

# **Fertility, Reproduction, Educational and Developmental Attainments in offspring: the FREDA study**

Dr Hannah Beckwith

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Kings College London

# Background

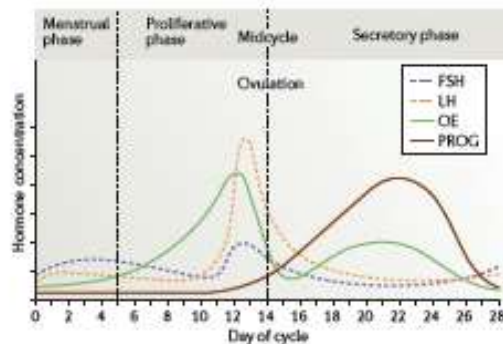
- We are interested in the relationship between reproductive health and kidney function



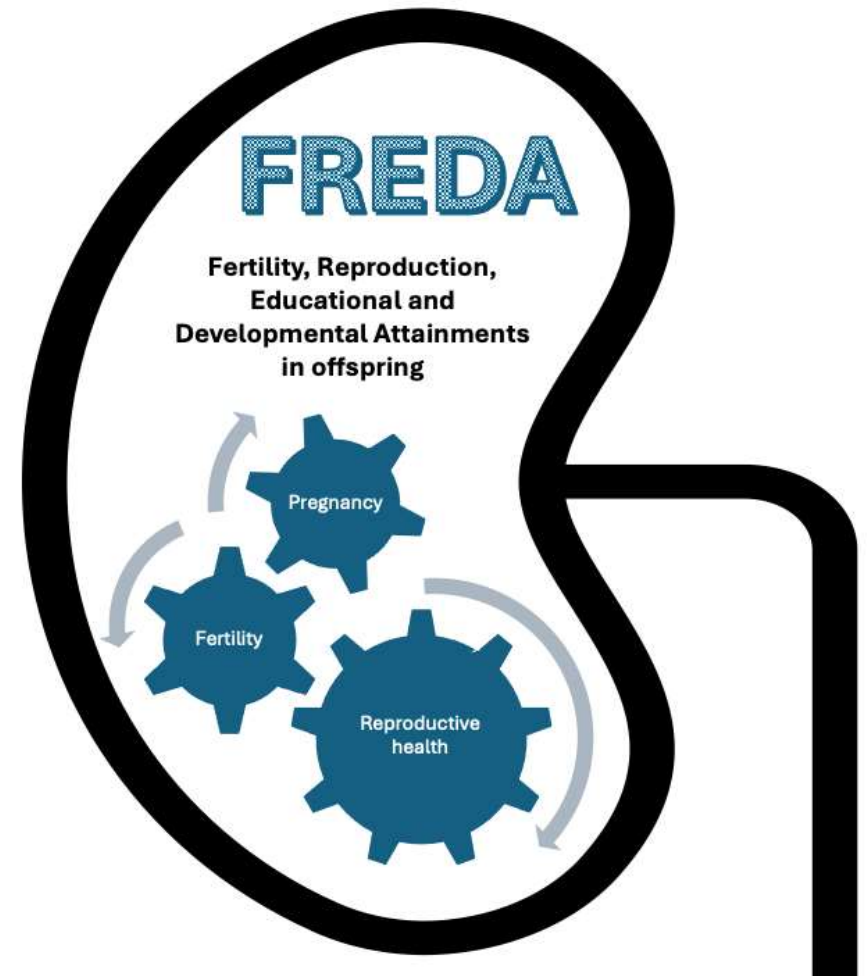
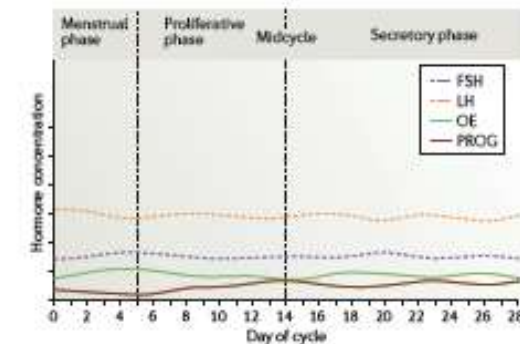
# Background

- We are interested in the relationship between reproductive health and kidney function
- We know kidney function affects hormone levels

a Physiological menstrual cycle

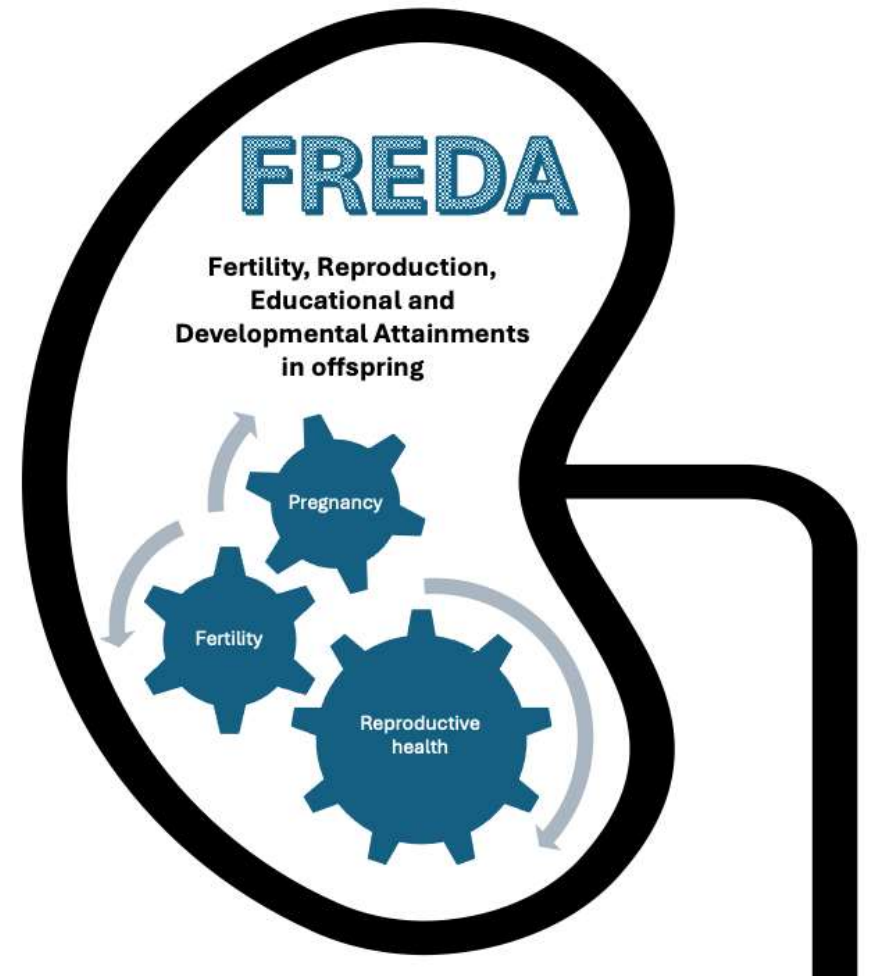


b Menstrual cycle in end-stage CKD



# Background

- We are interested in the relationship between reproductive health and kidney function
- We know kidney function affects hormone levels
- And kidney disease can affect fertility



# Background

- We are interested in the relationship between reproductive health and kidney function
- We know kidney function affects hormone levels
- And kidney disease can affect fertility
- But very little is known about the effects of menopause and HRT on kidney disease



# Menopause

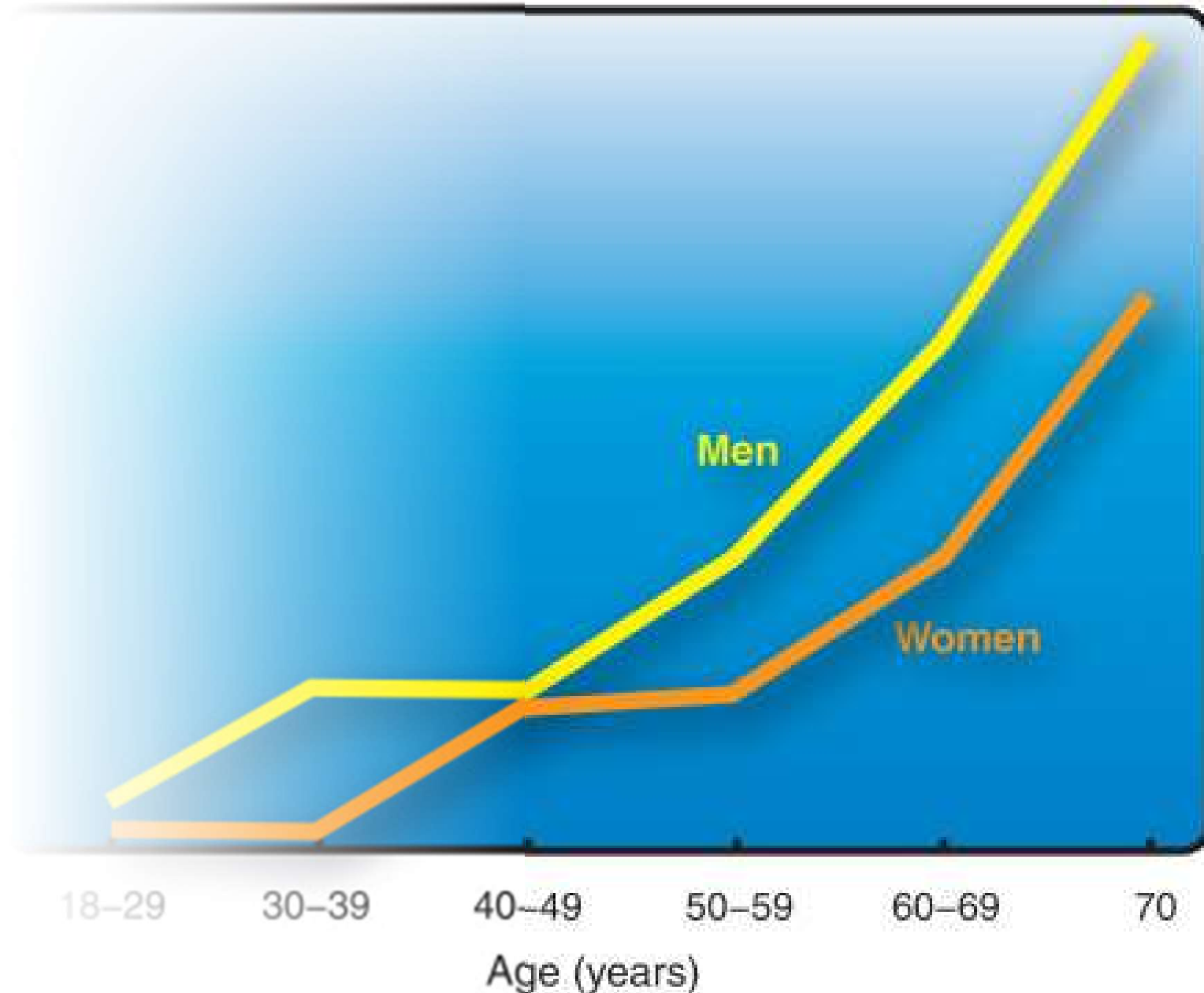
- The absence of periods for 12 months **and** an increase in FSH levels



# Menopause

- Until menopause, women appear to have slower progression of kidney disease compared to men
- After menopause, this protective factor is lost

Iseku, 2008



# Menopause

- The absence of periods for 12 months and an increase in FSH levels
  - Until menopause, women appear to have slower progression of kidney disease compared to men
  - After menopause, this protective factor is lost
- **Earlier menopause in CKD?**



# Menopause

- The absence of periods for 12 months and an increase in FSH levels
  - Until menopause, women appear to have slower progression of kidney disease compared to men
  - After menopause, this protective factor is lost
- Earlier menopause in CKD?
- Levels of estradiol drop by 80% in the menopause
  - Effect of replacing hormones unclear

# Data on HRT and kidney function is hugely conflicting

original article

<http://www.kidney-international.org>

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## Oral estrogen therapy in postmenopausal women is associated with loss of kidney function

Sofia B. Ahmed<sup>1,2</sup>, Bruce F. Culleton<sup>1,2</sup>, Marcello Tonelli<sup>2,3</sup>, Scott W. Klarenbach<sup>2,3</sup>, Jennifer M. MacRae<sup>1,2</sup>, Jianguo Zhang<sup>1,2</sup> and Brenda R. Hemmelgarn<sup>1,2</sup>, for the Alberta Kidney Disease Network

<sup>1</sup>Department of Medicine, University of Calgary, Calgary, Alberta, Canada; <sup>2</sup>Alberta Kidney Disease Network, Calgary, Alberta, Canada and <sup>3</sup>Department of Medicine, University of Alberta, Edmonton, Alberta, Canada



British Journal of Obstetrics and Gynaecology  
August 2000, Vol 107, pp. 1017–1021

## Postmenopausal hormone replacement improves proteinuria and impaired creatinine clearance in type 2 diabetes mellitus and hypertension

\*Bela Szekacs Associate Professor, †Zoltan Vajo Consultant, \*Szabolcs Varbiro Research Fellow, \*Reka Kakucs Research Fellow, †Lajos Vaslaki Consultant, \*Nandor Acs Assistant Professor, \*Istvan Mucsi Assistant Professor, †Eliot A. Brinton Associate Professor

\*Department of Medicine, Semmelweis University, Budapest, Hungary; †City Hospital Sopron, Hungary; ‡Section of Endocrinology, Veterans Affairs Medical Centre, Phoenix, Arizona, USA

**Objective** To determine whether hormone replacement therapy can reverse established renal microvascular damage in type 2 diabetes and hypertension.

**Design** Prospective, single centre clinical trial.

**Setting** Outpatient clinics.

**Participants** Sixteen diabetic and hypertensive postmenopausal women (age 47–57 years)

**Methods** Administration of a cyclic combination of oestradiol and norgestrel orally for 3.5 monthly cycles.

**Results** Comparing the baseline values, mean (SD) 24-hour urine protein excretion was reduced from 0.452 g (0.039) to 0.370 g (0.047) ( $P < 0.01$ ) and creatinine clearance was increased from 1.68 mL/sec (0.11) to 1.77 mL/sec (0.08) ( $P < 0.05$ ). Fasting plasma glucose also improved from 6.92 mmol/L (0.47) to 6.51 mmol/L (0.28) ( $P < 0.05$ ), as did serum total cholesterol from 7.26 mmol/L (0.28) to 6.65 mmol/L (0.14) ( $P < 0.05$ ). Blood pressure did not change significantly. Univariate linear regression analysis showed no significant correlation between the individual changes in blood pressure, fasting plasma glucose or serum cholesterol and the individual changes in proteinuria or creatinine clearance.

**Conclusions** This study shows that hormone replacement therapy may reduce proteinuria, and even improve creatinine clearance, in diabetic and hypertensive postmenopausal women. These effects are additive to nephroprotective therapy, and the mechanisms appear unrelated to conventional risk factors for vascular complications, such as high blood pressure, elevated plasma glucose or serum cholesterol.

# As are studies looking at HRT and kidney protein leak

## The Relationship Between Albuminuria and Hormone Therapy in Postmenopausal Women

Mamta Agarwal, MD, MS, Vani Selvan, MD, Barry I. Freedman, MD, Yongmei Liu, MD, PhD, and Lynne E. Wagenknecht, DrPH

- **Background:** Elevated urinary albumin excretion and hormone therapy (HT) are associated with increased risk for cardiovascular events. We assessed the relationship between albuminuria and the use of hormonal preparations in postmenopausal women. **Methods:** Data from the Insulin Resistance Atherosclerosis Study were obtained at baseline and 5-year follow-up for analysis. The generalized estimating equation procedure accounting for repeated measures was used for this analysis. HT was the main predictor variable, and  $\log_e$  urine albumin-creatinine ratio (ACR) was the main outcome variable. **Results:** Four hundred ninety-one menopausal women were included in the analysis, 36% ( $n = 179$ ) of whom received HT (either oral estrogen, progesterone, or combination therapy). At baseline, abnormal albuminuria ( $ACR \geq 25$  mg/g) was present in 11% of women on HT and 17% not on HT ( $P = 0.02$ ). After adjusting for demographics, the presence of diabetes and hypertension, and kidney function, HT was associated with a 19% reduction in ACR ( $P = 0.008$ ) and an odds ratio of 0.67 (95% confidence interval, 0.43 to 1.01;  $P = 0.06$ ) for the presence of abnormal albuminuria. Other predictors of abnormal albuminuria included diabetes, blood pressure, and triglyceride level. **Conclusion:** Results of this study suggest that HT is associated with a reduction in urinary albumin excretion in postmenopausal women. *Am J Kidney Dis* 45:1019-1025.

# As are studies looking at kidney protein leak

## HRT does not improve urinary albumin excretion in postmenopausal diabetic women

Patrick J. Manning\*, Wayne H.F. Sutherland, Anne R. Allum, Sylvia A. de Jong, Shirley D. Jones

*Departments of Medical and Surgical Sciences and Preventive and Social Medicine, Dunedin Hospital, University of Otago Medical School, PO Box 913, Dunedin, New Zealand*

Received 12 July 2002; received in revised form 21 October 2002; accepted 25 November 2002

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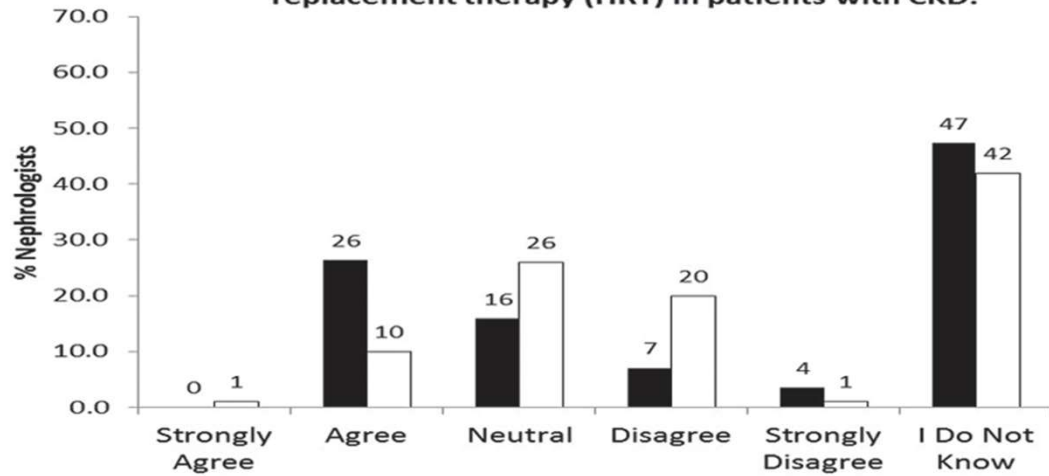
### Abstract

The effect of 6 months combined, continuous hormone replacement therapy (HRT) with conjugated equine oestrogen (0.625 mg) and medroxyprogesterone acetate (2.5 mg) on albumin/creatinine ratio (ACR) was determined in postmenopausal diabetic women in a randomised, controlled study. Mean (interquartile range) change in plasma ACR was not ( $P = 0.96$ ) different in women receiving HRT [2 (-11, 21) mg/g,  $n = 20$ ] compared with those randomised to placebo [2 (-1, 14) mg/g,  $n = 27$ ]. Also, the proportion of women with microalbuminuria did not change ( $P = 0.75$ ) during HRT (baseline, 0.45; end of study, 0.53). Furthermore, several risk factors for microalbuminuria including systolic blood pressure (SBP), fasting blood glucose, glycated haemoglobin (HbA1c) and adiposity did not vary significantly during HRT. These data suggest that 6 months HRT does not reverse microalbuminuria caused by prolonged hyperglycaemia and other risk factors that underlie leakage of albumin into the urine in postmenopausal women with type 2 diabetes.

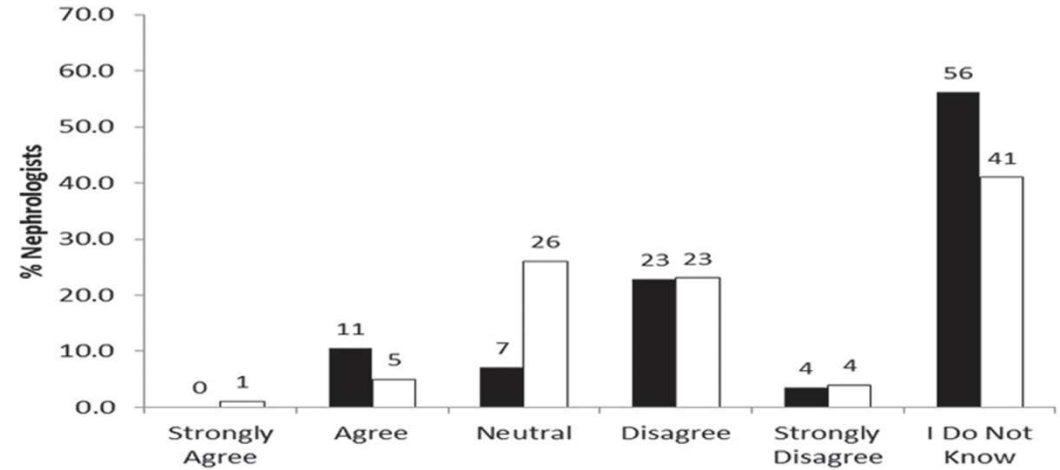
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# This uncertainty is reflected in clinical practice

**There is a role for postmenopausal hormone replacement therapy (HRT) in patients with CKD.**

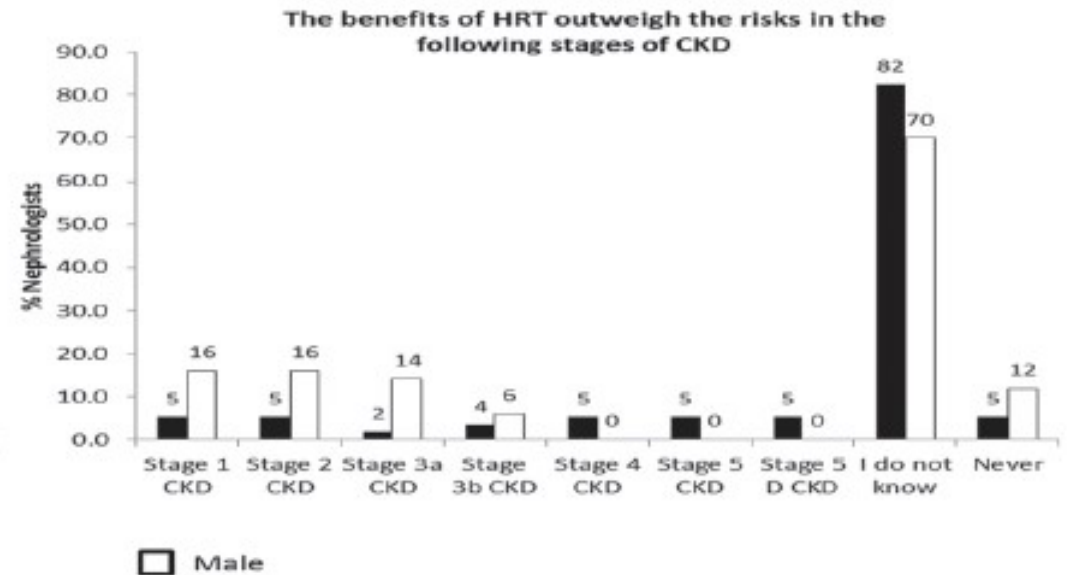
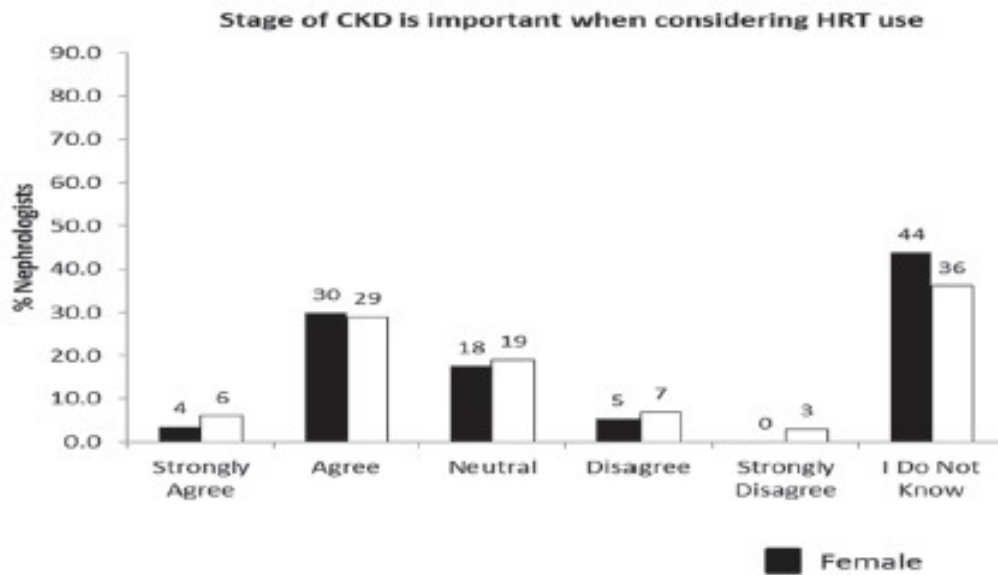


**The benefits of HRT far outweigh the risks in patients**



Ramesh, 2017

# This uncertainty is reflected in clinical practice



Ramesh, 2017



# It doesn't matter anyway

- Studies are old
- Largely irrelevant

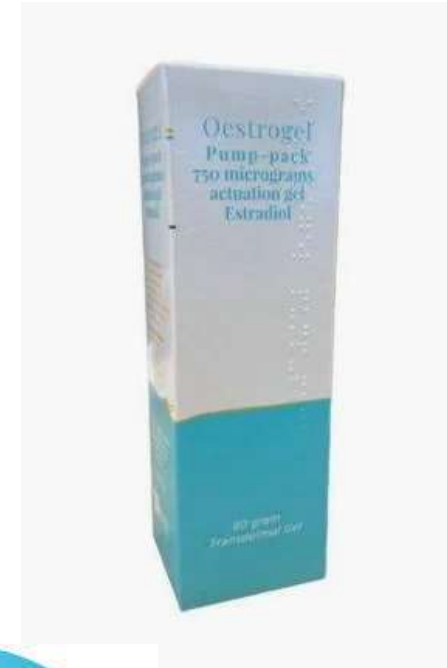
## Oral estrogen therapy in postmenopausal women is associated with loss of kidney function

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**I HAVE NO IDEA**



**WHAT I'M DOING**



Similarly, there is a lot we still don't know about pregnancy and kidney disease



*“Children of women with renal disease used to be born dangerously or not at all (not at all if their doctors had their way)”*

*(The Lancet, 1975)*

*“Planning for pregnancy allows women with CKD to get pregnant at the right time, while on the right medications and in the best possible health”*

*(UKKA, 2024).*

# What we do know

- Kidney disease affects about 1 in 30 (3%) of those of reproductive age

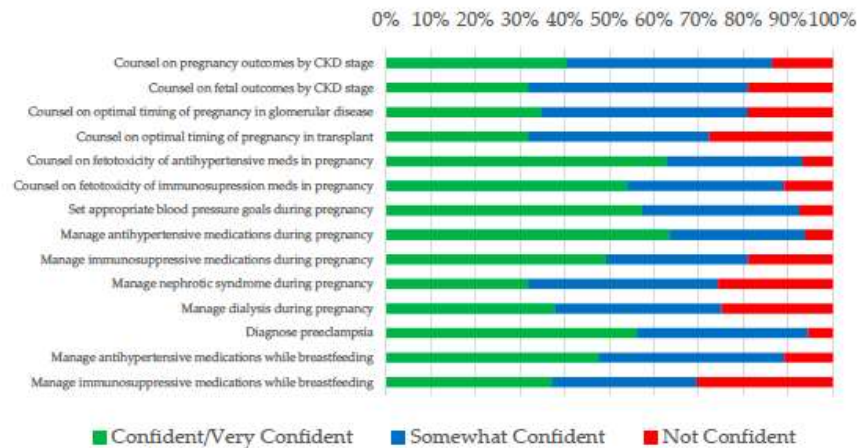
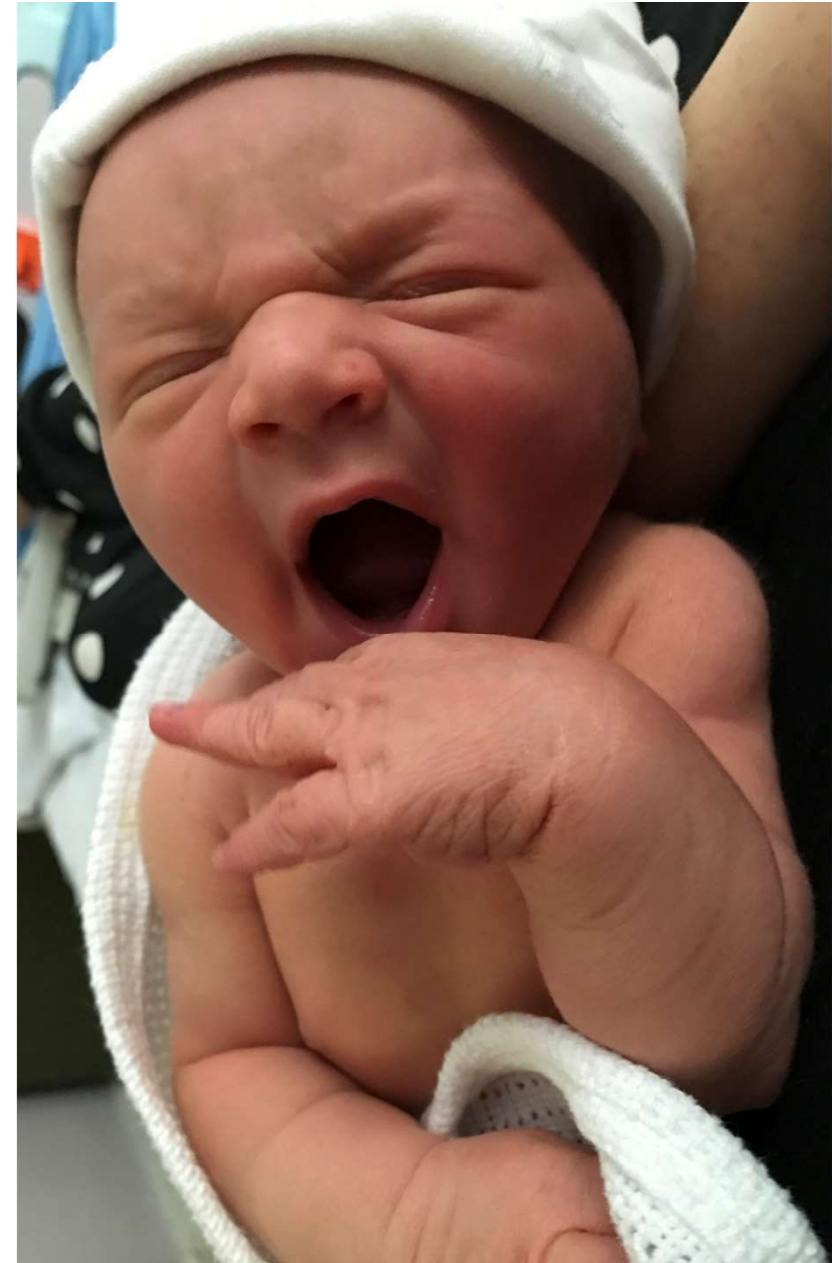


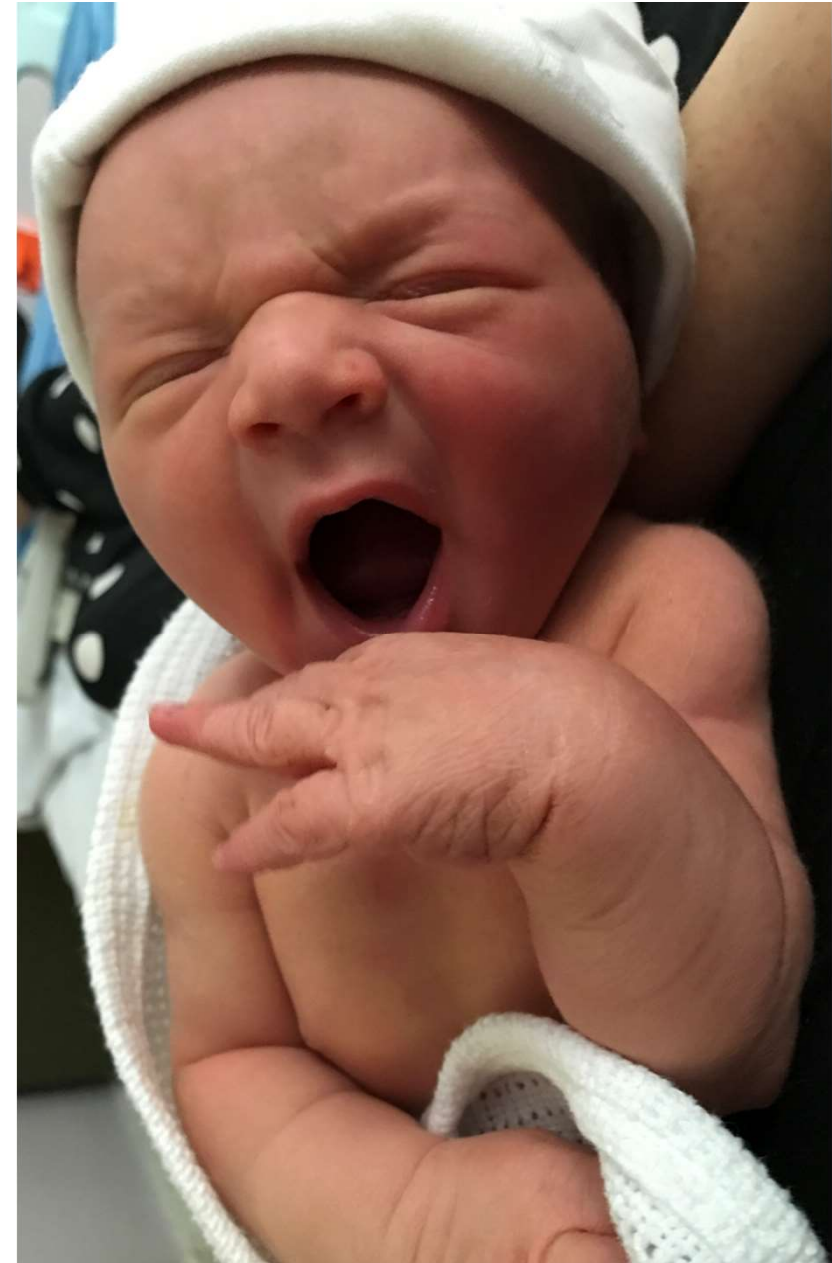
Figure 5. Nephrologists' confidence managing pregnancy-related topics.

Hendren, 2019



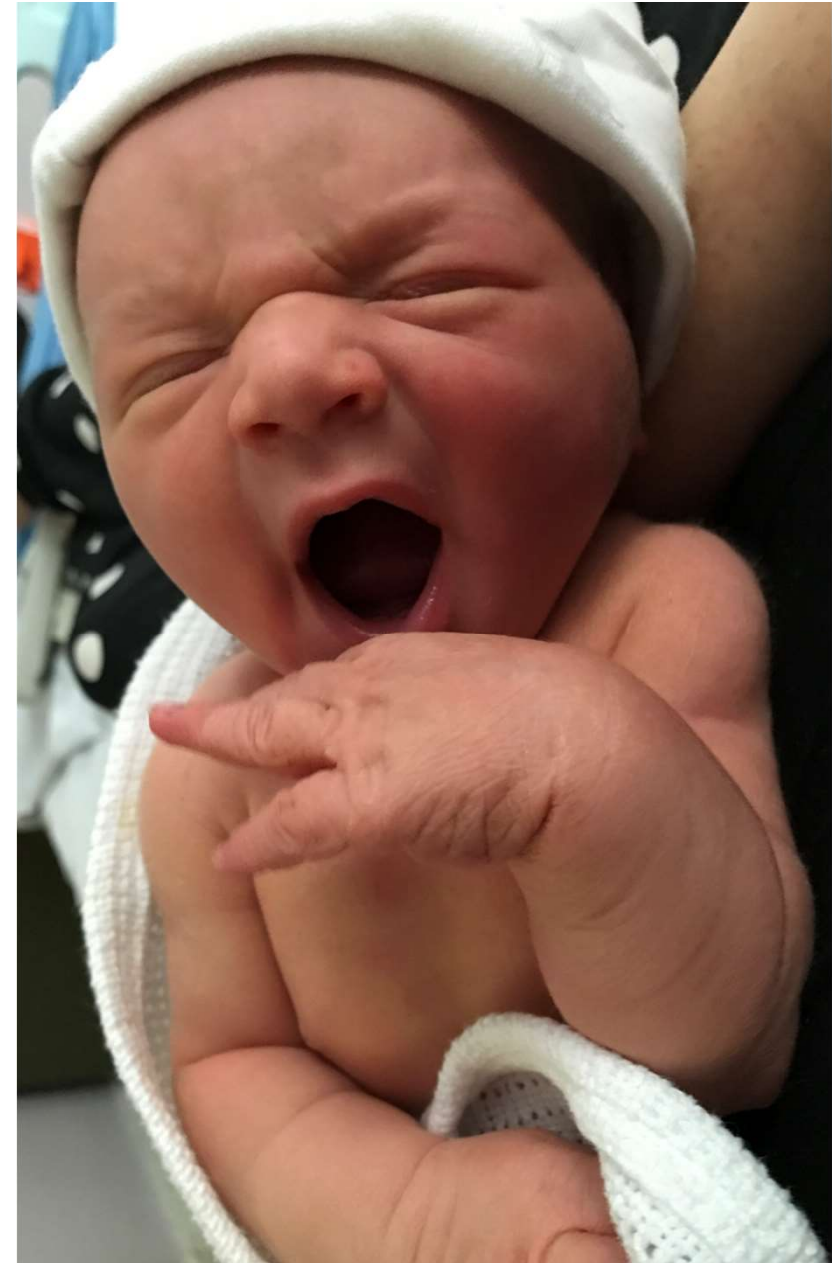
# What we do know

- Kidney disease affects about 1 in 30 (3%) of those of reproductive age
- Most pregnancies are successful and healthy babies are born



# What we do know

- Kidney disease affects about 1 in 30 (3%) of those of reproductive age
- Most pregnancies are successful and healthy babies are born
  - Increased chance of early delivery and smaller babies





# Existing literature:

- Pilot study of 24 children of CKD pregnancies and 33 controls
- “The children were **apparently healthy** but there was evidence in this small study of **significant antenatal and perinatal morbidity compared to controls**. Future larger multi-center studies are required to confirm these early findings.”

Pediatric Reports 2010; volume 2:e7

## Health outcomes of children born to mothers with chronic kidney disease: a pilot study

Indrani Banerjee,<sup>1</sup> Stephen Powis,<sup>2</sup> Mark Shevlin,<sup>3</sup> Jacqueline Barnes,<sup>4</sup> Audrey Soo,<sup>1</sup> Alastair G. Sutcliffe<sup>1</sup>

<sup>1</sup>General and Adolescent Paediatrics Unit, Institute of Child Health, University College London;

<sup>2</sup>Centre for Nephrology, University College London Medical School (Hampstead Campus);

<sup>3</sup>Psychology Research Institute, School of Psychology, University of Ulster;

<sup>4</sup>Institute for the Study of Children, Families and Social Issues, Birkbeck, University of London, UK

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### Abstract

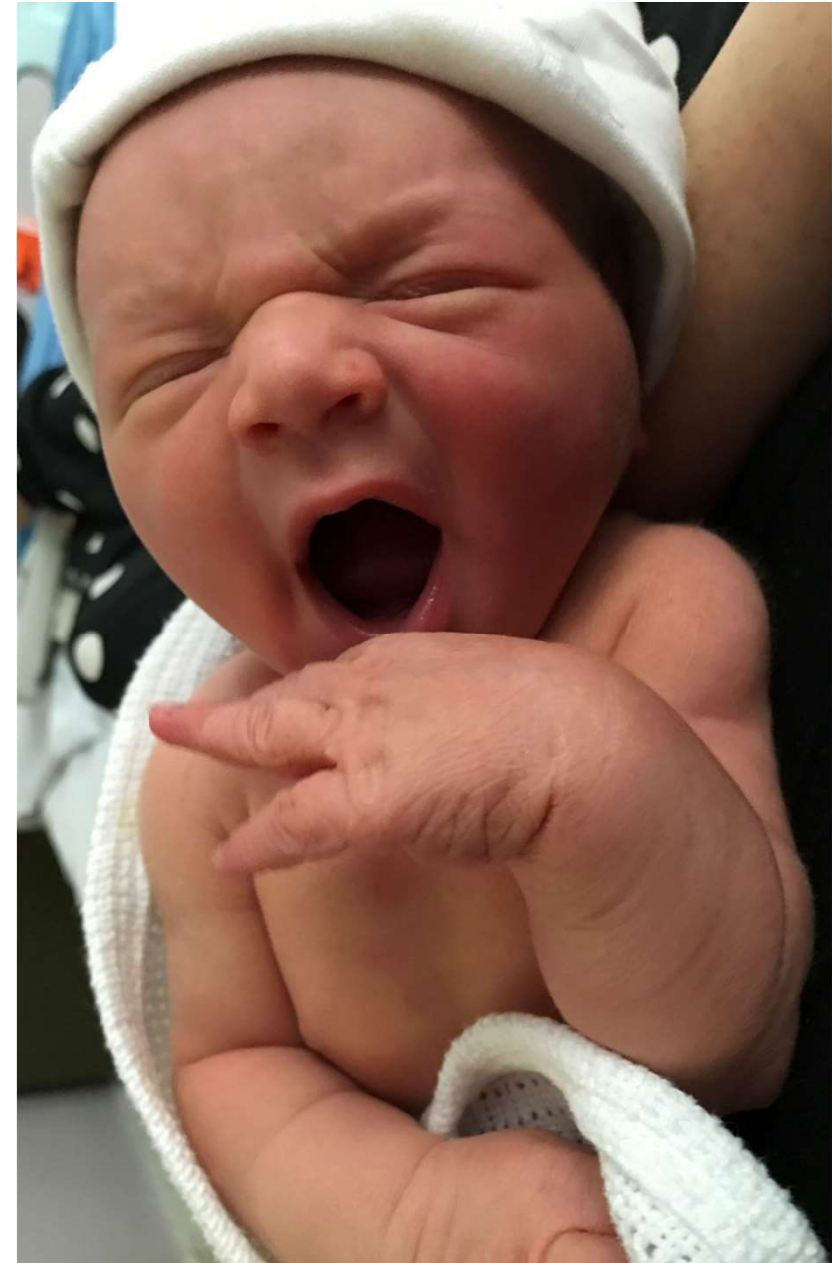
This study aimed to study the health of children born to mothers with chronic kidney disease. Twenty-four children born to mothers

women with renal disease used to be born dangerously or not at all (not at all if their doctors had their way<sup>1</sup>), reflecting an early view of the effect of kidney disease on pregnancy. In 1971, Confortini *et al.*<sup>2</sup> reported the first conception and successful delivery in a woman on maintenance hemodialysis. The first successful pregnancy following maternal renal transplantation was reported in 1963.<sup>3</sup> The donor and recipient were identical twin sisters and this child was 48-years old on March 10, 2006.<sup>4</sup> Subsequent progress in management of end-stage renal disease, most notably by means of renal transplantation, has resulted in many more women surviving to child bearing years. Such women were often discouraged from planning a family due to concerns about possible adverse effects on renal grafts and the potential offspring.<sup>5</sup> With advances in modern medical care, some are well enough to contemplate pregnancy without putting their health at significant risk.<sup>6,9</sup> However, no detailed developmental studies of their children has been performed.

It is well recognized that parents' physical illness can be detrimental to the well being of children (e.g. lower self esteem, higher levels of depression and poor academic attainment).<sup>10</sup> Similarly, mothers who are burdened with ill health and treatment face added challenges with parenting. Numerous potential

# What we do know

- Kidney disease affects about 1 in 30 (3%) of those of reproductive age
- Most pregnancies are successful and healthy babies are born
  - Increased chance of early delivery and smaller babies
  - **But what about the longer term?**



# Existing literature:

- Exploratory phone survey of 175 children of 133 women with kidney transplants on CsA
- *“This exploratory survey demonstrates the absence of developmental delay in 84% of offspring of female renal transplant recipients treated with CsA during pregnancy.”*



Transplantation Proceedings  
Volume 31, Issues 1–2, February–March 1999, Pages 241–242



Proceedings of the XVIIth World Congress of the Transplantation Society

## Developmental well-being in offspring of women receiving cyclosporine post-renal transplant ☆

C.W. Stanley <sup>a</sup>, R. Gottlieb <sup>a</sup>, R. Zager <sup>a</sup>, J. Eisenberg <sup>a</sup>, R. Richmond <sup>a</sup>, M.J. Moritz <sup>a</sup>, V.T. Armenti <sup>a</sup>

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[https://doi.org/10.1016/S0041-1345\(98\)01519-X](https://doi.org/10.1016/S0041-1345(98)01519-X)

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Successful pregnancy outcomes for female renal transplant recipients are common with no definite pattern of abnormality among their children, although the incidence of prematurity is high.<sup>1, 2, 3</sup>

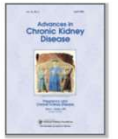
# Existing literature:

- Review article 2007
- ***“Unfortunately, very little information is available on the developmental outcome of children born to mothers with CKD, to those receiving dialysis, or to those with a functioning kidney transplant.”***



Advances in Chronic Kidney Disease

Volume 14, Issue 2, April 2007, Pages 199-205



Original article

## Outcome of Infants Born to Women with Chronic Kidney Disease

Douglas L. Blowey<sup>a, b</sup> ✉, Bradley A. Warady<sup>a</sup>

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<https://doi.org/10.1053/j.ackd.2007.01.014>

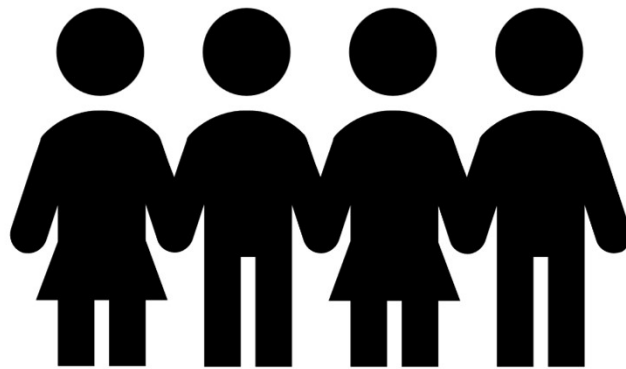
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Pregnancy in women with chronic kidney disease is not uncommon and is not without risk to the mother and child. This article reviews the literature on the outcome of infants from pregnancies in women with chronic kidney disease (CKD), including those receiving dialysis and those living with a functional kidney

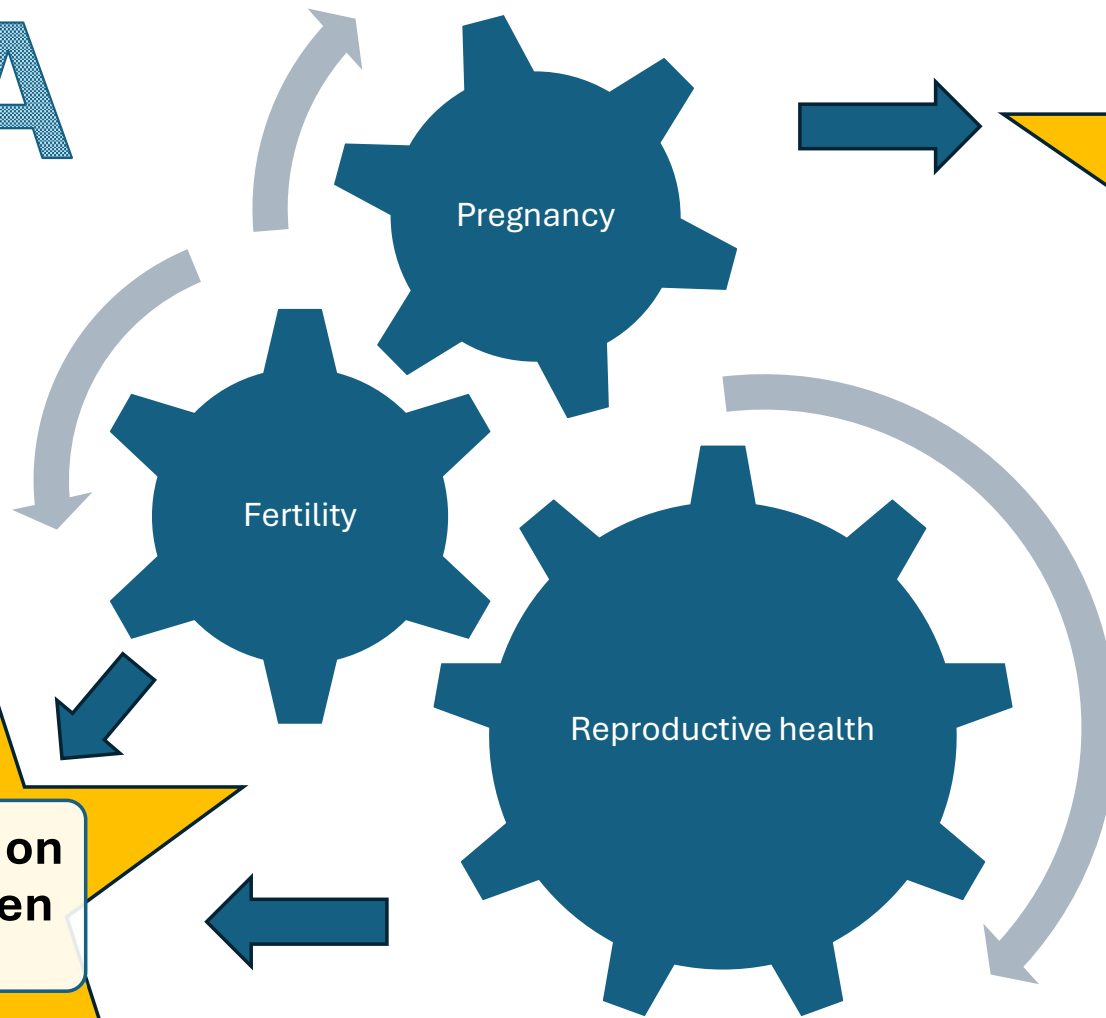
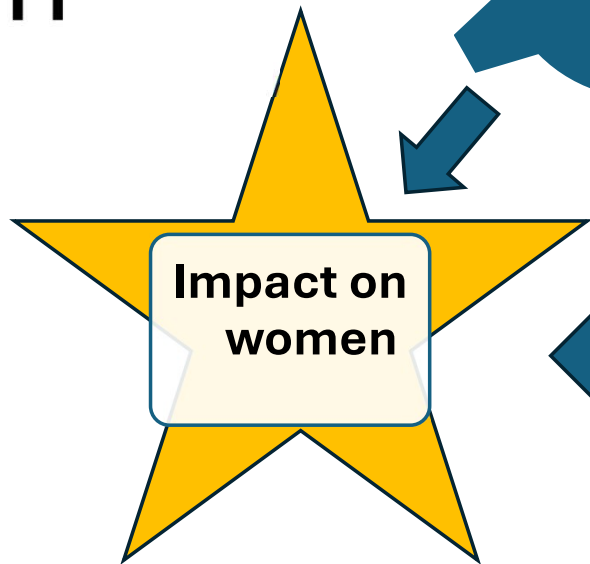
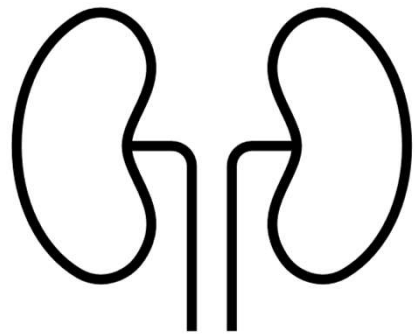


# Longer term outcomes?

- Very little knowledge about the longer-term health and development of children after pregnancy with kidney disease
- The information we have suggests that these children do not have any extra health problems, but we need to get more information

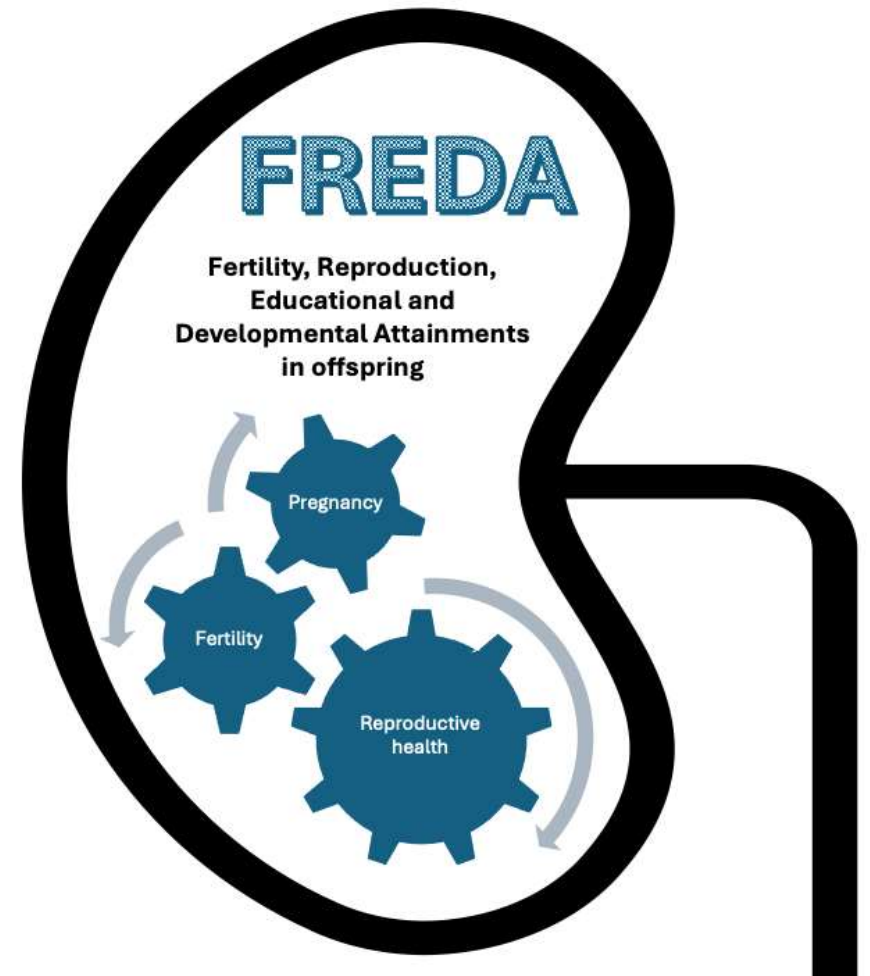


# FREDA



# What are we planning?

- Questionnaire study
- Members of RaDaR who
  - might have a biological child between the age of 2 and 25, and/or
  - may currently have periods or have had periods in the past
- Questionnaire will cover a wide area of women's health (periods, contraception, menopause) and pregnancies (including children)



# What are we hoping to achieve

- To better characterise the effects of CKD on periods and the menopause
- To identify if there is any signal of longer-term problems in children born to mums with kidney disease
  - If we pick up patterns, it will allow us to plan health checks to make sure they are picked up early.
- To improve the lived experience of women with kidney disease



**COMING**

**SOON**

**STAY TUNED!**

Are there any other areas of Women's Health you would like future research to focus on?



<https://forms.office.com/e/pGPz4iVTYx>