risk

PE	39	37	32	27	22	19	12	10
No PE	600	558	499	423	345	253	199	137

SIGNIFICANT RISE IN PRE-ECLAMSPIA RISK: IMPLICATIONS!

Palzer EF et al. Transplantation 2023

TAKE HOME MESSAGES

- mTOR inhibitors affect fertility
- Mycophenolic acid should not be stopped in future fathers
- Kidney function crucial determinant fertility and risk pre-eclampsia in KTR
- Tacrolimus clearance increases during pregnancy
- Rejection risk (also postpartum), mind immunized KTR
- Anticonception: IUD (copper/hormone)
- Pregnancy after kidney donation: discuss the risk
- Preconception counseling with shared decision-making imperative+ multi-disciplinary team