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Centre for Rare Diseases

Cystinosis Network Europe

FERTILITY AND PREGNANCY IN WOMEN WITH CYSTINOSIS

3rd CNE International Cystinosis Conference, July 2022

Dr Graham Lipkin

Consultant Kidney Specialist

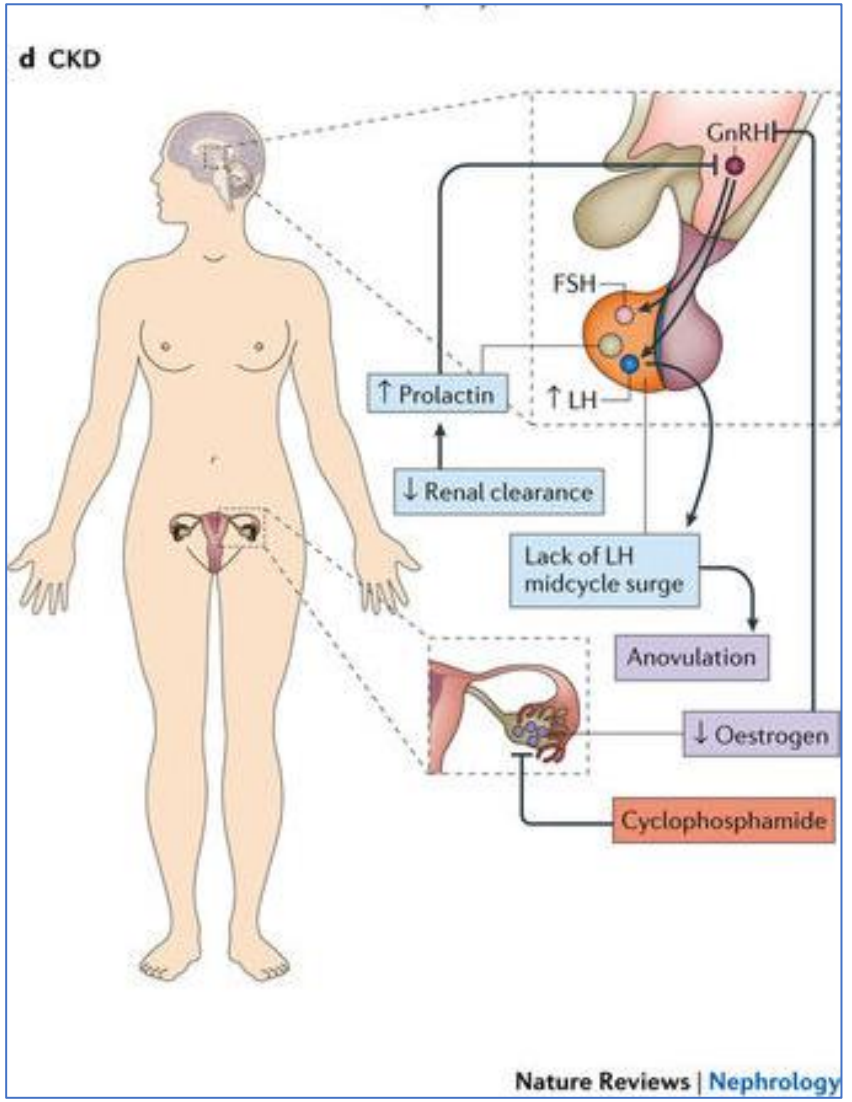
Queen Elizabeth Hospital Birmingham, UK

OVERVIEW

- Contraception and pre-conception counselling
- Pregnancy in renal transplant recipients
- Special issues and outcomes in cystinosis

Transplantation Restores Fertility

- Fertility is markedly reduced on dialysis.
- Related to disruption of normal link between brain (hypothalamus/pituitary) and ovaries:
  - Irregular menses, anovulation, decreased libido.
- Kidney transplantation **rapidly** restores fertility!

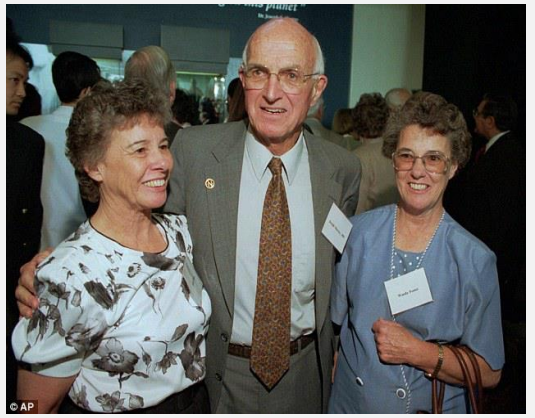


Wiles Nat Rev Neph 2018; 14:165-184

KIDNEY TRANSPLANTATION ENABLES NEW LIFE

- Edith Helm
  - 1st renal transplant pregnancy, 1958
  - Had 2 successful pregnancies.

- Many thousands of successful pregnancies have since been reported **worldwide**.



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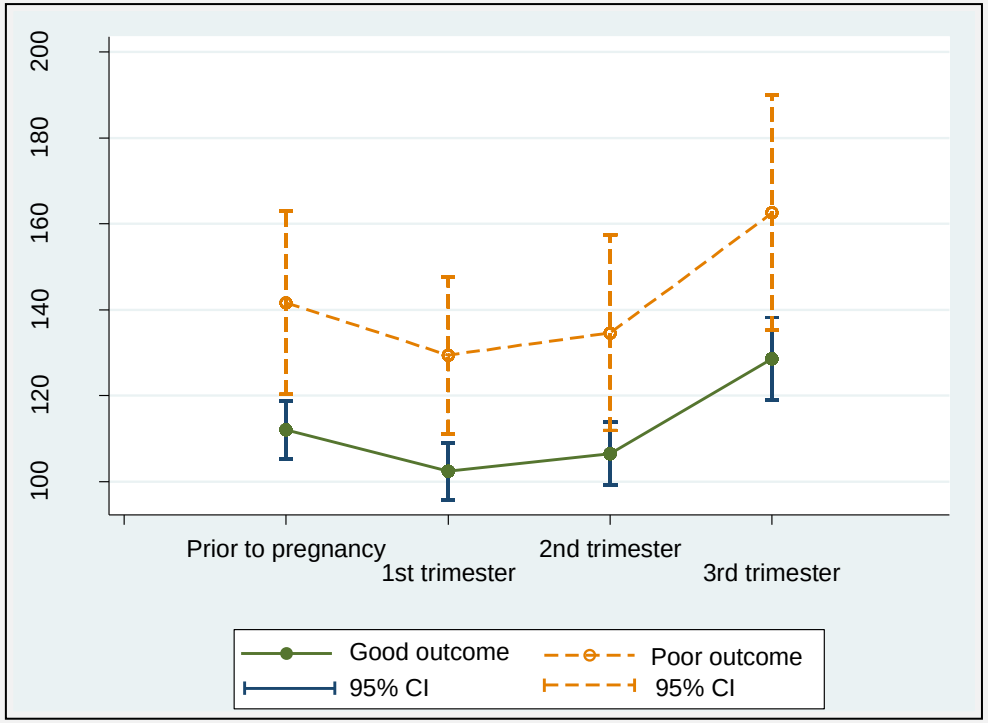
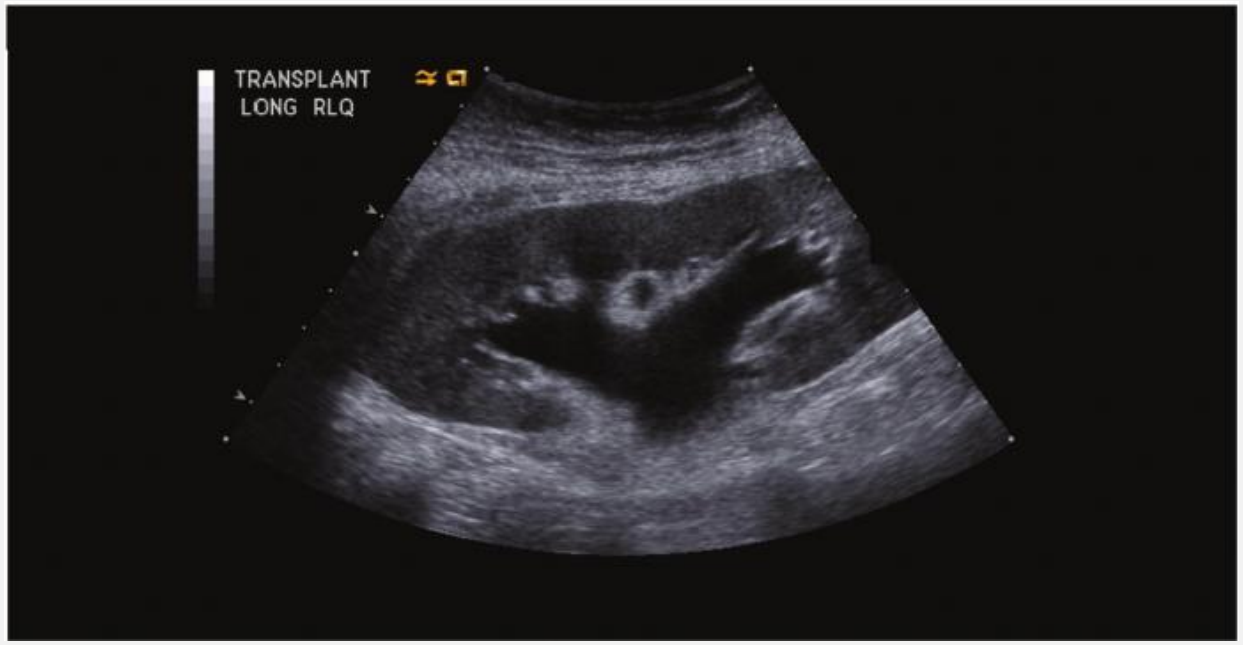
THE TRANSPLANT ADAPTS TO PREGNANCY PHYSIOLOGY

Improved function



Hydronephrosis



Bramham CJASN 2013; 8:290-298, Davison NDT 2002

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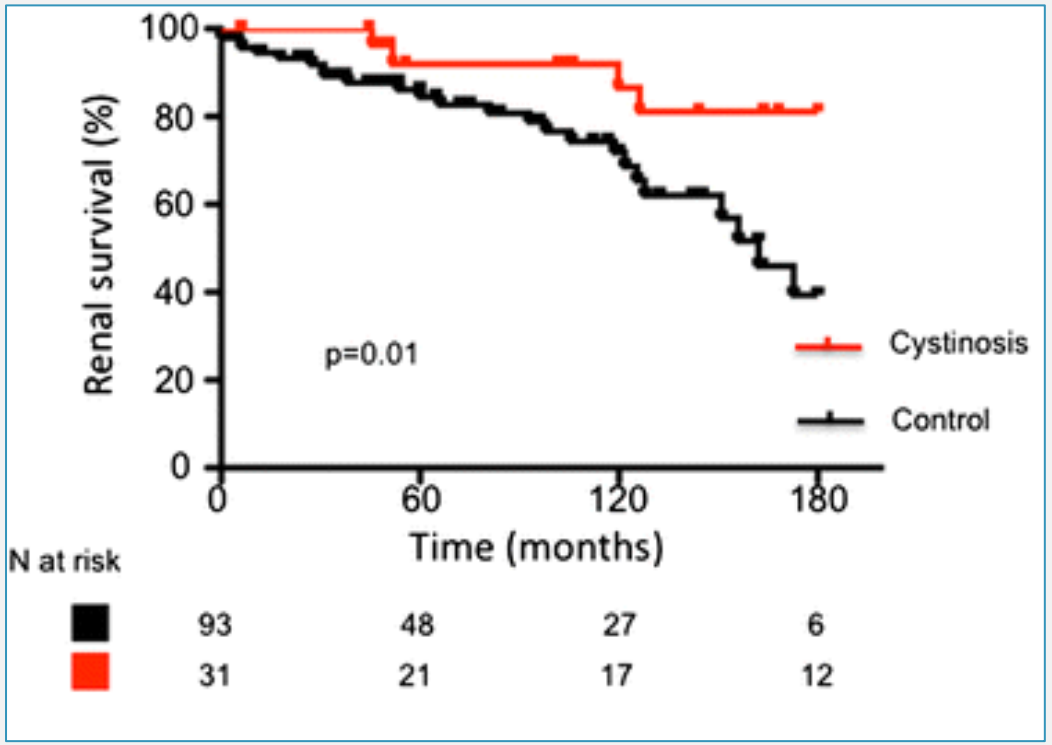
CYSTINOSIS IN ADULTS

Natural history has changed:

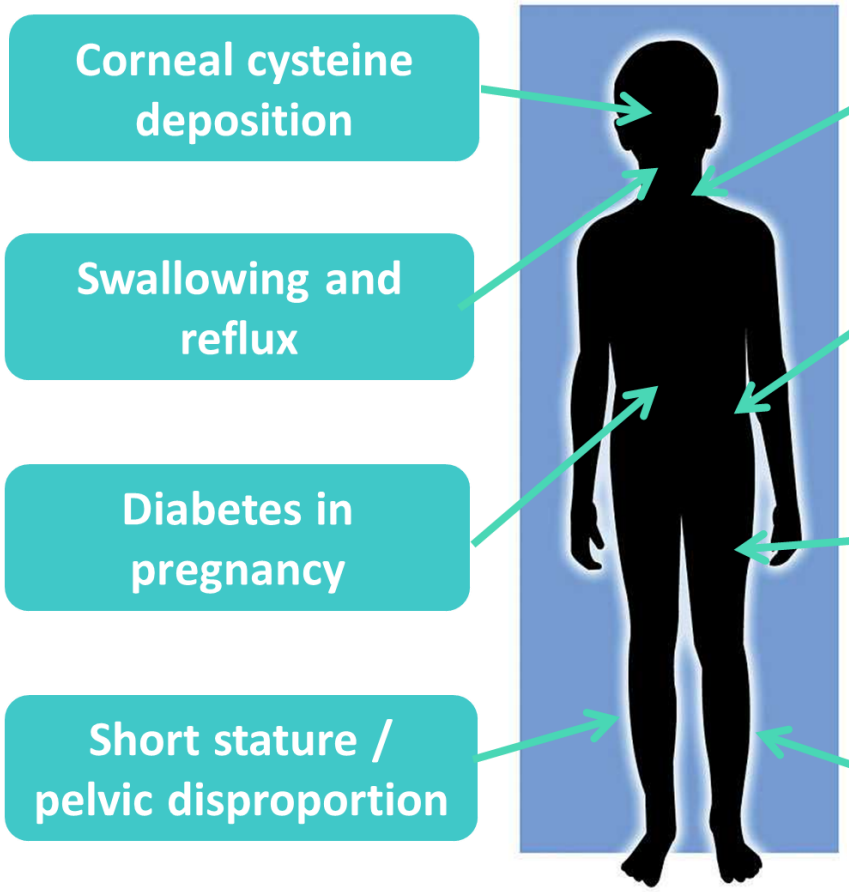
- Kidney Transplantation
- Oral Cysteamine
- Of over 200 patients in UK more than 100 are over 16 years old
  - Women with cystinosis are fertile



Brodin-Sartorius, Kidney Int (2012)
Cohen, Orphanet J of Rare Diseases (2015)

Organisation of Care for Adults with Cystinosis

SPECIAL ISSUES



- Corneal cysteine deposition
- Swallowing and reflux
- Diabetes in pregnancy
- Short stature / pelvic disproportion
- Hypothyroidism
- Kidney transplant
- Muscle weakness (incl chest)
- Heat intolerance

EXPERT GUIDANCE ON MANAGEMENT OF PREGNANCY IN WOMEN WITH CKD

Wiles *et al. BMC Nephrology* (2019) 20:401
https://doi.org/10.1186/s12882-019-1560-2

BMC Nephrology

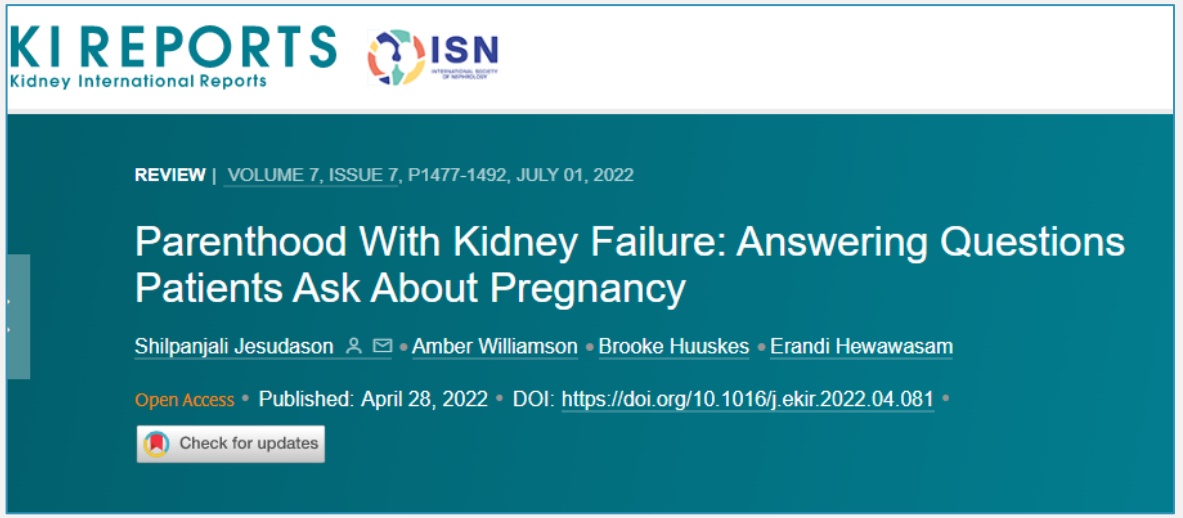
THE RENAL ASSOCIATION
founded 1950

GUIDELINES Open Access

Clinical practice guideline on pregnancy and renal disease

Check for updates

Kate Wiles[1*], Lucy Chappell[2], Katherine Clark[3], Louise Elman[4], Matt Hall[5], Liz Lightstone[6], Germin Mohamed[4], Durba Mukherjee[4], Catherine Nelson-Piercy[7], Philip Webster[8], Rebecca Whybrow[9] and Kate Bramham[10]



KI REPORTS
Kidney International Reports

ISN

REVIEW | VOLUME 7, ISSUE 7, P1477-1492, JULY 01, 2022

Parenthood With Kidney Failure: Answering Questions Patients Ask About Pregnancy

Shilpanjali Jesudason • Amber Williamson • Brooke Huuskes • Erandi Hewawasam

Open Access • Published: April 28, 2022 • DOI: https://doi.org/10.1016/j.ekir.2022.04.081 •

Check for updates

EXPERT GUIDANCE: PREGNANCY AND CYSTINOSIS

meeting report www.kidney-international.org

Controversies and research agenda in nephropathic cystinosis: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference

Craig B. Langman[1,2], Bruce A. Barshop[3], Georges Deschênes[4], Francesco Emma[5], Paul Goodyer[6], Graham Lipkin[7], Julian P. Midgley[8], Chris Ottolenghi[9,10], Aude Servais[11], Neveen A. Soliman[12], Jess G. Thoene[13] and Elena N. Levtchenko[14,15]; for Conference Participants[16]

Nephrol Dial Transplant (2014) 29: iv87–iv94
doi: 10.1093/ndt/gfu090

ndt Nephrology Dialysis Transplantation

Full Review

Nephropathic cystinosis: an international consensus document

Francesco Emma[1], Galina Nesterova[2], Craig Langman[3], Antoine Labbé[4,5], Stephanie Cherqui[6], Paul Goodyer[7], Mirian C. Janssen[8], Marcella Greco[1], Rezan Topaloglu[9], Ewa Elenberg[10], Ranjan Dohil[11], Doris Trauner[12], Corinne Antignac[13,14,15], Pierre Cochat[16], Frederick Kaskel[17], Aude Servais[18], Elke Wühl[19], Patrick Niaudet[20], William Van't Hoff[21], William Gahl[2] and Elena Levtchenko[22]

PREGNANCY:

- Follow recommendations for renal transplant recipients.
- Preconception counselling should be offered
- Discussion about optimal time for stopping cysteamine should be part of preconception counselling.

Pre-pregnancy counselling is Crucial

- Specific points in KT recipients:
  - When can I start trying for a baby?
  - Medication Management
  - What are the risks for my baby?
  - What are the risks for me and my kidney?

- Every patient is different - tailored counselling.

- Start with contraceptive advice early pre/post transplant.

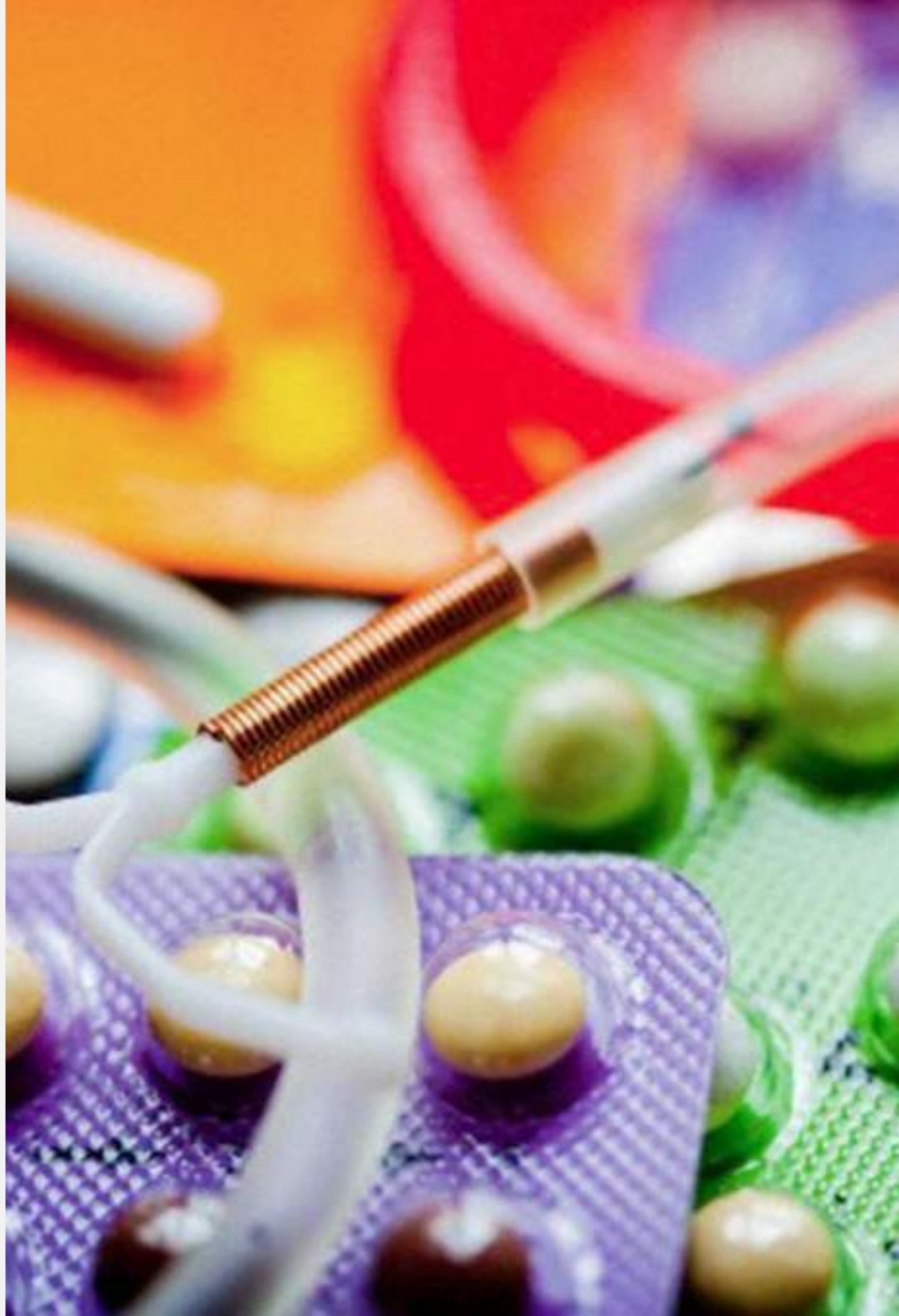
TRANSITION IN CYSTINOSIS: GETTING IT RIGHT

- Magnified challenges
- Complex - limited adult expertise
  - Many more adult centres
- Parents/carers needs
- High graft loss & unnecessary end organ damage
- Contraceptive advice

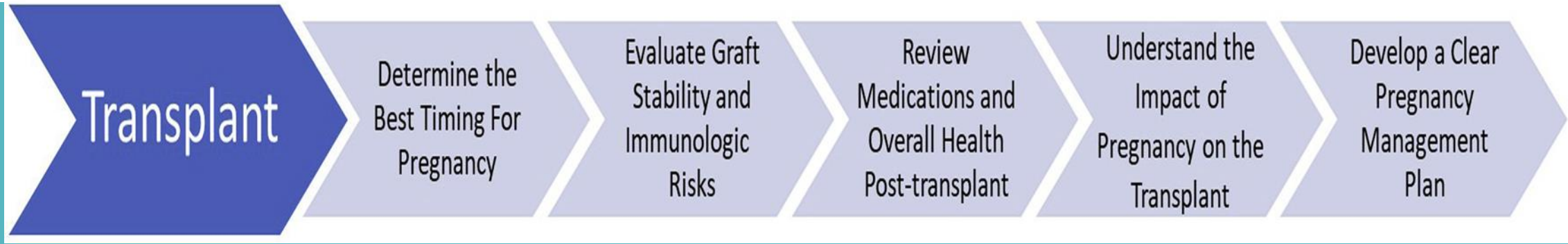
CONTRACEPTION

- Contraceptive advice in all transition and adult clinics
- Safe, tolerated, minimal interactions

- Preferred option: POP (desogestrol)
- Long acting reversible
  - Nexplanon Implant
  - Mirena IUS Coil safe and effective
- Combined OCP second line but suitable for some
- Emergency contraception safe



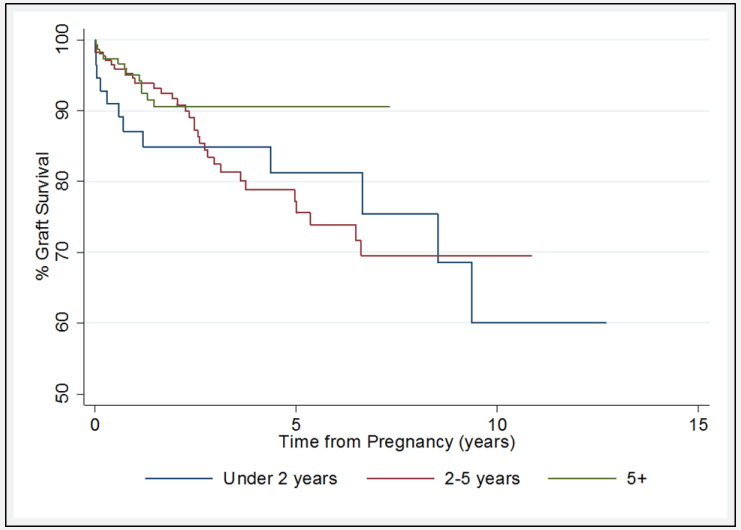
CAN I TRY FOR A PREGNANCY?



HOW LONG SHOULD I WAIT AFTER TRANSPLANT?

- > 1 year (strict guidelines inappropriate)
  - With well-controlled BP and low urine protein
  - Less CMV and rejection

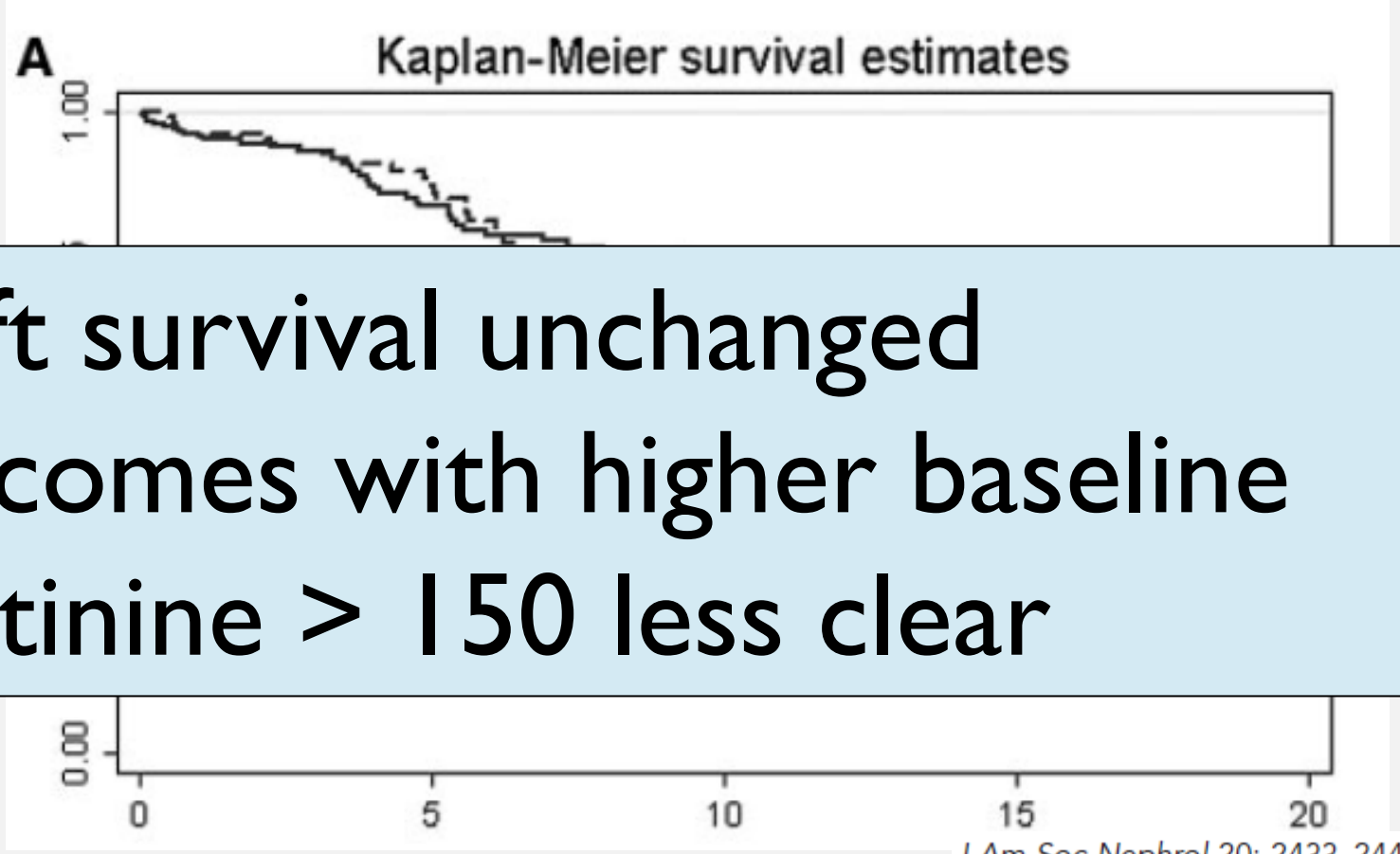
- Then 3-6 months stability after stopping mycophenolate



Sarween NDT 2016;31(suppl_1):i6-i6

WILL PREGNANCY DAMAGE MY KIDNEY?

Graft Survival

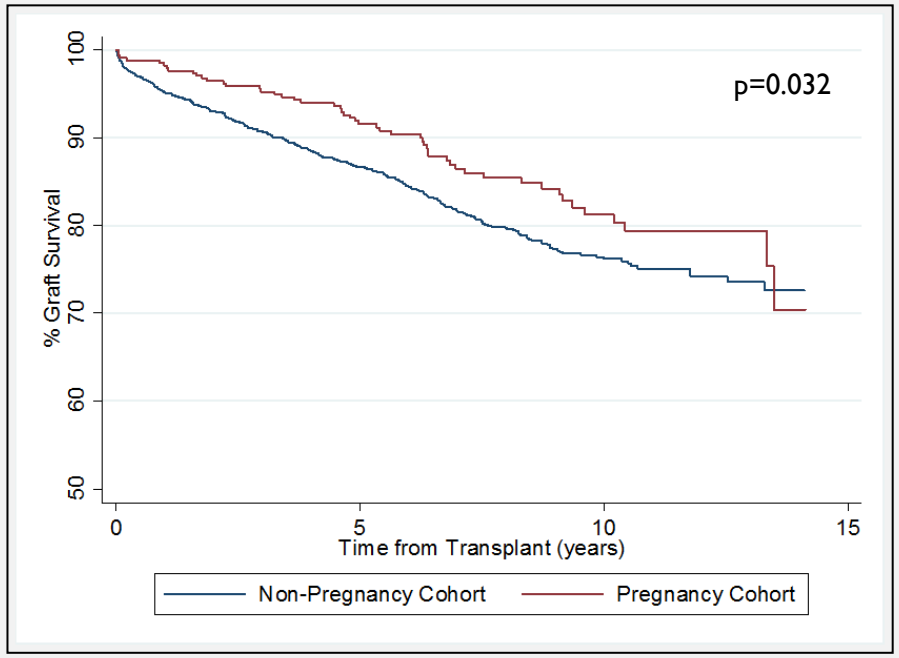


Graft survival unchanged
Outcomes with higher baseline creatinine > 150 less clear

J Am Soc Nephrol 20: 2433–2440, 2009.

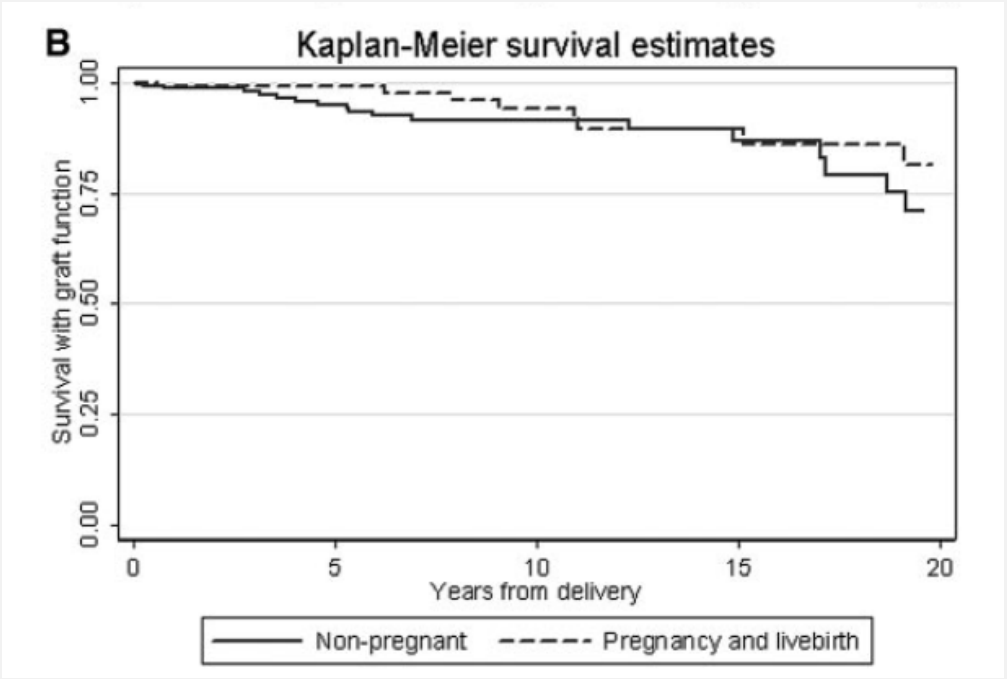
LONG-TERM TX OUTCOME FOLLOWING PREGNANCY

Graft Survival



Sarween NDT 2016;31(suppl_1):i6-i6

Patient Survival



Levidiotis J Am Soc Nephrol 2009;20:2433-2440

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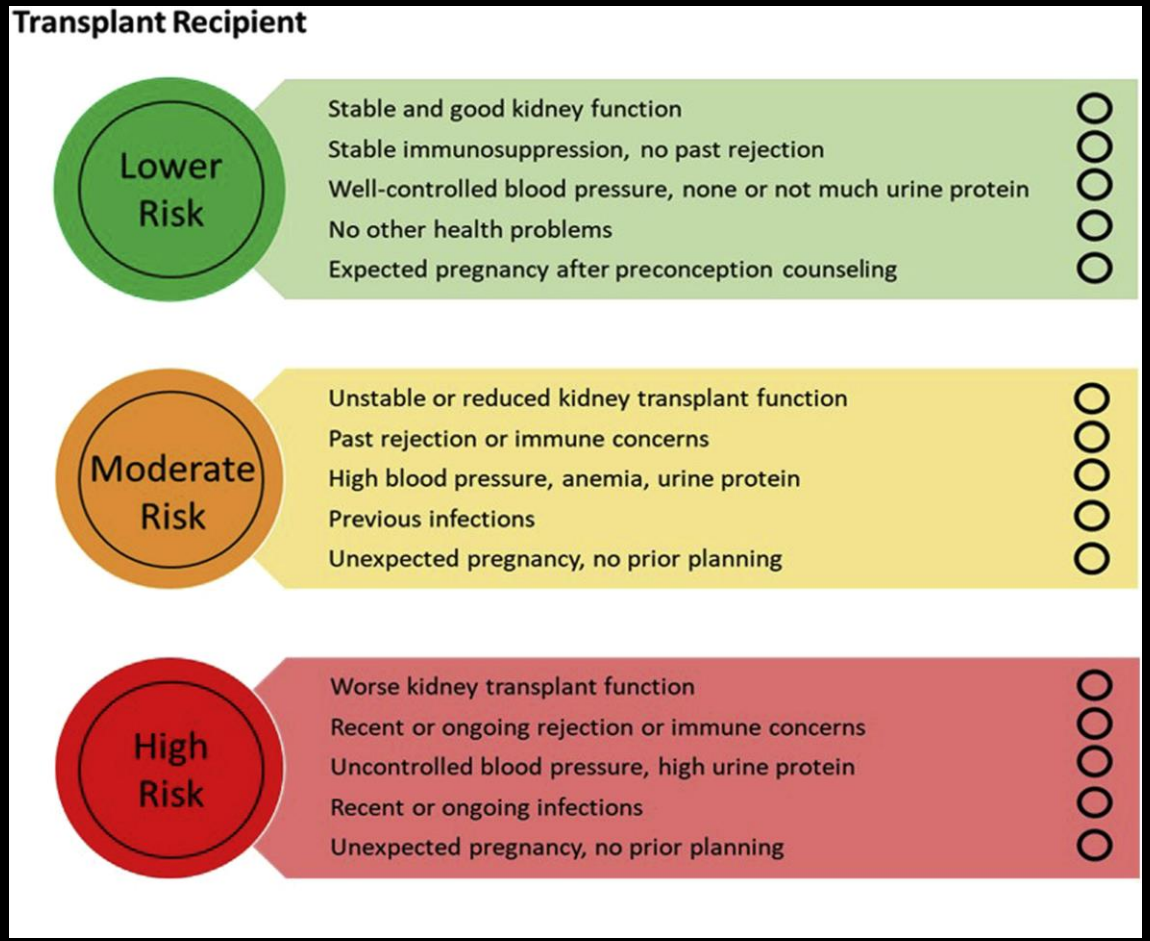
Carefull Assessment of Transplant Function, BP, Protein leak



Kidney International Reports 2022 71477-1492DOI: (10.1016/j.ekir.2022.04.081)

WILL I HAVE A SUCCESSFUL PREGNANCY OUTCOME?

Era	Terminations (%)	Miscarriage (%)	Stillbirth (%)	Live Birth (%)
76 to 85	18	9	4	69
86 to 95	15	7	3	75
96 to 05	5	12	0.5	83

Beyond the first trimester > 95% will result in a successful pregnancy outcome

Davison 2008 BMJ

WILL I HAVE A SUCCESSFUL PREGNANCY? HES DATA ENGLAND

Outcome in %	Tx population (n = 569)	General Population (n = 10,177,153)	p value
Termination	13.2	10.1	0.007
Miscarriage	17.5	7.6	<0.001
Ectopic Pregnancy	0	0.06	-
Still Birth	≤0.9	0.5	-
Live Birth	68.8	81.8	<0.001

Sarween NDT 2016;31(suppl_1):i6-i6

WHAT ARE THE RISKS TO MY HEALTH?

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	Transplant Cohort (%)	General Population (%)	p value
Gestational Diabetes	15.0	2.3	<0.001
Severe UTI			001
Puerperal Infecti			001
Pre-eclampsia (PET) 1st pregnancy	26.7	1.7	<0.001
DVT or PE	0	0.07	-

- Aspirin 75mg-150mg reduces risk of PET
- Delivery is the only treatment for PET

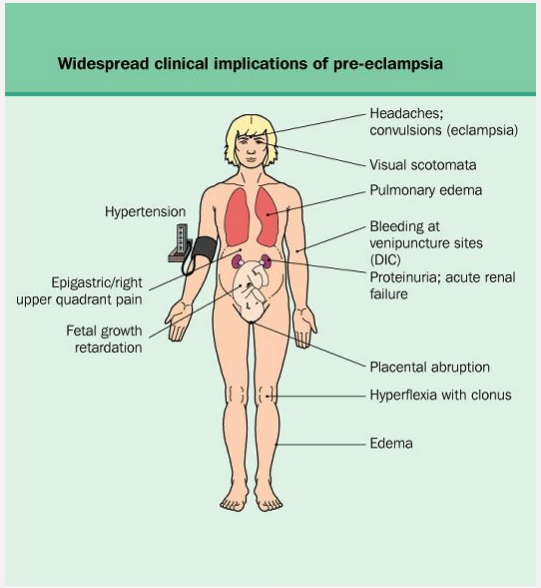
Sarween NDT 2016

TRANSPLANT DYSFUNCTION DURING PREGNANCY

- Investigation of transplant dysfunction is the same as for the non-pregnant situation.
- Pre-eclampsia should be part of the differential diagnosis of unexplained transplant dysfunction after 20 weeks.
- Renal transplant biopsy may be considered before fetal viability if safe.
- Acute rejection rates in pregnancy are similar to the non-pregnant state and can be treated with steroids

TRANSPLANT DYSFUNCTION VS PRE-ECLAMPSIA

	CKD	Pre-eclampsia
Time of onset	Usually 3rd trimester	>20 weeks
Rate of change in BP/proteinuria/renal function	Weeks	Hours to days
Peripheral oedema (swelling)	Possibly	Possibly
Uterine Doppler at 24 weeks	Normal	Abnormal 'notching' sometimes
Elevated liver transaminase and/or low platelets or TMA	No	Sometimes
Serum urate	High	High
Circulating angiogenic factors (sFlt/PlGF ratio)	Normal	High
Treatment	Support/monitoring	Delivery (if severe)



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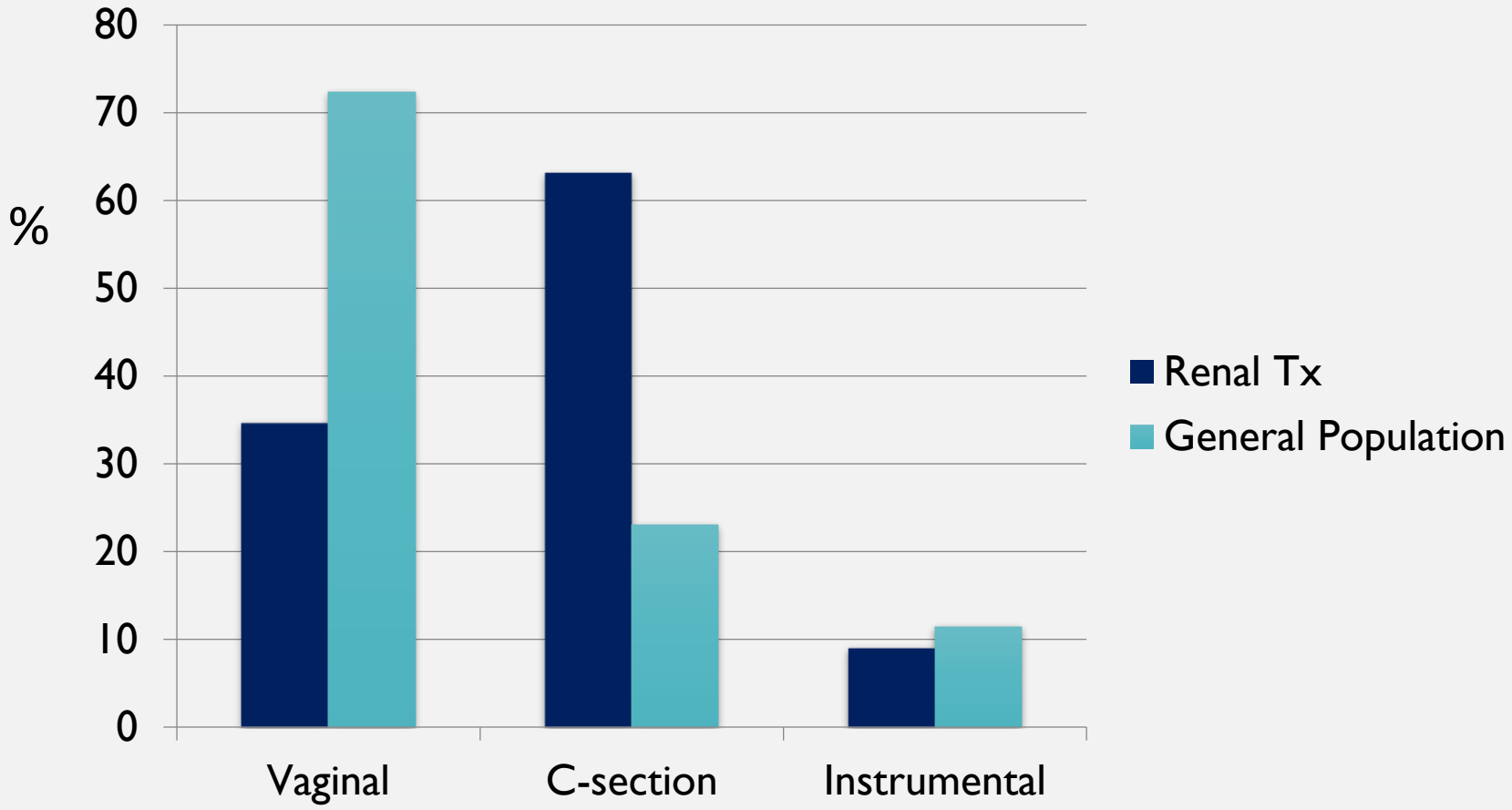
CAN I HAVE A NORMAL DELIVERY?



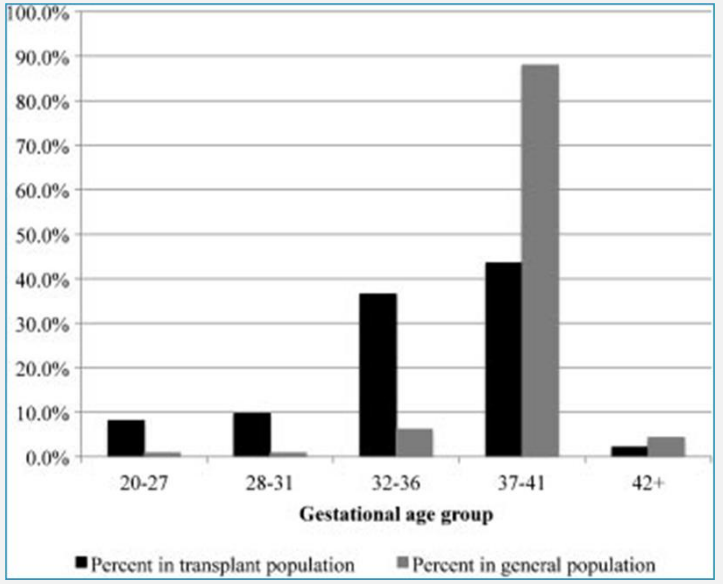
Sarween NDT 2016

WILL MY MEDICATIONS DAMAGE MY BABY?

	Comments	Safe?
Prednisolone	Screen for gestational diabetes	Y
Azathioprine	<2mg/Kg	Y
Ciclosporin	Dose increase	Y
Tacrolimus	Dose increase / risk of gestational diabetes	Y
Mycophenolate	**Convert 3-6m prior**	**No**

WILL MY BABY BE BORN EARLY OR SMALL?

	UKOSS 2013 (n=104)
Gestation	36 weeks
Birth weight	2.48 kg
Prematurity (<37 weeks)	52%
Low birth wt (<2.5 Kg)	48%
V low Birth wt (<1.5Kg)	9%

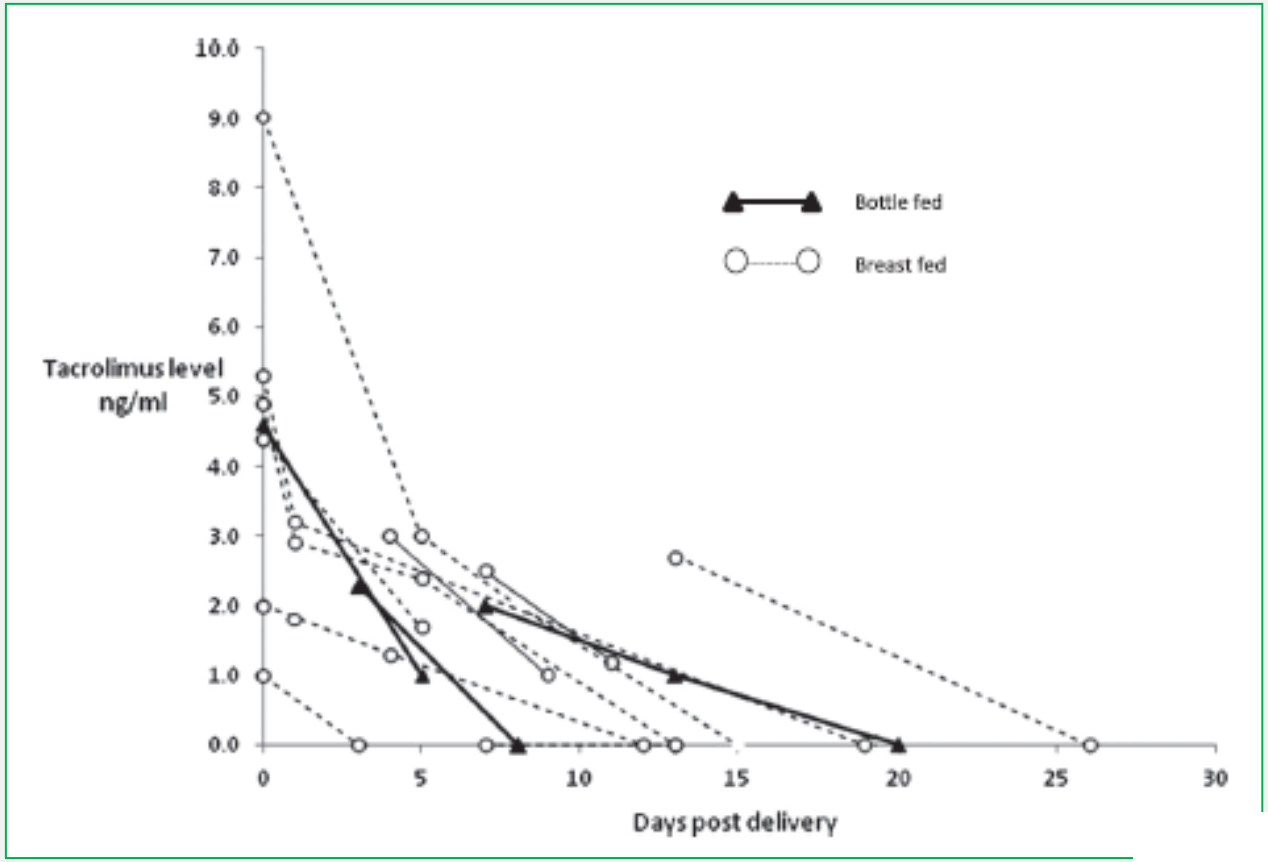


- 1 in 5 babies born < 32 weeks
- High requirement for NICU

Bramham CJASN 2013; 8:290-298

CAN I BREAST FEED MY BABY?
INDIVIDUAL DISCUSSION

	Transfer	Safe?
Prednisolone	Small	Yes
Azathioprine	V. Low	Yes
Cyclosorin	Tiny?	Yes
Tacrolimus	Tiny?	Yes



Bramham CJASN 2013: 8(4):563-7, Sau BJOG 2007;114:498-501

WHICH ANTI-HYPERTENSIVES ARE SAFE IN BREAST FEEDING?

- The following drugs have no adverse effects on babies receiving breast milk:
  - Labetalol
  - Nifedipine
  - Enalapril
  - Captopril
  - Atenolol
  - Metoprolol

NICE guidelines Hypertension in Pregnancy 2015

PRE-CONCEPTION GUIDELINES

- Contraception and Joint pre-conception Counselling are key.
- Manage jointly in Renal Obstetric Clinic
- Stable renal function, >1y post Tx.
- Creatinine<175 (<125), <1g protein/24h.
- BP< 140/90 on 2 or less drugs.
- Prednisolone (<15mg/day), azathioprine, ciclosporin & tacrolimus are safe.
- Convert mycophenolate to azathioprine 3-6 months prior.
- Aspirin 75-150mg reduces pre-eclampsia
- Stabilise patient pre-pregnancy-safe drugs.

McKay AJT 2005;5:1592, Lessan-Pezeshki NDT 2002

KEY POINTS

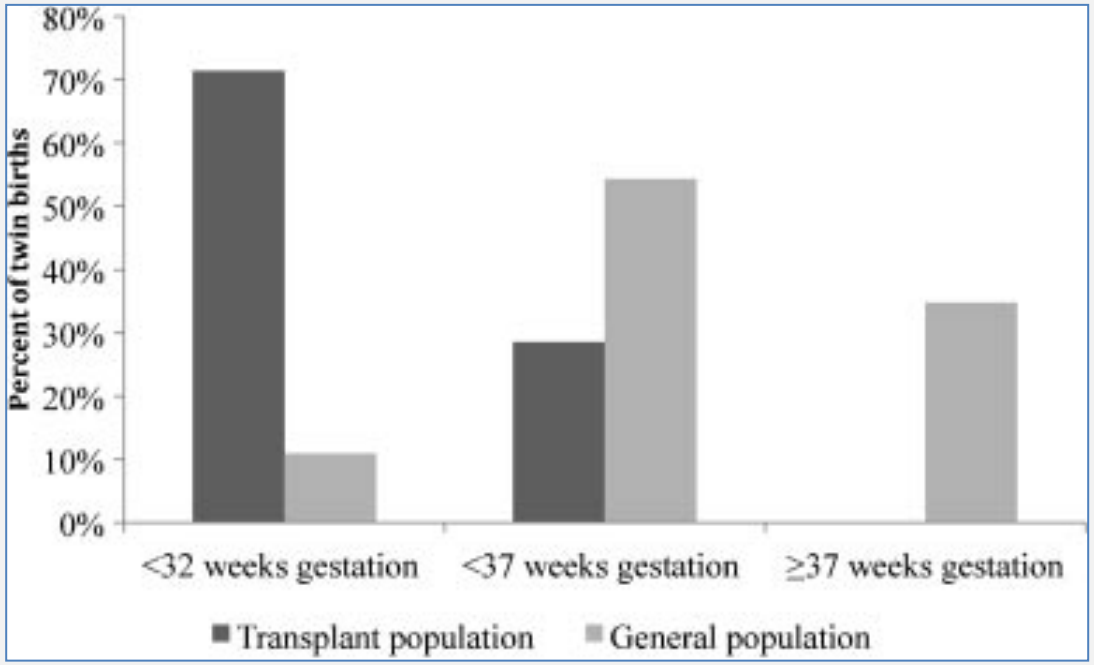
- Increased incidence of maternal complications:
  - PET, gestational diabetes, c-section delivery.

- Preserved Renal Transplant function & blood pressure control are the most important factors predictive of a favourable obstetric & Tx outcome.

- Transplant function not affected long term.

ASSISTED CONCEPTION TECHNIQUES ARE EFFECTIVE

SINGLE EMBRYO TRANSFER RECOMMENDED.

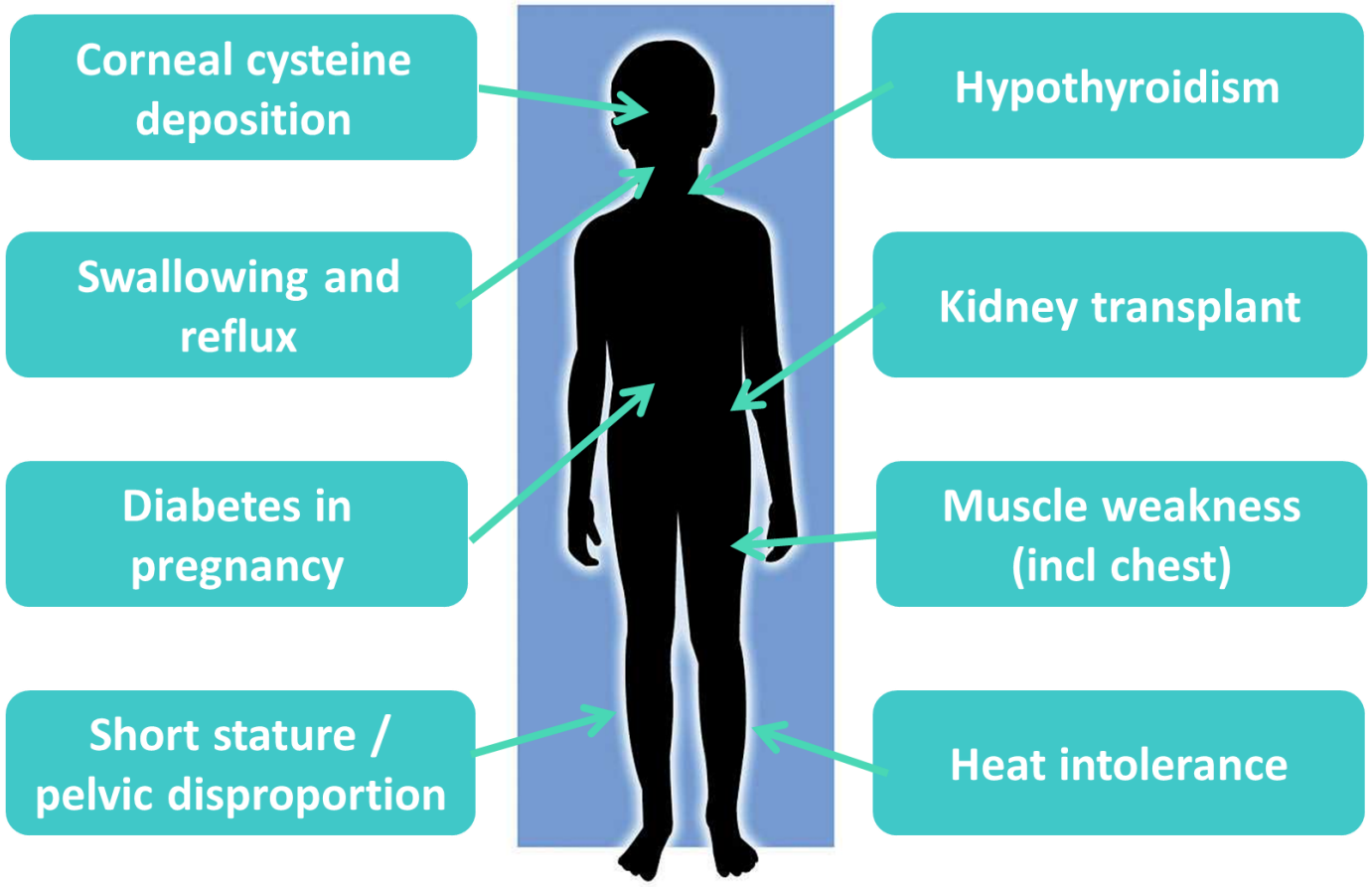


- Assisted reproductive techniques are effective.
- Ovarian hyper stimulation risks.
- Twin Pregnancies-poor outcomes

Wyld. Am J Transplant 2013; 20: 1-10

SPECIAL ISSUES IN CYSTINOSIS PATIENTS

SPECIAL ISSUES



PRE-CONCEPTION COUNSELLING

- All women with cystinosis can benefit
- Assess carefully for transplant and special complications of cystinosis
  - Pulmonary function testing
  - Formal swallowing assessment
  - Assess and optimise diabetes and thyroid replacement
  - Discuss timing of stopping and re-starting cysteamine
  - Pelvic size and discuss delivery
  - Monitoring over pregnancy
  - Don’t forget normal advice; weight, smoking, folic acid

OUTCOMES OF PREGNANCY IN CYSTINOSIS

ckj OXFORD era edta

Clinical Kidney Journal, 2019, vol. 12, no. 6, 855–858

doi: 10.1093/ckj/sfz047
Advance Access Publication Date: 28 April 2019
Exceptional Case

EXCEPTIONAL CASE

Pregnancy in women with cystinosis

Hannah Blakey[1], Jemma Proudfoot-Jones[2], Ellen Knox[3] and Graham Lipkin[1]

Table 1. Summary of published cases of pregnancy in cystinosis patients

References	Maternal age at delivery (years)	Modality of RRT	Cysteamine prior to pregnancy (yes/no)	Cysteamine during pregnancy (yes/no)	Pregnancy/neonatal complications	Gestation (weeks + days)	Mode of delivery	Requirement for NICU (yes/no)
Reiss *et al.* [2]	20	Transplant	No	No	Mild preeclampsia, Group B strep amnionitis, skin abscess, UTI	35 + 3	Caesarean section	No
Andrews and Sacks [3]	30	Transplant	Yes	No	Preeclampsia, cephalopelvic, disproportion	33 + 5	Caesarean section	No
Haase *et al.* [4]	21	Haemodialysis	Yes	Yes	Premature rupture of membranes, polyhydramnios	31 + 5	Vaginal	Yes (3 days)
Ramappa and Pyatt [5]	Not known	Haemodialysis	Yes	No	Stillbirth, pregnancy-associated cardiomyopathy causing cardiac failure postnatally	25	Vaginal	NA
Chuang *et al.* [6]	25	Transplant	No	No	None	Not known	Vaginal	No
Lindsay *et al.* [7]	31	Haemodialysis, previous failed transplant	Unknown	No	Intra-uterine growth restriction, infantile death (severe bronchopulmonary dysplasia)	24 + 2	Caesarean section	Yes (113 days)

RRT, renal replacement therapy; UTI, urinary tract infection.

DOI: 10.1002/jimd.12529

ORIGINAL ARTICLE

JIMD SSIEM WILEY

Pregnancy in cystinosis patients with chronic kidney disease: A European case series

Aude Servais[1] | Mirian C. H. Janssen[2] | Hannah Blakey[3] | Marcella Greco[4] | Sandrine Lemoine[5] | Paloma L. Martin-Moreno[6] | David Game[7] | Elena Levtchenko[8] | Graham Lipkin[3] | on behalf of the Metabolic Nephropathy Workgroup of the European Reference Network for Rare Kidney Diseases (ERKNet) and the ERA working groups on inherited kidney diseases (WGIKD)

JIMD 2022

TABLE 1 Pre-pregnancy maternal characteristics

N pregnancies	19
Maternal age (years)	28.5 (21–36)
Age at cystinosis diagnosis (years)	1.4 (0.5–4.0)
Height (cm)	150.5 (122.0–159.0)
Weight (kg)	53.4 (30.0–60.0)
Diabetes mellitus	2 (10.5%)
Hypertension	12 (63.2%)
Pre-pregnancy CKD stage	
1–3	0
4	1 (5.3%)
5	18 (94.7%)
Renal replacement modality for CKD 5	
Hemodialysis	1 (5.6%)
Kidney transplant	17 (94.4%)
Pre-pregnancy serum creatinine (μmol/L)	121 (53–329)
Pre-pregnancy eGFR (ml/min/1.73 m^2)	50 (23–111)
Pre-pregnancy urine protein/creatinine ratio (mg/mmol)	7 (0–61)
Cysteamine stopped?	
Pre-pregnancy	7 (36.8%)
On confirmation of pregnancy	11 (57.9%)
Later in pregnancy	1 (5.3%), at 5 weeks
Continued through pregnancy	0

MATERNAL OUTCOMES

High incidence of Pre-eclampsia

1 in 2

Live Birth rate after early pregnancy High 87%

Outcome	$n = 19$ pregnancies
Live birth	13 (68.4%)
Pregnancy failure	
Spontaneous early miscarriage	3 (15.8%)
Ectopic pregnancy	1 (5.3%)
Early pre-eclampsia (21 weeks)	1 (5.3%)
Pre-term with neonatal death	1 (5.3%)
Pre-eclampsia	7/15 (46.7%)
Gestational diabetes	2/15 (13.3%)
Induction of labor	14/15 (93.3%)
Serum creatinine 6 months postpartum (μmol/L) 1 patient with stage 4 CKD pre-pregnancy progressed to ESRD post-pregnancy	129 (66–400)
eGFR 6 months postpartum (ml/min)	43.0 (11.6–114.0)

PREGNANCY OUTCOMES

Outcome of babies born to women who stopped cysteamine on diagnosis of pregnancy equivalent to those stopped before

JIMD 2022

Live births	**13 (68.4%)**
Gestational age (weeks)	34 (24–37)
Birth weight (g)	2175 (620–3374)
Requirement for neonatal intensive care unit	5 (38.5%)
Mode of feeding	
Breast	2 (15.4%)
Bottle	11 (84.6%)
Age of infant at last follow-up (years)	3.9 (0.5–35.0)

Note: Median (range), N, number (percentage).

CYSTEAMINE IN PREGNANCY

- Fetotoxic at high dose in rats
- 1 human pregnancy reported on oral cysteamine
  - Baby born at 31 weeks
  - Healthy at 3 month follow up

- Recommend stopping on confirmation of pregnancy and restarting after delivery

- Breastfeeding?

Haase, J Nephrol (2006). Brodin-Sartorius, Kidney Int (2012)

PATIENT 1

- Planned induction of labour at 37 weeks
- Delivered healthy baby girl weighing 3203g by C-section
- Restarted Cysteamine after delivery
- Bottle fed

- Further successful pregnancy in 2018
- Delivered healthy baby girl 3374g at 37 weeks by C-section

PATIENT 2

- 33 year old female
- Renal history:
  - Deceased donor transplant aged 15
  - Pre-pregnancy eGFR 43, creatinine 125, ACR 3.6
  - Normotensive (BP 115/74)
- Extra-renal complications:
  - Hypothyroidism
  - Corneal crystal deposition
  - Restrictive lung defect

PATIENT 2 – PREGNANCIES 1-5

- Obstetric history (Pregnancies 1-4):
  - 4 previous first trimester miscarriages.
  - No structural cause
  - Borderline positive for lupus anticoagulant.
- Pregnancy 5:
  - Ectopic pregnancy at 7 weeks' gestation Rx Laparoscopic salpingectomy.

PATIENT 2 – PREGNANCY 6

- Medication changes:
  - Cysteamine stopped. Aspirin and Enoxaparin started
- Declining renal function:
  - Gradual rise in creatinine from 25 weeks' without proteinuria or hypertension.
  - Tacrolimus levels therapeutic, mild transplant hydronephrosis on USS.
  - Creatinine peak of 260 at 29 weeks' → admitted.
- Delivery:
  - Emergency Caesarean section at 29^{+5} weeks' (fetal distress on CTG, and maternal respiratory compromise).
  - Delivered a baby girl weighing 1207g, requiring 8-week hospital admission. Managed for postpartum preeclampsia.
- 2 months postpartum: eGFR 40, creatinine 133.

BREAST FEEDING AND CYSTEAMINE (PROCYSBI)
PROBABLY SAFE; DISCUSSION

Table 1. Breastmilk cysteamine concentration relative to dose of delayed-release cysteamine bitartrate at steady state

Time postdose (h)	Breastmilk cysteamine concentration (mg/l)
0	0.12
2	0.76
4	1.87
6	0.51

Kidney International Reports (2022) **7**, 1716–1719

Total 24h exposure of baby to cysteamine
From breast milk = 0.54mg

Kidney Int Rep (2022) 7, 1716–1719;
https://doi.org/10.1016/j.ekir.2022.05.013ª 2022

KEY POINTS

- Women with cystinosis are fertile
- Reported outcomes are good.
- High rate of complications: PE and early delivery
- Renal/Obstetric Pre-pregnancy counselling is key!
  - Discussion around timing of stopping cysteamine (and mycophenolate)
- Aspirin 75mg from first trimester: reduces risk of PET
- Regular review throughout pregnancy in renal antenatal clinic
- Breast feeding is likely to be safe.


Baby joy for triple transplant patient