Reproductive health and pregnancy in women with chronic kidney disease

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REPRODUCTIVE HEALTH AND PREGNANCY IN WOMEN WITH CHRONIC KIDNEY DISEASE

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PRESENTATIONS AND PUBLICATIONS ARISING FROM THIS WORK

Original Research

Wiles K, Bramham K, Vais A et al. Pre-pregnancy counselling for women with chronic kidney disease: a retrospective analysis of nine years' experience. BMC Nephrology 16:28, 2015

Wiles K, Bramham K, Seed PT et al. Serum creatinine in pregnancy: a systematic review. Kidney International Reports 4(3): 408-419, 2019

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Wiles K, Bramham K, Seed PT et al. Diagnostic indicators of superimposed pre-eclampsia in women with CKD. Kidney International Reports 4:842-853, 2019

Submitted manuscripts

Wiles K, Webster P, Seed PT et al. The Impact of Chronic Kidney Disease Stages 3-5 on Pregnancy Outcomes.

Wiles K, Bramham K, Seed PT et al. Placental and novel biomarkers in the prediction of superimposed pre-eclampsia in women with chronic kidney disease.

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K. Wiles, E. Wayman, C. Nelson-Piercy, et al. Anti-Müllerian hormone in women with chronic kidney disease, American Society of Nephrology, San Diego, California, 2018 [poster].

K. Wiles, K. Bramham, C. Gill et al. Diagnostic biomarkers in women with chronic kidney disease and superimposed pre-eclampsia. International Society for the Study of Hypertension in Pregnancy, Berlin, 2017 [poster].

K. Bramham, A. Gautam, K. Wiles, et al. Ovarian Reserve and fertility hormone profiles in women with CKD. American Society of Nephrology, Chicago, 2016 [poster].

STATEMENT OF MY OWN WORK

I wrote the study protocol, prepared the participant information documentation and submitted the ethics committee application for the Pregnancy Adaptations In Renal disease Study (PAIRS). I designed the electronic database on the MedSciNet platform. I was Trial Manager for PAIRS, writing the necessary paperwork for ethical approval at all four study sites. I recruited participants at all four sites, with assistance from research midwives at three sites. I completed the collection of outcome data, with administrative support available at two of the four sites. I reviewed all clinical data in order to make a final diagnosis in 232 women with CKD in pregnancy and 164 pregnant women without CKD.

I designed the systematic review. Kate Bramham and I performed the necessary database searches and data extraction in duplicate. Patient data from the women with CKD stages 3-5 at four of six study sites was provided by Dr. Philip Webster, who assisted with data cleaning, analysis and manuscript preparation (chapter 5).

I performed the following analyses on all biological samples: active renin, hyaluronan, intercellular adhesion molecule, vascular cell adhesion molecule, P-selectin, E-selectin, complement factors (C3a, C5a, complement factor H, C5b-9), kidney injury molecule-1 and urinary lipocalin-2. Dr Lesia Kurlak performed quantification of angiotensinogen. Quantification of placental growth factor, soluble fms-like tyrosine kinase sFlt-1 and anti-Müllerian hormone assays were completed on automated platforms.

Statistical analysis for chapter 3, 5, 6 and 7 was completed jointly with Paul Seed.

All the chapters are my own work, with figures taken from other published work arising from this thesis, or with references provided.

I have written all of the manuscripts included in this thesis (Chapters 3, 4, 5, 6 and 7) and edited all revisions following feedback from co-authors. I have addressed reviewers' comments from the manuscripts submitted for publication (Chapters 3, 4, 5, 6 and 7).

I designed the search terms for the Pregnancy and Renal Disease Guideline, coordinated the national consensus survey, contributed to and edited all content.

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To all the participants in this research. Thank you for agreeing to take part. I hope that this project is able to improve the experience of women with CKD planning and undertaking pregnancy; if not for those that completed their pregnancy whilst this study was being undertaken, then for the women like you who walk in your footsteps, and all the children to come.

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ABBREVIATIONS LIST

AC	Afro-Caribbean
ACEi	angiotensin converting enzyme inhibitor
ACR	albumin:creatinine ratio
ADPKD	autosomal dominant polycystic kidney disease
AER	albumin excretion rate
aHUS	atypical haemolytic uraemic syndrome
AKI	acute kidney injury
ALT	serum alanine transferase
Ang-(1-7)	angiotensin-(1-7)
AST	serum aspartate transferase
AMH	anti-Müllerian hormone
AST	serum aspartate transferase
AT1	angiotensin II type 1
AT1-AA	agonistic autoantibody to angiotensin II type 1 receptor
aOR	adjusted odds ratio
AUC	area under the curve
AUROC	area under the receiver operating curve
BP	blood pressure
BMI	body mass index
BUN	blood urea nitrogen
BSR	British Society of Rheumatology
C	cross-sectional
CAKUT	congenital anomalies of the kidney and urinary tract
CFH	complement factor H
CHT	chronic hypertension
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	chronic kidney disease epidemiology collaboration

CKD-MBD	chronic kidney disease mineral and bone disorder
CNI	calcineurin inhibitor
CNS	central nervous system
Cr	serum creatinine
CrCl	creatinine clearance
CV	cardiovascular
dBP	diastolic blood pressure
DM	diabetic mellitus/diabetic nephropathy
dsDNA	double stranded deoxyribonucleic acid (DNA)
eGFR	estimated glomerular filtration rate
EPC	endothelial progenitor cells
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FGR	fetal growth restriction
Flt-1	fms-like tyrosine kinase 1
FSH	follicle-stimulating hormone
GFR	glomerular filtration rate
GnRH	gonadotropin-releasing hormone
GnRH	gonadotropin-releasing hormone agonists
GROW	gestation-related optimal weight
HD	haemodialysis
HELLP	haemolysis, elevated liver enzymes, low platelet syndrome
HIF	hypoxia-inducible factor
HIV	human immunodeficiency virus
HUS	haemolytic uraemic syndrome
ICAM	intercellular adhesion molecule
ICD	international classification of disease
IUD	intra-uterine device
IQR	interquartile range
IV	intravenous

IVIg	intravenous immunoglobulin
KDIGO	Kidney Disease: Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
kg	kilogram
KIM-1	kidney injury molecule-1
/L	per litre
L	longitudinal
LH	luteinising hormone
LHRH	luteinising hormone releasing hormone
LMWH	low molecular weight heparin
LRR	laboratory reference range
m	metre
MBRRACE	Mothers and Babies: Reducing Risk through Audit and Confidential Enquiries
MDRD	modification of diet in renal disease
Med	Mediterranean
MEOWS	modified early obstetric warning system
MMF	mycophenolate mofetil
NA	not available
NGAL	neutrophil gelatinase-associated lipocalin
NICE	National Institute of Health and Care Excellence
NNU	neonatal unit
NP	normal pregnancy
NTPR	National Transplantation Pregnancy Registry
OE	oestrogen
OR	odds ratio
PAI-1	plasminogen activator inhibitor-1
PAIRS	Pregnancy Adaptations In Renal disease Study
PCR	protein:creatinine ratio
PD	peritoneal dialysis
PlGF	placental growth factor

Plts	platelets
PROG	progesterone
RBF	renal blood flow
RAAS	renin angiotensin aldosterone system
RAS	renin angiotensin system
RCOG	Royal College of Obstetricians and Gynaecologists
ROC	receiver operating characteristic
RR	relative risk
RRT	renal replacement therapy
sBP	systolic blood pressure
sFlt-1	soluble fms-like tyrosine kinase 1
SGA	small for gestational age
SE	standard error
SLE	systemic lupus erythematosus
SSA	Sjögren syndrome type A antigen (Ro)
SSB	Sjögren syndrome type B antigen (La)
SPE	superimposed pre-eclampsia
T1	first trimester
T2	second trimester
T3	third trimester
TMA	thrombotic microangiopathy
TPMT	Thiopurine-S-methyltransferase
uACR	urinary albumin:creatinine ratio
ULN	upper limit of normal
uPCR	urinary protein:creatinine ratio
UTI	urinary tract infection
VCAM	vascular cell adhesion molecule
VEGF	vascular endothelial growth factor
VTE	venous thromboembolism
WE	white European

ABSTRACT

The aims of my PhD were to understand physiological and pathophysiological factors that influence outcomes in reproductive health and pregnancy for women with chronic kidney disease (CKD) before, during and after pregnancy.

Standard assessment of renal function in pregnancy is by measurement of serum creatinine concentrations yet normal gestational ranges had not been established. Serum anti-Müllerian hormone (AMH) is a biomarker of ovarian reserve, but the clinical interpretation of AMH in women with CKD is ambiguous and had not been examined in early stage CKD. There are limited contemporary data available to inform counselling and surveillance of women with moderate and severe kidney disease (CKD stages 3-5) undertaking pregnancy, with outcomes restricted to small and historical cohorts. Mechanistic links between superimposed pre-eclampsia and CKD include endothelial dysfunction, renin-angiotensin system activation, complement activation and tubular injury, which offer the potential for novel diagnostic indicators. Placental growth factor (PlGF) concentrations in isolation and in combination with soluble fms-like tyrosine kinase-1 (sFlt-1:PlGF) have been recently implemented as diagnostic adjuncts in women with suspected pre-eclampsia, yet data on the utility of these markers in women with CKD are limited. Given that the diagnosis of superimposed pre-eclampsia in women with CKD is complicated by the presence of hypertension and proteinuria due to kidney disease, an evaluation of the utility of PlGF, sFlt-1, and other novel biomarkers in the prediction of superimposed pre-eclampsia in women with CKD was warranted.

Methods used in this thesis included a systematic review and meta-analysis of 4421 serum creatinine concentrations in pregnancy, a prospective cohort study of AMH concentrations in 163 reproductive-age women with CKD, a retrospective cohort study of obstetric and renal outcomes in 178 pregnancies in women with pre-pregnancy CKD stages 3-5, a nested case-control study of novel biomarkers in the diagnosis of

superimposed pre-eclampsia in women with CKD; and a prospective multicentre study of 232 pregnancies in women with CKD, examining the accuracy of placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) in predicting the need for delivery due superimposed pre-eclampsia.

The upper limits of the reference interval for serum creatinine in pregnancy were 85%, 80% and 86% of the upper limit outside of pregnancy in sequential trimesters. This means that for an upper reference limit of 90µmol/L for serum creatinine in non-pregnant females, values greater than 76µmol/L in the first trimester, 72µmol/L in the second trimester, and 77µmol/L in the third trimester should be considered abnormal in pregnancy, and warrant investigation to exclude a diagnosis of CKD or acute kidney injury in pregnancy.

Serum AMH concentrations in women with CKD aged less than 35 years were lower than in women without CKD, across all CKD stages. Women with CKD aged 20-24 years had comparable serum AMH concentrations to women aged 35 years and over without CKD.

Pregnancies in women with pre-pregnancy CKD stages 3-5 were complicated by preterm delivery, low birthweight and loss of maternal renal function. Chronic hypertension was the strongest predictor of delivery before 34 weeks' gestation, with additional risk if the gestational fall in serum creatinine was less than 10% of pre-pregnancy values. Pre- or early pregnancy proteinuria was the strongest predictor of birthweight below the 10^{th} centile. There was a step-decline in renal function in relation to pregnancy in most women with pre-pregnancy CKD stages 3-5, equivalent to between 1.7 and 4.9 years of background renal disease depending on pre-pregnancy CKD stage and rate of decline in kidney function prior to pregnancy. There was no evidence that renal transplantation conferred additional risk in women with pre-pregnancy CKD stages 3-5.

Superimposed pre-eclampsia affected one third of women with CKD. Although plasma PlGF concentrations were lower in women with CKD who developed superimposed pre-eclampsia, mean concentrations did not fall below 100pg/ml. Plasma PlGF (Quidel) concentrations below 150pg/ml had the highest sensitivity and negative predictive value for the prediction of delivery due to superimposed pre-eclampsia in women with CKD. High plasma hyaluronan and VCAM concentrations discriminated both pre-eclampsia and superimposed pre-eclampsia from uncomplicated pregnancy, supporting existing pathogenic theories that pre-eclampsia is a disease of endothelial dysfunction. However, predictive performances for hyaluronan and VCAM were lower than for plasma PlGF concentrations. Quantification of PlGF, sFlt-1 and sFlt-1:PlGF ratio in serum did not usefully predict the need for delivery due to superimposed pre-eclampsia in women with CKD. There was no demonstrable diagnostic role for factors derived from the renin-angiotensin and complement systems.

This thesis was a multifaceted study of a heterogeneous disease. It addressed knowledge gaps for women with CKD across the spectrum of reproductive health including disease definition, pre-pregnancy assessment, diagnosis and prediction of superimposed pre-eclampsia in pregnancy, and long-term renal outcomes. It also formed the basis for the first national guideline for women with kidney disease in pregnancy in the UK.

1 INTRODUCTION

1.1 Chronic kidney disease in the non-pregnant population

1.1.1 Definitions of chronic kidney disease in the non-pregnant population

Chronic Kidney Disease (CKD) is an umbrella term encompassing a heterogeneous group of diseases with abnormal kidney structure or function, with implications for the health of the individual (Levin and Stevens, 2014). The classification of CKD is based upon glomerular filtration rate (GFR) and/or an abnormal level of albumin measured in urine (Table 1.1 and 1.2). Chronicity of kidney disease is defined as persistence of abnormal glomerular filtration and/or pathological urinary sediment for more than three months.

Glomerular filtration is the process by which an ultrafiltrate is produced from blood as it passes through the glomerular capillaries. It is the best measure of kidney function in both health and disease (Levey et al., 2003). Although the kidney has metabolic and endocrine roles in addition to excretory function, glomerular filtration predominates, as most other kidney functions fall in parallel with a decline in GFR (KDIGO, 2013).

The inclusion of aetiology and albuminuria in CKD disease definitions aims to improve upon older classifications, which were based on GFR in isolation (National Kidney Foundation, 2002). This multidimensional definition of CKD reminds clinicians of the importance of both the underlying pathological process and the associated risk conferred by proteinuria. However, the language of CKD 'staging' into five categories of increasingly severe kidney disease persists. In CKD stages 3-5, the loss of glomerular filtration is clinically significant and kidney disease is classified as moderate to severe. Renal replacement therapies including dialysis and transplantation may be indicated for those with CKD stage 5.

Table 1.1 Glomerular filtration rate (GFR) categories in CKD (Levin and Stevens, 2014).
[a]=only CKD if other evidence of kidney damage e.g. albuminuria, haematuria, structural kidney disorder

GFR category	GFR (ml/min/1.73m^2)	Renal function terminology	Stage (National Kidney Foundation, 2002).
G1[a]	≥90	Normal or high	1
G2[a]	60-89	Mildly decreased	2
G3a	45-59	Mildly to moderately decreased	3a
G3b	30-44	Moderately to severely decreased	3b
G4	15-29	Severely decreased	4
G5	<15	Renal failure	5

Table 1.2 Albuminuria categories in CKD (Levin and Stevens, 2014).

Albuminuria category	Albumin excretion rate (AER) mg/24h	Albumin-to-creatinine ratio (ACR)		Albuminuria terminology
		mg/mmol	mg/g	
A1	<30	<3	<30	Normal to mildly increased
A2	30-300	3-30	30-300	Moderately increased
A3	>300	>30	>300	Severely increased

Disease definitions are based on a 'true' GFR. However, GFR cannot be measured directly in humans and is derived from the clearance of endogenous or exogenous solutes that are eliminated by glomerular filtration (Levey and Inker, 2017). Clinical practice utilises estimates of GFR based on serum concentrations of creatinine. Serum creatinine in isolation is an insensitive surrogate marker of GFR because it is influenced by both GFR and non-GFR determinants including muscle mass, dietary intake, tubular secretion and extra-renal elimination by the gastrointestinal tract (KDIGO, 2013). The influence of such non-GFR determinants means that there is a wide range of possible glomerular filtration rates for a single creatinine concentration. For example, a serum creatinine of 1.5mg/dL (132µmol/L) can correspond to a measured GFR anywhere from 20 to 90ml/min/1.73m^2 (Levey and Inker, 2017). The inaccuracy of isolated serum creatinine measurement has led to the generation of formulae, which estimate GFR from serum creatinine concentrations using a combination of age, gender and

ethnicity as surrogates for unmeasured, non-GFR determinants. Routine reporting of kidney function in terms of estimated glomerular filtration rate (eGFR) was introduced in the UK in 2006 using the Modification of Diet in Renal Disease (MDRD) formula. The MDRD formula was generated from a cohort of 1628 patients with kidney disease including 645 women and 197 patients of black ethnicity (Levey et al., 1999). This was superseded by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, developed from a cohort of 5504 participants both with and without kidney disease, including 2391 women. CKD-EPI was demonstrated to be more precise, less likely to underestimate GFR at higher values, and demonstrated better correlation with adverse outcomes (Matsushita et al., 2012). eGFR derived by CKD-EPI is recommended for the clinical assessment of kidney function by both the National Institute for Health and Care Excellence (NICE) (NICE, 2015a) and Kidney Disease: Improving Global Outcomes (KDIGO) (KDIGO, 2013).

The use of eGFR formulae for the diagnosis and staging of CKD requires an awareness of potential sources of error include extremes of body size and diet, and the concomitant use of drugs that modify either tubular secretion or non-renal clearance of creatinine (KDIGO, 2013). In addition, eGFR formulae require serum creatinine concentrations to be in a steady state of generation and excretion. This precludes their use in non-steady state conditions such as acute kidney injury and pregnancy (see section 1.2).

1.1.2 Epidemiology of chronic kidney disease in the non-pregnant population

The introduction of a common language for the diagnosis and classification of CKD has improved the understanding of CKD including prevalence, complications and implications for long-term health and resources (NICE, 2015a), as well as highlighting CKD as a global public health issue (Levey et al., 2007). A meta-analysis of 51 observational studies reporting gender-specific prevalence of CKD demonstrated a

higher prevalence of CKD in women (14.6%, 95% confidence interval (CI): 12.7-16.7%) compared to men (12.8%, 95% CI 10.8-11.9%), including a higher prevalence of more advanced kidney disease (CKD stages 3-5) in women (12.1%, 95% CI 10.6-13.8%) compared to men (8.1%, 95% CI: 6.3-10.2%) (Hill et al., 2016). The prevalence of CKD in the UK is estimated to be 3.5-6% in men and 7-10.6% in women based on national survey data (Roth et al., 2013), electronic health records (Stevens et al., 2007) and primary care records that contain at least two consecutive eGFR measurements below 60ml/min/1.73m^2 (Kearns et al., 2013). Although these UK data are not stratified by age, a meta-analysis of 94 observational studies from varied health and socioeconomic settings worldwide, showed that that the mean prevalence of all stage CKD and CKD stages 3-5 were 13.7% (10.8-16.6%) and 8.9% (9.9%-14.1%) in those aged 30-39, and 12.0% (9.9-14.1%) and 8.7% (6.9%-10.5%) in those aged 40-49; compared to global mean prevalence of 13.4% (11.7-15.1) and 10.6% (9.2-12.2%) respectively (Hill et al., 2016).

In 2015, the Global Burden of Disease Study estimated that 5-10 million people die annually from kidney disease (Kassenbaum et al., 2016; Wang et al., 2016). In high-income countries, where provision of renal replacement therapy is available, the mortality associated with CKD is largely due to an associated increase in cardiovascular disease, which is estimated to be 57% higher in those with a GFR below 60ml/min/1.73m^2 and 63% higher in those with albuminuria, compared to those without CKD (Perkovic et al., 2008; Di Angelantonio et al., 2007). Cancer incidence is also increased in CKD, with immunosuppressive therapy, cystic kidney disease, and immune dysregulation due to uraemia hypothesised to be causative (Webster et al., 2017a).

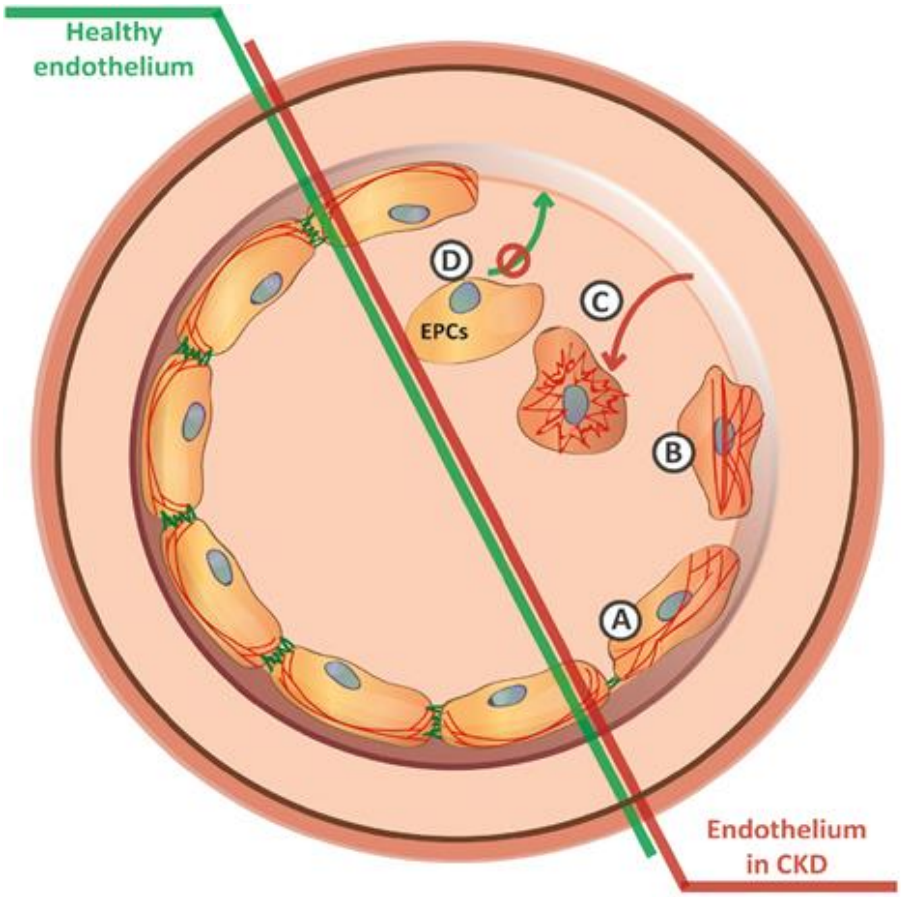
1.1.3 Pathophysiology of chronic kidney disease

CKD includes diverse disease pathways that irreversibly alter the function and/or structure of the kidney. These pathways include diabetes, hypertension, vascular

disease, glomerulonephritis, and genetic and congenital conditions affecting the kidney and urinary tract; though the aetiology of CKD is uncertain in the majority of individuals with CKD worldwide (Levin et al., 2017). Heterogeneity of aetiology, race, ethnicity, socioeconomic status and comorbidity contribute to the complexity of CKD, and knowledge of mechanisms that cause progressive loss of kidney function and its associated complications remain insufficient (Levin et al., 2017).

The excess of cardiovascular disease in CKD is not fully explained by traditional risk factors including hypertension, diabetes and hyperlipidaemia (Muntner et al., 2002). Endothelial dysfunction, which is implicated in the pathogenesis of cardiovascular disease (Endemann and Schiffrin, 2004), has emerged as the likely mechanism of accelerated vascular disease in CKD (Fliser et al., 2011; Vila Cuenca et al., 2019) and CKD progression (Webster et al., 2017a). The vascular endothelium forms the inner lining of the circulatory system and is responsible for normal structural integrity, and the regulation of an appropriate barrier between circulation and vasculature. Endothelial dysfunction in CKD, including abnormal cell-cell and cell-matrix adhesion (Carbó et al., 2008; Maciel et al., 2018), reduced vasodilatory capacity (Yilmaz et al., 2011; Kopel et al., 2017), decreased nitric oxide production (Baylis, 2008), and a reduced capacity for endothelial repair (Jie et al., 2010), has been demonstrated in experimental cohorts and in-vitro studies (Figure 1.1). Endothelial dysfunction is hypothesised to be a shared pathological mechanism across different aetiologies of CKD resulting in podocyte loss, with pro-inflammatory responses contributing to mesangial proliferation and tubular damage. Over time, the unsuccessful healing of these lesions results in glomerulosclerosis, tubular atrophy, and kidney fibrosis, which are final common manifestations of CKD (Webster et al., 2017a).

Figure 1.1 Endothelial dysfunction in CKD: A=disruption of cell-matrix and cell-cell adhesion, B=rearrangement of the cellular cytoskeleton and reduced bioavailability of nitric oxide, C=contraction of endothelial cell with disassociation from the basement membrane, D=limited number of circulating endothelial progenitor cells (EPCs) lead to abnormal recovery. From (Vila Cuenca et al., 2019)



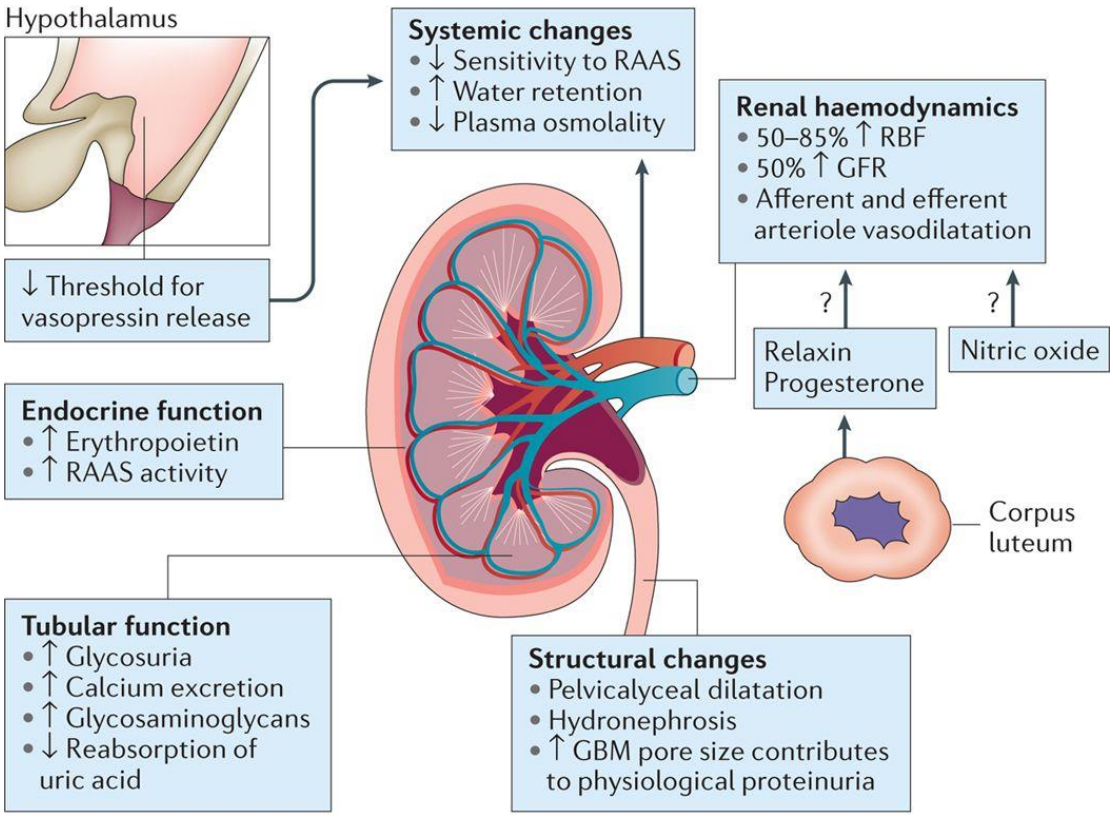
1.2 Chronic kidney disease in pregnancy

1.2.1 Kidney physiology in pregnancy

The physiological changes that occur during pregnancy include haemodynamic, tubular, endocrine, and structural alterations in the kidney (Figure 1.2) During pregnancy, renal blood flow increases by 50–85%, leading to an increment in glomerular filtration (Davison and Dunlop, 1980). This physiological hyperfiltration of pregnancy, mediated by vasodilatation of both afferent and efferent arterioles, occurs

in the absence of glomerular hypertension (Helal et al., 2012) and is therefore different from the pathological hyperfiltration associated with glomerular injury and CKD. Pregnancy and multiparity are therefore not associated with a decline in maternal kidney function in the absence of CKD. Experimental amino acid loading during pregnancy can further increase both renal blood flow and glomerular filtration, which suggests that renal filtration capacity is not maximised by pregnancy, and that additional capacity exists (Milne et al., 2002). Dextran clearance modelling suggests that a physiological increase in glomerular membrane pore size occurs in pregnancy, leading to gestational proteinuria in the absence of a change in hydrostatic force (Roberts et al., 1996; Milne et al., 2002). As haemodynamic changes to the renal tract are measurable from as early as 8 weeks' gestation, they are not thought to be mediated by the fetoplacental unit, which is still underdeveloped at this stage. Instead, the observed rise in glomerular filtration, which is evident in both the luteal phase of the menstrual cycle as well as pregnancy, may be mediated by relaxin, released by the corpus luteum (Conrad and Davison, 2014), acting via matrix metalloproteinase 2 and endothelin receptor type B (Jeyabalan et al., 2003). Both ovariectomy and administration of neutralizing relaxin antibodies impaired the renal adaptation to pregnancy in rats (Novak et al., 2001). However, other unknown factors, possibly progesterone and nitric oxide (Cadnapaphornchai et al., 2001), also have a role, as evidenced by physiological renal adaptation to assisted-conception pregnancies in which the corpus luteum is absent and relaxin is not detectable (Conrad and Baker, 2013).

Figure 1.2 Haemodynamic, tubular, and endocrine changes to the renal tract in pregnancy, with systemic effects mediated by changes to the renin-angiotensin axis and vasopressin. Relaxin, progesterone and nitric oxide are hypothesised mechanisms by which haemodynamic changes to the kidney occur. From (Wiles et al., 2018), adapted from (Williams and Davison, 2008). GFR=glomerular filtration rate, RBF=renal blood flow; RAAS=renin-angiotensin-aldosterone system.



During pregnancy, several changes occur that affect kidney tubular function. Glycosuria occurs due to an increase in filtration in conjunction with reduced tubular reabsorption (Davison and Dunlop, 1980). Although calcium excretion is increased, simultaneous rises in urinary glycoproteins are thought to protect the kidneys against the formation of renal calculi and nephrolithiasis (Gambaro et al., 1988; Butler et al., 2000). Furthermore, reabsorption of uric acid is reduced in normal pregnancy, resulting in increased renal excretion.

Other adaptations in pregnancy relate to the renal synthesis of, or renal response to hormones. Pregnancy is a state of physiological vasodilatation, with likely mediators

including progesterone, nitric oxide and prostaglandins; although recent research demonstrates that the magnitude of fall in blood pressure in pregnancy is less than traditionally assumed (Loerup et al., 2019; Green et al., 2020). Gestational vasodilatation occurs despite evidence of increased renal renin production and activation of the renin-angiotensin-aldosterone system, therefore suggesting that pregnancy is a state of relative renin-angiotensin resistance. By contrast, despite the hypertensive phenotype, the renin-angiotensin-aldosterone system is measurably supressed in patients with pre-eclampsia compared to normal pregnancy, suggesting an increased sensitivity in pre-eclampsia (see section 1.6.4.1). Vasopressin is an antidiuretic hormone released by the posterior pituitary gland, which stimulates water reabsorption in the kidney in response to an increase in osmolality or a reduction in extracellular fluid volume. Gestational arterial vasodilatation is thought to lead to non-osmotic stimulation of vasopressin, effectively lowering the osmotic threshold for vasopressin release, contributing to water retention and a reduction in plasma osmolality in pregnancy (Davison and Lindheimer, 1989).

1.2.2 Definitions of chronic kidney disease in pregnancy

The dynamic changes in renal blood flow and filtration fraction that occur with physiological renal adaptation to pregnancy lead to a sustained increase in glomerular filtration until term (Odutayo and Hladunewich, 2012) and a corresponding fall in serum creatinine concentrations. Hence, MDRD (Smith et al., 2008) and CKD-EPI (Alper et al., 2010) formulae underestimate GFR and are not valid for use in pregnancy. Caution should be taken when interpreting data from publications that use eGFR equations in pregnancy (Piccoli et al., 2015), which might underestimate pre-pregnancy CKD severity.

Cystatin C provides an alternative surrogate measure of GFR as it is freely filtered at the glomerulus. In pregnancy, synthesis of cystatin C is not thought to be affected by the utero-placental unit (Kristensen et al., 2007a; Kristensen et al., 2008). However,

serum concentrations of maternal cystatin C fail to correlate with other measures of GFR in pregnancy, including iohexol clearance (Strevens et al., 2002), serum creatinine (Bramham et al., 2009) and eGFR formulae (Larsson et al., 2010). This may be due to an increase in glomerular negative charge that reduces excretion of anionic cystatin C (Strevens et al., 2002).

Serum creatinine concentrations therefore remain the only standard, single-point assessment for kidney function in pregnancy, yet a normal range for serum creatinine in pregnancy has not been established. The upper limit (95^{th}-97.5^{th} centile) of creatinine concentration in healthy pregnancy varies between published cohorts. Published reference interval limits include values of 72µmol/L (Larsson et al., 2008), 80µmol/L (Abbassi-Ghanavati et al., 2009), 89µmol/L (Girling, 2000) and 95µmol/L (Lokitch, 1993). Such data have limited generalizability without correction for factors known to cause variance in serum creatinine including ethnicity, gestation, and different creatinine assay methods. The most widely cited study of trimester-specific creatinine concentrations includes only 29 healthy pregnant women (Lokitch, 1993). The largest contemporary data are from a retrospective, cross sectional, population study in Canada which demonstrated a 95^{th} centile value of 81µmol at the time of delivery in women with a least two measures of serum creatinine in pregnancy (Harel et al., 2019). Although women with known CKD, gestational hypertension and pre-eclampsia were excluded from these data, the indication for serum creatinine testing, which is not routine in pregnancy in Canada, was unknown, and details of ethnicity are not provided. Contemporaneous statements regarding creatinine concentrations in pregnancy are largely based on expert opinion including a 'normal' range of 0.4-0.8mg/dl (35-71µmol/L) (Fischer, 2007; Maynard and Thadhani, 2009), an 'average' creatinine in pregnancy of 53µmol/L (August, 2013), and a recommendation that serum creatinine concentrations greater than 75µmol/L should raise suspicion of kidney injury in pregnancy (Lightstone, 2015). The absence of a gestational reference interval for serum creatinine complicates the diagnosis of CKD when it presents for the

first time in pregnancy, a phenomenon that is estimated to occur in up to one-third of women with CKD in pregnancy (Piccoli et al., 2012).

1.2.3 Epidemiology of chronic kidney disease in pregnancy

In the absence of robust epidemiological data, CKD is estimated to affect 3% of pregnant women in high-income countries (Piccoli et al., 2010). This commonly cited statistic is supported by historical data from a population study undertaken between 1995 and 1997 that included 5655 singleton pregnancies in 3405 predominantly white (>97%) women. CKD defined by pre-pregnancy eGFR was evident in 3.3% of pregnancies, with 2.4% classified as CKD stage 1, 0.8% as CKD stage 2 and 0.1% as CKD stage 3. However albuminuria was quantified in only 15% of women and there was no assessment of disease progression prior to pregnancy, with measurement of eGFR taking place up to eight years prior to pregnancy (Munkhaugen et al., 2009). Population trends of rising maternal age and obesity in the intervening decades may mean that these data underestimate contemporary CKD prevalence in pregnancy, with ethnicity, socioeconomic status and comorbidities known to be associated with CKD also likely to contribute. In the absence of population screening for CKD, and with gestational changes in proteinuria and serum creatinine complicating the diagnosis of early stage CKD in pregnancy, robust prevalence data for CKD in pregnancy are lacking.

1.2.4 Fertility and chronic kidney disease

1.2.4.1 Pregnancy rates in women with chronic kidney disease

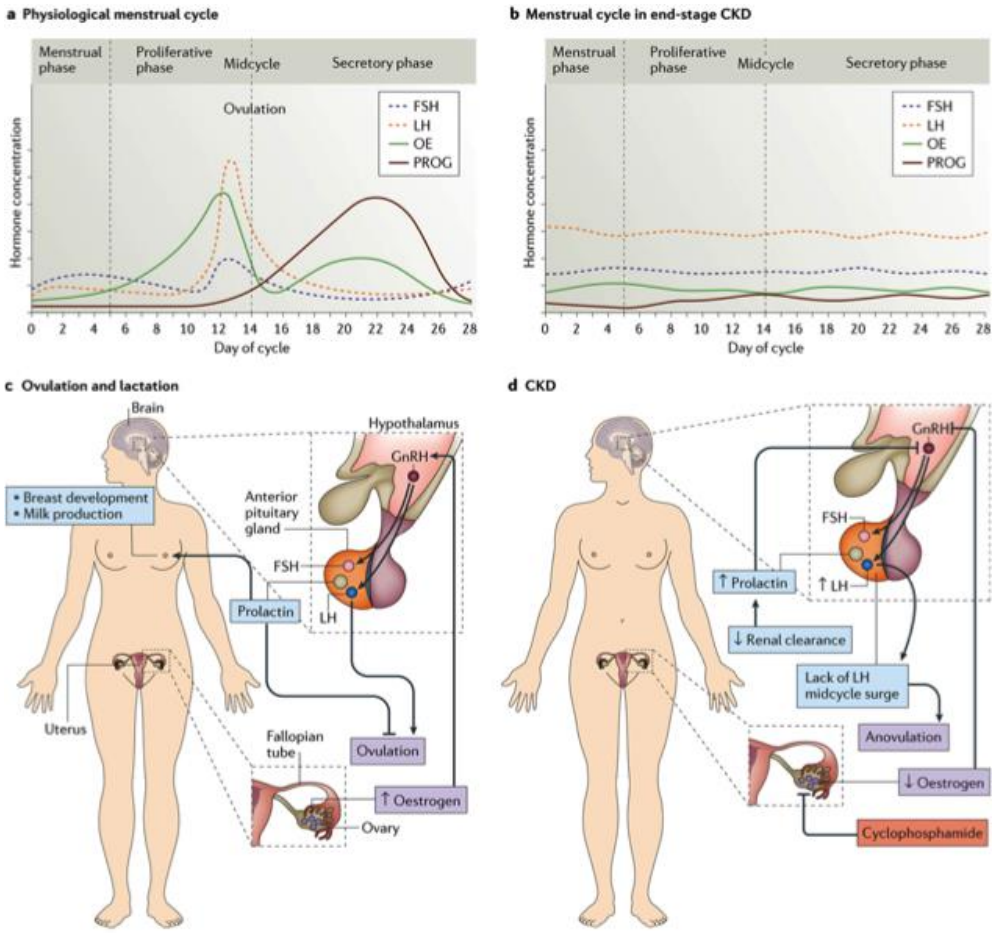
Fertility of women with CKD is difficult to precisely evaluate on a population level as pregnancy rates for women with CKD can only be measured when both CKD prevalence and the total number of pregnancies are known. In the absence of population screening for CKD, prevalence rates remain an approximation at best for most women of reproductive age. Pregnancy rates can, however, be calculated for

specific CKD populations. The UK Obstetric Surveillance System (Knight et al., 2005) identified all pregnancies in kidney transplant recipients (Jan 2007-Jan 2010) (Bramham et al., 2013) and in women on dialysis (Feb 2012-Dec 2013) in the UK. Combination of these data with national renal registry data indicated pregnancy rates of 7.6 per 1,000 patients per year for women with a functioning kidney transplant and 1.4 per 1,000 patients per year for women on dialysis, compared with national conception rates of 79.1–79.5 per 1,000 women per year (Office for National Statistics, 2015). Comparable data from Italy reveal a live-birth rate of 5.5–8.3 per 1,000 women with a functioning transplant and 0.7–1.1 per 1,000 women on dialysis, compared with 72.5 per 1,000 women nationally (Piccoli et al., 2014). Thus, pregnancy rates among kidney transplant recipients and dialysis patients compared to rates in the general population approximate to 1:10 and 1:100 respectively**.** Whether these data represent a true assessment of fertility or indicate the impact of CKD on the decision to conceive remains unknown.

1.2.4.2 Mechanistic effects of chronic kidney disease

In women with CKD, oligomenorrhoea progresses to amenorrhoea as GFR declines. However, the threshold GFR at which this becomes clinically significant for reproductive health is unknown due to a lack of data. In a cohort of 76 women on dialysis aged less than 55 years, 42% reported a regular menstrual cycle, compared with 75% prior to the start of dialysis (Holley et al., 1997). Small-cohort studies indicate that amenorrhoea is present in 37–59% of women on dialysis (Lim et al., 1980; Holley et al., 1997). Although the effect of CKD on menstruation and fertility is hypothesized to be proportional to the severity of kidney disease, the effect of mild kidney dysfunction remains unclear. However, the effects of CKD on the hypothalamic–pituitary–ovarian axis (Figure 1.3) are thought to be reversible, and normalisation of gonadotrophin (luteinising hormone (LH) and follicle-stimulating hormone (FSH)), prolactin and oestrogen concentrations are seen following kidney transplantation (Wang et al., 2010).

Figure 1.3 Menstrual cycle changes in chronic kidney disease (CKD) From (Wiles et al., 2018).
a | During the late follicular (mid-cycle) phase of the menstrual cycle, high concentrations of oestrogen (OE) confer positive feedback, sensitizing the pituitary to gonadotropin-releasing hormone (GnRH) from the hypothalamus. As a result, a surge of luteinizing hormone (LH) stimulates ovulation. Progesterone (PROG) is the secreted from the corpus luteum, preparing the endometrium for implantation. If implantation does not occur, PROG levels fall and menstruation follows.
b | Hypothesized hormone profile in CKD. Serum LH levels are increased, but the LH surge is absent so ovulation does not occur. Without development of a corpus luteum, PROG levels do not rise. OE levels are low throughout the cycle. The severity of CKD at which these changes occur remains unknown.
c | The anterior pituitary gland secretes follicle-stimulating hormone (FSH), LH and prolactin under hypothalamic control. FSH and LH act synergistically to regulate gonad function, including sex steroid production and gametogenesis in the ovary. Positive OE feedback leads to a surge in LH, which triggers ovulation. Prolactin production is increased only in pregnancy and lactation, when it stimulates breast development and lactation and inhibits ovulation.
d | In CKD, low OE levels confer negative feedback to the hypothalamus–pituitary axis. The absence of an LH surge leads to anovulation. Impaired renal clearance of prolactin causes inhibition of GnRH secretion from the hypothalamus. Cyclophosphamide is gonadotoxic and associated with age- and dose-dependent premature ovarian failure. The severity of CKD at which these changes occur remains unknown.



Although LH concentrations are increased in women receiving dialysis compared to levels in age-matched controls with regular menstrual cycles (Palmer and Clegg, 2017), concentrations do not vary in women on dialysis as they do in healthy individuals (Holley and Schmidt, 2013) (Figure 1.3). Dysfunctional oestrogen feedback to the hypothalamus and pituitary in patients with CKD results in an absence of pre-ovulatory surges in both oestrogen and LH, which leads to failure of ovulation (Lim et al., 1980, Palmer and Clegg, 2017). However, the stage of CKD associated with clinically significant dysfunctional LH release, and consequently suppression of ovulation, is unknown. In addition, renal clearance of prolactin in women on dialysis is reduced (Yavuz et al., 2005; Holley and Schmidt, 2013). Reduced prolactin excretion, in conjunction with autonomous secretion that appears resistant to stimulatory factors (for example, hypoglycaemia or arginine) and suppressive factors (dopamine) (Palmer and Clegg, 2017), also contributes to the suppression of ovulation.

1.2.4.3 Anti-Müllerian hormone

Anti-Müllerian hormone (AMH) is expressed in the granulosa cells of developing follicles. Serum concentrations of AMH therefore reflect the number of small antral follicles and are considered to be the best currently available biomarker of ovarian reserve (Broer et al., 2014). AMH is proposed to be clinically superior to other biomarkers because serum concentrations are unaffected by the growth of a dominant follicle in the latter half of the menstrual cycle meaning that there is lower intra- and inter cycle variability (van Disseldorp et al., 2010). AMH concentrations can be used to predict response to fertility treatment and individualise dosing for ovarian stimulation (NICE, 2013; Dewailly et al., 2014; Iliodromiti et al., 2015). There is also evolving evidence demonstrating the use of serum AMH concentrations in the assessment of iatrogenic gonadotoxicity and prediction of the female reproductive lifespan (Broer et al., 2014; Iwase et al., 2018), including women with systemic lupus erythematosus (Lawrenz et al., 2011) and vasculitis (Clowse et al., 2011).

The mechanistic effects of CKD upon fertility, voluntary childlessness, sexual dysfunction; and the use of cyclophosphamide, which is known to be gonadotoxic (Ioannidis et al., 2002; Boumpas et al., 1993); contribute to the complex clinical scenario in which women with CKD present for fertility advice and investigation. Yet the interpretation of AMH concentrations in women with CKD remains poorly understood. Published data regarding the assessment of ovarian reserve in women with CKD are limited to three small cohort studies (Sikora-Grabka et al., 2016; Stoumpos et al., 2018; Szydłowska et al., 2018), which report higher AMH concentrations in haemodialysis patients compared to other stages of CKD even though the molecular size of AMH (140kDa) is too large to be substantially influenced by dialytic clearance. These studies are limited by manual methods of AMH quantification and the absence of assay-specific normal ranges (Sikora-Grabka et al., 2016; Szydłowska et al., 2018). To date, no analysis of AMH according to stage of CKD has been published. Serum AMH concentrations in women with early stage CKD (eGFR >60ml/min/1.73m2) have never been described, yet these women represent the majority of women with CKD presenting for pregnancy advice in the UK (Wiles et al., 2015).

1.2.4.4 Contraception

Pregnancy planning for women with CKD is important because of the increased risk of adverse pregnancy outcomes and use of fetotoxic/teratogenic medications. Although CKD is associated with reduced fertility, unplanned pregnancies, which are associated with an increased risk of obstetric complications even in the absence of co-morbidity (Shah et al., 2011), occur at all CKD stages and in kidney transplant recipients. It is estimated that 33–50% of all pregnancies among kidney transplant recipients are unintended (Yildirim and Uslu, 2005; Bramham et al., 2013). Contraceptive counselling for women on dialysis is often lacking due to presumed infertility, yet intensified dialysis is associated with an increased conception rate compared with standard

dialysis regimens (Hladunewich and Schatell, 2016). Unfortunately, evidence suggests that few nephrologists discuss fertility issues and contraception with their patients. Although no published contemporary data exist, questionnaire data from a cohort of 76 women with CKD showed that despite 50% being sexually active, only 36% used contraception, and only 13% had discussed reproductive health issues with their nephrologist (Holley et al., 1997). Contraceptive counselling, and the provision of safe and effective contraception remain inadequate for many women with CKD. The risks and acceptability of different contraceptive methods must be balanced against the risks of an unplanned pregnancy. In addition, assessment of contraceptive efficacy should be based on 'typical use', rather than presuming 'perfect use', as discrepancies exist in the failure rate of some contraceptive methods (Trussell, 2011) (Table 1.3).

Table 1.3 Contraceptive options for women with chronic kidney disease.
[a]=Percentage of couples experiencing an unplanned pregnancy in the first year of use. Data from (Trussell, 2011)

Contraceptive	**Perfect use failure rate (%)[a]**	**Typical use failure rate (%)[a]**
Safe and effective methods for women with CKD		
Progesterone-only pill	0.3	9
Progesterone intra-uterine device	0.2	0.2
Progesterone-only subdermal implant	0.05	0.05
Female sterilization	0.5	0.5
Unsafe and/or ineffective methods for women with CKD		
Oestrogen-containing methods (pill, patch, ring)	0.3	9
Male condom	2	18
Female condom	5	21
No method	85	85

Progesterone-only contraceptives including the 'mini pill', intra-uterine device (IUD) or a subdermal implant are considered safe in women with CKD including patients on dialysis and transplant recipients. The ability of oral progesterone-only therapies to inhibit ovulation varies, depending on the synthetic progestogen used. One study showed that desogestrel conferred consistent inhibition of ovulation in 102 out of 103

women, with inhibition maintained even after 12-hour delays before re-dosing (Korver et al., 2005), with potential benefit in terms of typical use efficacy over other progestogens that require re-dosing within a 3-hour window each day. The IUD (Mirena®) and the subdermal implant (Nexplanon®) are progesterone-only, long-acting reversible contraceptives that provide effective contraception for 5 and 3 years respectively. Moreover, these contraceptives do not rely on daily adherence and have a typical-use failure rates comparable to that of sterilization (Trussell, 2011) (Table 1.3).

Theoretical concerns exist regarding the efficacy of IUDs in women with CKD taking immunosuppressive medications due to potential inhibition of the uterine inflammation that forms part of their contraceptive mechanism. However, the uterine milieu is predominantly populated by macrophages, whereas immunosuppression used in the management of immunological kidney disease and following transplantation acts predominantly via lymphocyte inhibition, suggesting that different pathways are involved. No evidence of an excess of intrauterine device failures following transplantation has been reported (Estes and Westhoff, 2007; Krajewski et al., 2013). Furthermore, concern regarding pelvic infection in the context of immunosuppression also seems to be unfounded, with no measurable correlation between infective complications and numbers of $CD4^+$ T-cells in women with HIV-mediated immunosuppression (Morrison et al., 2001). Similarly, a retrospective study of 484 months of progesterone-IUD use in 11 women with kidney transplants reported no cases of pelvic infection or unplanned pregnancy (Ramhendar and Byrne, 2012).

Oestrogen-containing contraceptives include the ‘combined pill’, the transdermal patch and the vaginal ring. All of these methods confer a risk of hypertension, venous thromboembolism (VTE), arterial thrombosis and cervical cancer (Brynhildsen, 2014). These risks are particularly relevant for women with CKD due to associations with chronic hypertension, vascular disease; coagulopathy in the context of anti-phospholipid antibodies and nephrotic syndrome; and neoplasia in the context of

immunosuppression. Oestrogen-containing methods are therefore likely to be contraindicated for many women with CKD, particularly given the availability of safer, more effective methods. Although condoms are effective against the transmission of HIV and sexually transmitted infection, barrier methods are unforgiving of imperfect use. Approximately 1 in 5 women conceive within a year (Trussell, 2011) meaning that barrier methods are not an effective long-term contraceptive option for women with CKD who do not wish to conceive. Emergency contraceptives in the UK do not contain oestrogen and can therefore be used safely in patients with CKD to prevent pregnancy within 72 (levonorgestrel) to 120 (ulipristal) hours of unprotected intercourse.

1.3 Pregnancy outcomes in women with CKD

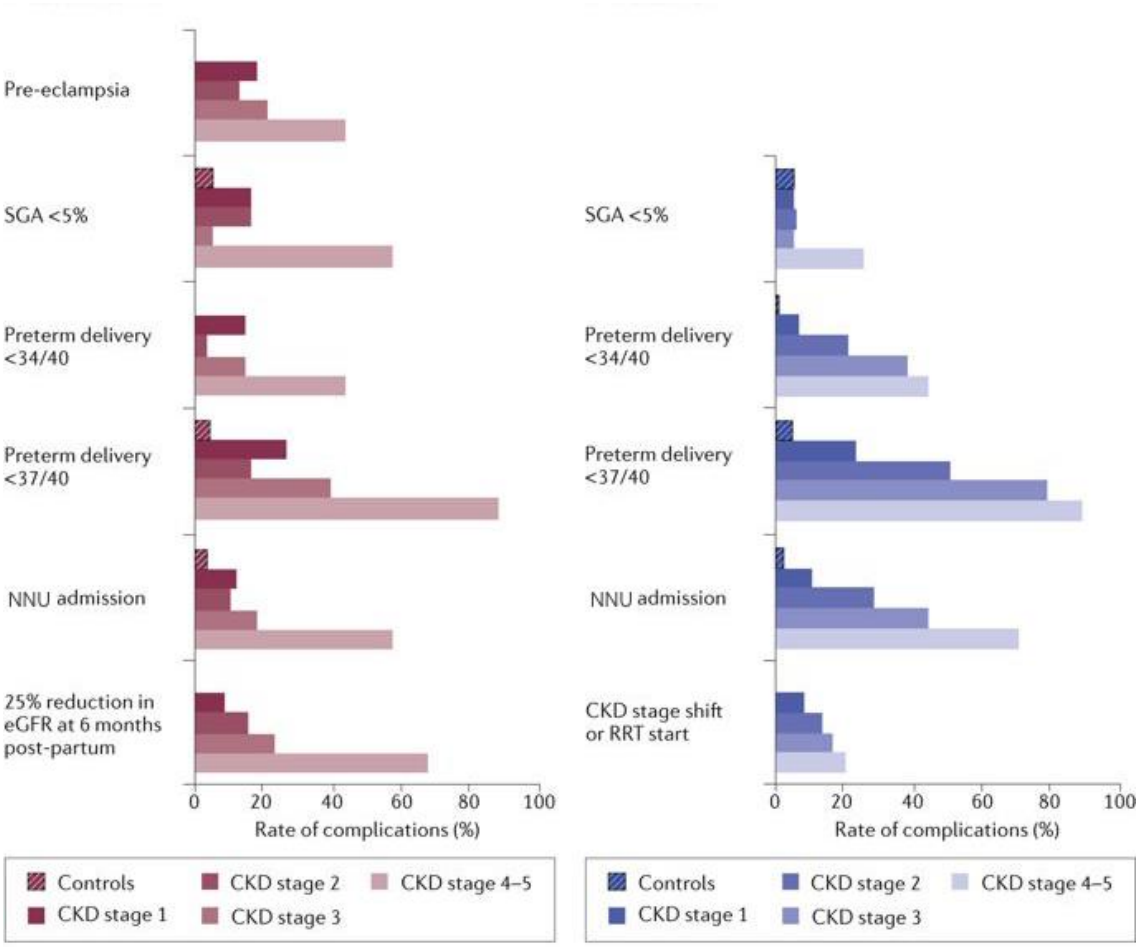
1.3.1 Pregnancy and neonatal outcomes

Historically, clinicians advised avoidance of pregnancy for women with CKD (Lancet Editors, 1975), a recommendation that qualitative assessment has shown to be associated with frustration, anger and regret (Tong et al., 2015a; Tong et al., 2015b). However, over recent decades, the focus of advice has changed owing to advances in obstetric surveillance and neonatal care. Effectively communicated, individualised pre-pregnancy counselling based on disease aetiology and severity, rate of eGFR decline, obstetric history and the presence of additional risk factors can enable women with any stage of CKD and their partners to make an informed choice regarding pregnancy. Pre-pregnancy counselling is recommended for all women with pre-existing medical conditions (Knight et al., 2014). In a recent survey of 179 women with CKD, 92% of respondents reported that expert pre-pregnancy counselling assisted with decision-making (Wiles et al., 2015).

Data from a population study including 778 women with CKD (Kendrick et al., 2015), a large contemporary cohort of 504 women with CKD (Piccoli et al., 2015), and a meta-analysis of 23 studies including 1514 pregnant women with CKD (Zhang et al., 2015)

show that women with CKD have worse maternal and neonatal outcomes compared to women without CKD. These include including higher rates of superimposed pre-eclampsia, preterm delivery, small-for-gestational-age infants, admission to neonatal care and perinatal death. Absolute rates of adverse outcome vary between studies and are affected by cohort size, measure of renal function and variance in clinician thresholds for iatrogenic pre-term delivery and neonatal admission. However, an increment in all complications exists with worsening renal function (Piccoli et al., 2015) (Figure 1.4).

Figure 1.4 Pregnancy outcomes in women with CKD. Two cohort studies ((Bramham et al., 2016) (red), (Piccoli et al., 2015) (blue)) show that worsening of renal function as assessed by CKD stage correlates with a consistent increment in several pregnancy complications: preterm delivery; pre-eclampsia; neonatal unit (NNU) admission; loss of residual maternal renal function; and small-for-gestational-age (SGA) infants. Cohort size, the use of estimated glomerular filtration rate (eGFR) in pregnancy and different thresholds for iatrogenic preterm delivery and NNU admission may contribute to variance in data. Pre-eclampsia was excluded from the control group in one study (Bramham et al., 2016) and not measured as an outcome in the other (Piccoli et al., 2015). RRT=renal replacement therapy.



Additional factors associated with adverse pregnancy outcomes that are independent of kidney disease severity include pre-existing hypertension (Piccoli et al., 2015), kidney transplantation (Piccoli et al., 2017b), lupus nephritis (Moroni et al., 2016), proteinuria (Piccoli et al., 2017a) and superimposed pre-eclampsia (Chapman et al., 1994). The largest contemporary cohort reported an increased risk of adverse

pregnancy outcomes in women with stage 1 CKD even in the absence of systemic disease, hypertension and proteinuria (Odds Ratio (OR) 1.88, 95% CI: 1.27-2.79), leading to the hypothesis that CKD in itself confers risk in pregnancy. However, the calculation of eGFR in pregnancy in this cohort may have underestimated CKD stage in some women (Piccoli et al., 2015).

1.3.2 Progression of maternal kidney disease

Until the last decade, the understanding of CKD progression in pregnancy was limited to findings from two small cohort studies (Jones and Hayslett, 1996; Imbasciati et al., 2007). A retrospective study of 70 pregnancies in 58 women with a mean serum creatinine of 168μmol/L during early pregnancy reported a 25% reduction in kidney function in 43% of women in the six weeks after delivery, with 11% of the cohort progressing to end-stage kidney disease by six months post-partum (Jones and Hayslett, 1996). Similarly, a prospective Italian study of 49 pregnancies reported that women with a pre-pregnancy MDRD eGFR less than 40 ml/min/1.73 m^2 and proteinuria greater than 1g/day had an accelerated decline in kidney function (1.17±1.23ml/min per month) at six months post-partum compared with pre-pregnancy rates (0.21±0.20 ml/min per month) (Imbasciati et al., 2007). Loss of maternal kidney function in later cohorts include a deterioration in function by one CKD stage (or a new requirement for renal replacement) in 7.3% (37/504) (Piccoli et al., 2015) and a 25% reduction in eGFR at 6 months post-partum in 8.3% (10/120) (Bramham et al., 2016) across all stages of CKD. Although one study reported a decline in kidney function in relation to pregnancy in women with CKD stage 1, with 7.6% (28/370) progressing to CKD stage 2 or more (Piccoli et al., 2015), this finding could relate to the calculation of eGFR during pregnancy and an underestimation of pre-pregnancy kidney disease severity. A meta-analysis from 2015 that compared kidney disease progression in 552 women with CKD undertaking pregnancy with 716 women without a pregnancy reported no significant difference (OR 0.96; 95% CI 0.69–1.35); however, in that study ‘progression’ was crudely defined as a doubling of serum

creatinine level or a >50% reduction in eGFR, and only women with CKD stages 1–3 were included (Zhang et al., 2015).

1.3.3 Chronic kidney disease stages 3-5

Serum creatinine concentrations in isolation fail to reflect the complexity and heterogeneity that exists under the umbrella term of CKD, which includes stable and progressive disease, systemic and local disease, chronic hypertension and normotension, and nephrotic and non-proteinuric CKD. Such variance means that the decision to undertake a pregnancy cannot be based on CKD stage alone. However, in the context of an increased risk in adverse pregnancy outcomes with advancing CKD stage, counselling with regards to pregnancy is more complex for women with moderate and severe CKD. The interplay between hypothesised predictors of adverse pregnancy outcomes including chronic hypertension (Bramham et al., 2014; Bramham et al., 2016), proteinuria (Imbasciati et al., 2007; De Castro et al., 2017), and advanced kidney disease (Piccoli et al., 2015; Imbasciati et al., 2007), remains poorly defined, with limited contemporary data available for risk counselling prior to pregnancy (Piccoli et al., 2018). In addition, the impact of pregnancy upon maternal CKD is not clear with published data both suggesting (Jones and Hayslett, 1996; Trevisan et al., 2004) and refuting (Piccoli et al., 2015; He et al., 2018) an association between CKD stage and loss of maternal kidney function.

CKD stages 3-5 are estimated to complicate 1 in 750 pregnancies (Piccoli et al., 2018) with a higher incidence of adverse outcomes demonstrated in small (Piccoli et al., 2015; Bramham et al., 2016) and historical (Jones and Hayslett, 1996) cohorts, and by non-systematic review of published data (Williams and Davison, 2008). The outcomes from the largest published cohort, which included 82 pregnancies from 1971-1993, predates the use of eGFR and does not reflect contemporary standards of obstetric and renal care (Jones and Hayslett, 1996). The only other cohort with comparable numbers of women moderate-severe CKD was from Brazil, where only 64% had

antenatal monitoring and mean haemoglobin was 67g/L (Trevisan et al., 2004). All CKD cohort data contain a limited number of women with moderate-severe CKD and do not examine the trajectory of kidney function decline prior to pregnancy (Table 1.4). Thus, there is a need for larger, contemporaneous datasets using up-to-date staging of CKD for risk stratification and an analysis of kidney function prior to, as well as following pregnancy, in order to inform pre-pregnancy counselling and appropriate surveillance.

Table 1.4: Studies reporting pregnancy outcomes in women with moderate and severe CKD. CKD=chronic kidney disease, CKD-EPI=chronic kidney disease epidemiology collaboration formula Cr=serum creatinine concentration, CrCl=creatinine clearance, DM=diabetic nephropathy, eGFR=estimated glomerular filtration rate, ICD=international classification of disease, KDIGO=Kidney Disease: Improving Global Outcomes, KDOQI=Kidney Disease Outcomes Quality Initiative, MDRD=modification of diet in renal disease formula.

Study	**CKD definition**	**Number of pregnancies**	**Number with moderate-severe CKD**	**Definition of moderate-severe CKD**
Gazarek, 1966	Not reported	1257	Unknown	
Houser et al., 1979	Biopsy	7	Unknown	
Leppert et al., 1979	CKD in childhood	114	26%	Cr >106µmol/L
Nagai et al., 1989	IgA nephropathy	19	Unknown	
Kimmerle et al., 1995	DM, CrCl<80	40	10	Cr >98 µmol/L in 1st trimester
Holley et al., 1996	Cr>70µmol/L in 1st trimester	43	5	Cr >125µmol/L
Jones and Hayslett, 1996	Creatinine ≥124 µmol/L	82	76	Pregnancy Cr >124µmol/L
			15	Pregnancy Cr >221µmol/L)
Miodovnik et al., 1996	DM	56	11	CrCl <80
			1	CrCl <50
Rosenn et al., 1997	DM proteinuria >500mg/day <16 weeks	73	Unknown	
Fink et al., 1998	ICD9-code	169	Unknown	
Murakami et al., 2000	Biopsy	19	Unknown	
Fischer et al., 2004	Medical coding	911	Unknown	
Misra et al., 2003	Known renal disease	51	7	Cr >106µmol/L
Trevisan et al., 2004	Creatinine >133	75	75	Cr >133 µmol/L
Imbasciati et al., 2007	MDRD eGFR	49	49	Unspecified eGFR or Cr >124µmol/L

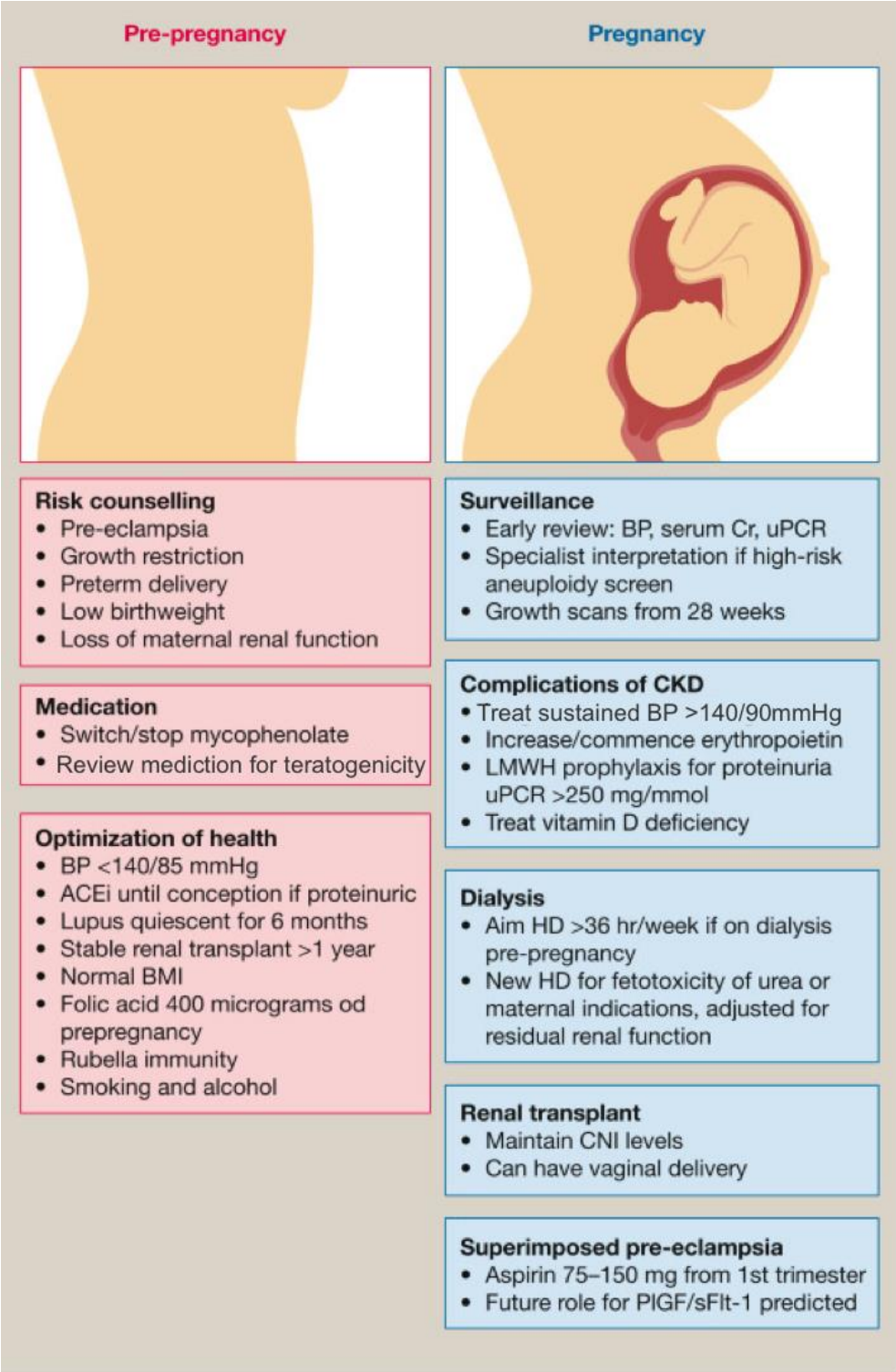
Gladman et al., 2010	Lupus nephritis	81	Unknown	
Kim et al., 2010	IgA nephropathy	90	Unknown	
Shimizu et al., 2010	IgA nephropathy	29	8	Unspecified eGFR
Piccoli et al., 2010	KDOQI criteria	91	15	Cockcroft-Gault, MDRD pre-conception and intrapartum
Liu et al., 2014	IgA nephropathy	62	2	CKD-EPI
Piccoli et al., 2015	KDOQI criteria	305	47	CKD-EPI pre-conception and intrapartum
Bramham et al., 2016	Known kidney disease	120	33	MDRD pre-conception or pregnant Cr +25%
Su et al., 2017	IgA nephropathy	116	11	CKD-EPI
He et al., 2018	Known kidney disease	300	30	Unspecified eGFR
Park et al., 2017	IgA nephropathy	59	14	MDRD
Ibarra-Hernandez et al., 2019	KDIGO criteria	62	≥20	Dialysis requiring

1.4 The management of pregnancy in women with chronic kidney disease

Existing guidance on the management of CKD in pregnancy includes statements of care from the UK Consensus Group on Pregnancy in Renal Disease from 2014 (Bramham et al., 2018), position statements from an Italian Study Group on kidney disease and pregnancy (Cabiddu et al., 2016; Cabiddu et al., 2018; Cabiddu et al., 2015; Piccoli et al., 2017c), and expert review. The Kidney Disease Outcomes Quality Initiative (KDOQI), Kidney Disease: Improving Global Outcomes (KDIGO), National Institute of Health and Care Excellence (NICE) and the UK Renal Association have not provided guidance on the management of kidney disease in pregnancy.

There is no specific literature to guide antenatal and postnatal schedules of care for women with CKD. Generic aspects of care for women with CKD in pregnancy are outlined in Figure 1.5. Aspects of pregnancy care related to specific aetiologies of CKD are outlined below. Blood pressure, and the diagnosis and management of superimposed pre-eclampsia in women with CKD are considered in Section 1.6.

Figure 1.5 An overview of the management of chronic kidney disease (CKD) in pregnancy. From (Wiles and Smith, 2019). ACEi=ACE inhibitor, BMI=body mass index, BP=blood pressure, CNI=calcineurin inhibitor (tacrolimus/ciclosporin), Cr=serum creatinine, HD=haemodialysis, LMWH=low-molecular-weight heparin, PlGF=placental growth factor, uPCR=urinary protein:creatinine ratio, sFlt-1=soluble fms-like tyrosine kinase-1.



1.4.1 Autosomal dominant polycystic kidney disease

Although normotensive women with autosomal dominant polycystic kidney disease (ADPKD) reportedly have comparable pregnancy outcomes to those of unaffected family members, pre-existing hypertension is a recognised risk factor for adverse pregnancy outcomes in ADPKD (Chapman et al., 1994). Neonatal risk has been shown to be comparable between 54 women with ADPKD compared with 92 women with simple cysts, although maternal complications, including hypertension and pre-eclampsia, were increased in patients with ADPKD (Wu et al., 2016a). Isolated case studies support the theory that kidney volume is unaffected by pregnancy, and the condition does not compromise uterine growth (Jung et al., 2014).

The probability of inheritance of ADPKD is markedly reduced using pre-implantation genetic diagnosis to identify relevant mutations in embryos prior to implantation. However, the ethics of genetic testing for an adult-onset disorder, which may be asymptomatic for many years, need to be weighed. In a single-centre study of 96 women with ADPKD, 50% of patients with CKD and 63% of those with end stage renal disease would have opted for pre-implantation genetic diagnosis if it were available (Swift et al., 2016). Single-embryo transfer is recommended in women with CKD due to the additive risks associated with multifetal pregnancy, including pre-eclampsia and preterm delivery.

1.4.2 Primary glomerulonephritis.

Limited data on pregnancy outcomes in women with primary glomerulonephritis are available to guide counselling and management, as highlighted in a systematic review (Blom et al., 2017). For example, published literature includes only two studies of pregnancy in women with minimal change disease (Jungers et al., 1986; Abe et al., 1985). However, the association of pre-existing hypertension, proteinuria and renal impairment with worse pregnancy outcomes is consistent between studies of different

glomerulonephritides. Proteinuria has been found to be an important determinant of outcome in IgA nephropathy, which is the most common primary glomerulonephritis in pregnant women (Blom et al., 2017)**.** Proteinuria and birth weight are negatively correlated (Packham et al., 1988), and the presence of urinary protein excretion greater than 1g/day has been shown to be associated with loss of residual renal function independently of pregnancy (Limardo et al., 2010). A comparison of pregnancy outcomes between women with IgA nephropathy and other glomerular diseases has not been carried out.

1.4.3 Lupus nephritis

Systemic lupus erythematosus (SLE) predominantly affects women of reproductive age, with lupus nephritis occurring in approximately 40% of cases (Hoover and Costenbader, 2016). Although the risk of adverse pregnancy outcomes is increased in women with active lupus nephritis (Imbasciati et al., 2009) even in the context of preserved kidney function (Bramham et al., 2011a), pregnancy outcomes are improved when disease remission is achieved prior to pregnancy. Pregnancy, however, can trigger disease relapse, as evidenced by a findings from meta-analysis of 37 studies comprising 2,751 pregnancies, which showed that lupus flares and lupus nephritis occur in 26% and 16% of pregnancies, respectively (Smyth et al., 2010). A prospective cohort study of 61 pregnant women demonstrated that an increase in lupus disease severity score was associated with a proportional and significant increase in the risk of preterm delivery (Moroni et al., 2016). Similarly, the presence of lupus nephritis increases the risk of preterm delivery among women with SLE (Bramham et al., 2011b). Other risk factors for adverse pregnancy outcomes in lupus nephritis include black (Chakravarty et al., 2005) and Hispanic (Buyon et al., 2015) ethnicity, pre-existing hypertension (Imbasciati et al., 2009), and severity of proteinuria (Moroni et al., 2016). Therefore, delayed conception until six months after lupus disease activity is recommended, and pre-pregnancy kidney biopsy might be useful to exclude active disease if proteinuria is persistent. Given the risks associated with lupus nephritis, in

conjunction with the clinical difficulties in distinguishing active lupus nephritis from pre-eclampsia (Table 1.5), women with current or previous lupus nephritis should be seen in pregnancy by physicians and obstetricians with expertise in SLE and kidney disease.

Table 1.5 Clinical features of normal pregnancy, pre-eclampsia/HELLP and kidney disease presenting in pregnancy. dsDNA=double stranded DNA, ESR=erythrocyte sedimentation rate, HELLP=haemolysis, elevated liver enzymes, low platelets, HUS=haemolytic uraemic syndrome, T1=first trimester, T2=second trimester, T3=third trimester, uPCR=urinary protein:creatinine ratio

Features	Normal pregnancy	Pre-eclampsia /HELLP	Lupus nephritis	Atypical HUS
Gestation	All	>20 weeks	Any	Typically peri/post-partum
Skin changes/rash	+	-	+	-
Hair loss	+	-	+	-
Oedema	+	++	+	+
Hypertension (BP>140/90mmHg)	-	++	+	+
Proteinuria (uPCR>30mg/mmol)	-	+	+	+
Haematuria	Trace	-	+	-/+
Anaemia	+	+	+	-/+
Thrombocytopenia (platelets<100x10^9/l)	-	+	+	++
Haemolysis	-	+ improves 48-72 hours post delivery	Rare	++ persists >72 hours after delivery
Serum creatinine	⇓ T1, ⇓⇓ T2, rise to pre-pregnancy values in T3	⇑	⇑	⇑⇑
Transaminitis	No	Yes	No	No
ESR	⇑	-	⇑	⇑
dsDNA	⟷	⟷	⇑	⟷
Complement	Can ⇑	⟷	⇓ (within normal range)	⇓ in 30-50%

For women with lupus nephritis in association with antiphospholipid antibodies, active disease and/or proteinuria, prophylaxis against venous thromboembolism using low-molecular-weight heparin should be considered; however, the threshold urinary protein:creatinine ratio at which the risk of this complication becomes clinically relevant remains unknown (RCOG, 2015). Unless contraindicated, women with lupus nephritis should be offered hydroxychloroquine (see section 1.5) for disease control in pregnancy and low-dose aspirin for pre-eclampsia prophylaxis (see section 1.6).

Fetal complications in lupus nephritis may arise through exposure to maternal autoantibodies against intracellular ribonucleoproteins Sjögren syndrome type A antigen (SSA; also known as Ro) and SSB (also known as La), which undergo placental transfer and confer a 2% risk of congenital heart block and a 16% risk of neonatal cutaneous lupus (Cimaz et al., 2003). Whereas neonatal cutaneous lupus is benign and resolves with elimination of the maternal antibody, congenital heart block and endocardial fibroelastosis are associated with neonatal morbidity and mortality. Therefore, surveillance of fetal heart rate and echocardiography for suspected cardiac involvement is recommended for women with SSA and SSB antibodies. Weekly fetal echocardiography is recommended from 16 weeks gestation for women with a previous affected infant, although the clinical benefits and cost effectiveness of equivalent surveillance in women without an affected child remain unknown (Andreoli et al., 2017). Maternal hydroxychloroquine is associated with a reduced risk of congenital heart block in the offspring of women with SLE and previously affected pregnancies (Izmirly et al., 2012).

1.4.4 Diabetic kidney disease

Kidney disease is evident in 2.5–6.5% of pregnancies in women with type 1 diabetes mellitus (Klemetti et al., 2015), although rates of up to 25% are described when disease definitions include microalbuminuria with a normal eGFR (Piccoli et al., 2013b). Type I and type II diabetes are associated with an increased risk of obstetric

complications, progression of retinopathy, ketoacidosis, exacerbation of pre-existing cardiovascular disease and fetal death independent of whether or not there is co-existing kidney disease. A retrospective analysis of 43 pregnancies in women with diabetic kidney disease who had a median pre-pregnancy serum creatinine of 68µmol/L, reported much higher rates of adverse pregnancy outcomes than expected for the level of renal impairment, including pre-eclampsia in 42% and preterm delivery in 77% of patients (Klemetti et al., 2015). Gestational proteinuria can be substantial and the risk of venous thromboembolism should be considered, although only limited data regarding the proteinuric threshold for heparin prophylaxis are available (RCOG, 2015). Fetal growth surveillance in patients with diabetic kidney disease may be falsely reassuring, as growth restriction due to underlying CKD can be masked by hyperglycaemia-induced macrosomia. Congenital malformation rates increase with poor glycaemic control around the time of conception, but diabetic kidney disease confers an additional risk of fetal malformation compared to women without nephropathy (adjusted OR 2.5; 95% CI 1.1–5.3) (Bell et al., 2012). Some evidence supports intensification of renin-angiotensin blockade prior to pregnancy, although this needs to be discontinued in pregnancy due to fetotoxicity (see section 1.5). Data from single-arm studies with between 8 and 24 participants show that pre-conception proteinuria is reduced by pre-pregnancy renin-angiotensin blockade with an associated decrease in pregnancy-induced proteinuria (Hod et al., 1995; Bar et al., 1999). The use of intensified targets for blood pressure (<135/85 mmHg) and proteinuria (<300mg per day), in conjunction with pre-conceptual renin-angiotensin blockade, is associated with obstetric outcomes that are comparable to those of women with diabetes in the absence of proteinuria (Nielsen et al., 2009).

1.4.5 Renal replacement therapy in pregnancy

1.4.5.1 Haemodialysis in pregnancy

There has been a marked increase in the reported number of pregnancies in women receiving dialysis. Systematic review data reported 90 cases between 2000 and 2008, with an increase to 574 cases only six years later (Piccoli et al., 2016). Augmentation of haemodialysis dose is associated with fewer fetal deaths (Hou, 1994; Hou, 2004), and meta-analysis shows a continuous inverse correlation between the number of haemodialysis hours per week and rates of preterm birth ($p=0.044$; $r^2=0.22$) and small for gestational age infants ($p=0.017$; $r^2=0.54$) (Piccoli et al., 2016). In a contemporary cohort of 22 pregnancies in 17 women, intensive haemodialysis (defined as an average of 43 hours per week) conferred a 86% live birth rate at a mean gestational age of 36 weeks, compared with a live birth rate of 61% at a mean gestational age of 27 weeks in 70 women receiving haemodialysis for a mean of 17 hours per week (Hladunewich et al., 2014). Provision of dialysis for 48 hours per week is thought to optimise maternal physiology, with patients achieving gestational blood pressures of 112/72–122/81mmHg with minimal use of antihypertensive agents, and pre-dialysis urea concentrations of 8–14mmol/L, although increased dialysate provision of potassium, calcium and phosphate may be required (Barua et al., 2008). Nonetheless, complication rates remain high even in women receiving intensive haemodialysis, and more than 75% of such women require preterm delivery (Hladunewich et al., 2014; Piccoli et al., 2016). Pregnancy on haemodialysis remains a high-risk option, and the decision to undergo pregnancy should be weighed carefully with options for transplantation within the window of reproductive age. Maternal indications for initiating haemodialysis in pregnancy mirror indications outside of pregnancy and include fluid overload, hyperkalaemia and acidosis that are resistant to medical management. However, the most common trigger for dialysis initiation in pregnancy is the fetotoxicity of urea, although the maternal serum urea threshold at which dialysis should be commenced in pregnancy continues to be a subject of on-going debate.

Historically, dialysis initiation in pregnancy was commenced a urea concentration of 17–20mmol/L, due to correlation between higher urea levels and delivery <32 weeks and birth weight <1500g, both of which are associated with adverse neonatal prognosis (Asamiya et al., 2009). However, given the positive correlation between hours of haemodialysis provision and pregnancy outcomes, the emerging consensus is that dialysis initiation should be considered at lower concentrations of urea (15mmol/L) in women with progressive kidney dysfunction, with dialysis provision matched to residual renal function (Hladunewich and Schatell, 2016). Specific guidance on antenatal surveillance and the technical aspects of care in women receiving haemodialysis in pregnancy are available (Wiles and de Oliveira, 2018).

1.4.5.2 Peritoneal dialysis.

The incidence of pregnancy in women on peritoneal dialysis is lower than for haemodialysis (Piccoli et al., 2016), which has been attributed to factors such as high dialysate osmolality and fallopian tube injury secondary to peritoneal infection. Although successful pregnancies are possible, fewer than 100 reported cases of peritoneal dialysis in pregnancy have been reported worldwide (Malin et al., 2018). Systematic review data reveal a higher rate of small-for-gestational-age infants in women undergoing peritoneal (67%) compared with haemodialysis (31%), which could be due to placental development being adversely affected by peritoneal dialysis (Piccoli et al., 2016), although limitations of cohort size and publication bias should also be considered.

Peritoneal dialysis offers potential benefits for pregnancy including continuous ultrafiltration, avoidance of haemodynamic fluctuation, and no requirement for anticoagulation at the time of delivery. However, progressive distension of the uterus may necessitate reduced dialysate volumes and affect catheter position leading to concern about capacity to intensify dialysis during pregnancy. Haemodialysis therefore remains the modality of choice in pregnancy in order to facilitate controlled

intensification of dialysis. However, the supplementation of peritoneal dialysis with intermittent haemodialysis in order to augment clearance has been described (Ross et al., 2016).

1.4.5.3 Kidney transplantation and pregnancy

Pregnancy rates are lower in women of reproductive age with kidney transplants compared to the general population (Gill et al., 2009; Levidiotis et al., 2009; Wiles et al., 2018), though it is unclear whether this is due to impaired fertility or an elective decision not to conceive. Women with kidney transplants usually have successful pregnancy outcomes, but maternal and neonatal complications remain higher compared to the general population (Deshpande et al., 2011). A prospective UK cohort study of 105 pregnancies in 95 women with kidney transplants compared with 1360 healthy controls, showed an increased risk of pre-eclampsia (adjusted odds ratio (aOR)=6.31), induction of labour (aOR=2.67) caesarean delivery (aOR=4.57), preterm delivery <37 weeks (aOR=12.57) and <32 weeks (aOR=4.15), and small-for-gestational age babies (aOR=2.92) (Bramham et al., 2013).

The impact of pregnancy upon kidney transplant function is variably reported. A recent study of Medicare data demonstrated that graft loss was higher in women who conceived within two years of transplantation, but those who waited three years or more were not at greater risk of graft lost compared those with kidney transplants and no pregnancy (Rose et al., 2016). Other factors to consider regarding timing of pregnancy include recent episodes of rejection, stability and level of graft function, presence of cytomegalovirus, maternal age, diabetes, and blood pressure control though direct evidence regarding impact of these factors on pregnancy and graft outcomes is limited.

There are limited data examining timing of pregnancy in women with kidney transplants. Older reports suggested that a shorter interval from transplant to

pregnancy was associated with worse pregnancy outcomes (Armenti et al., 2000; Stratta et al., 2003). A more recent meta-analysis examined transplant-to-pregnancy intervals of less than 2 years (4 studies, 149 pregnancies), 2–3 years (15 studies, 835 pregnancies), and more than 3 years (44 studies, 3182 pregnancies). This showed higher live birth rate rates in pregnancies undertaken within 2 years, or more than 3 years, after transplantation, though rates of pre-eclampsia were higher in pregnancies more than 2 years after kidney transplantation (Shah et al., 2019). Such data are subject to registry reporting bias and interpretation is limited by heterogeneity of maternal age, baseline kidney function, chronic hypertension, proteinuria, obstetric risk factors and global differences in medical care.

In 2002, European guidelines recommended a delay of 24 months between transplantation and conception (EBPG, 2002), but American guidelines subsequently advised a delay of only 12 months provided graft function was stable (McKay et al., 2005). Standard immunosuppression regimens in the UK routinely include mycophenolate mofetil in the first year after transplantation (NICE, 2017). Due to the teratogenicity of mycophenolate mofetil, switching to alternative agents is recommended before pregnancy (see section 1.5), and thus at least a year after transplantation is advised before attempting to conceive in the UK.

An analysis of long-term renal outcomes after pregnancy in women with kidney transplants was performed by the Australian and New Zealand Dialysis and Transplant Women with renal transplants that did (n=120) and did not (n=120) undertake a pregnancy were matched by year of transplantation, duration of transplant, age at transplantation ±5 years, and pre-delivery creatinine concentration. This study demonstrated that a first live birth in women with kidney transplants was not associated with shorter graft or patient survival over 20 years (Levidiotis et al., 2009).

1.5 Therapeutics in pregnancy in women with chronic kidney disease

Prescribing in pregnancy balances the risks to the women of uncontrolled disease, with real and/or theoretical harm to the fetus. Inappropriate cessation or failure to initiate therapy may be more harmful than judicious use to maintain maternal health. Medication should be prescribed in pregnancy if the benefit to the woman (and therefore the fetus) outweighs the potential or theoretical risk to the fetus. The woman should be involved in discussions about medication in pregnancy, which should ideally take place before the pregnancy as part of pre-pregnancy counselling (Götestam Skorpen et al., 2016)

Very few drugs are licensed for use in pregnancy. Surveillance of pregnancy outcomes in women exposed to drugs is therefore used to assess safety in pregnancy. Such outcomes may be confounded by the underlying medical conditions for which treatment is required, and clinical interpretation of data must be balanced and pragmatic. There are no randomised controlled trials of medication in pregnancy in women with CKD. Where randomised controlled trial data are available, generalisation from unselected obstetric cohorts is required (Henderson et al., 2014; Rolnik et al., 2017).

Table 1.6 Summary of the safety data for medications commonly used in women with CKD in relation to conception, pregnancy and lactation. Adapted from (Wiles et al., 2018) IV=intravenous, TPMT=thiopurine-S-methylltransferase, VTE=venous thromboembolism

Medication	**Conception**	**Pregnancy**			**Lactation**	**References**
		Overall	Maternal considerations	Fetal considerations		
Antihypertensive drugs (see section 1.6.6.3)						
Labetalol	Safe.	Safe.	License for pregnancy. Consider other comorbidities e.g. asthma.	No association with congenital abnormalities. An association with reduced birth weight is based on historical data including the use of atenolol and unadjusted observational data in women with hypertension treated with labetalol. For women with cardiac disease birthweight between differences labetalol and methyldopa were not considered clinically significant. Screening for neonatal hypoglycaemia is recommended.	Safe	NICE, 2011; NICE, 2019; LactMed, 2006-
Nifedipine	Safe.	Safe.	None.	No association with congenital abnormalities.	Safe.	NICE, 2011; NICE, 2019; LactMed, 2006-
Amlodipine	Safe	Limited data.	None.	Limited data. No adverse effects reported.	Safe.	Vigil-De Gracia et al., 2014; Morgan et al., 2017; LactMed, 2006-
Methyldopa	Safe.	Safe.	Avoid in depression or if risk of depression.	No association with congenital abnormalities.	Avoid due to risk of postnatal depression.	NICE, 2011; NICE, 2019; LactMed, 2006-

Doxazosin	Safe	Limited data	None.	No evidence of harm in animal studies.	<1% maternal dose detected.	NICE, 2011; NICE 2019; LactMed, 2006-
Hydralazine	Safe	Safe	Risk of hypotension, tachycardia.	No association with congenital abnormalities.	Safe.	NICE, 2011; NICE 2019; LactMed, 2006-
Beta-blockers	Safe	Limited data on individual drugs	Avoid if asthmatic. Use in pregnancy determined by maternal indication.	No association with congenital abnormalities. Clinical significance of reduced birthweight unclear. Neonatal bradycardia (1%) and hypoglycaemia (3%).	No adverse effects reported.	Bateman et al., 2016; Bergman et al., 2018; Meidahl Petersen et al., 2012; Duan et al., 2018; LactMed, 2006-
Angiotensin converting enzyme inhibitors	No increase in risk with first trimester use when data corrected for hypertension/ diabetes. Continue provided early diagnosis of conception.	Unsafe.	None.	Fetotoxic in second and third trimesters leading to fetal and neonatal kidney failure, bone and aortic arch malformations, oligohydramnios, and pulmonary hypoplasia.	Safety data available for captopril and enalapril.	NICE, 2011; NICE, 2019;
Angiotensin receptor antagonists	Insufficient data on exposure in early pregnancy. Discontinue in advance of pregnancy.	Unsafe.	None.	Fetotoxicity in second and third trimesters comparable to angiotensin converting enzyme inhibitors.	No data.	NICE, 2011; NICE 2019; LactMed, 2006-
Thiazide diuretics	Insufficient early pregnancy data. No evidence of harm.	Unsafe.	Reduced plasma volume expansion in pregnancy (n=10).	No evidence of thrombocytopenia, jaundice, hypokalaemia, hyponatraemia in meta-analysis (n=5292).	Potential suppression of lactation. Avoid.	Collins et al., 1985; Sibai et al., 1984; LactMed, 2006-

Immunosuppressant drugs						
Corticosteroids	Safe.	Safe.	Potential risks: diabetes, hypertension, pre-eclampsia, infection, preterm rupture of membranes. Aim for minimum maintenance dose.	Fetus exposed to <10% maternal dose due to placental deactivation. No evidence of increase in congenital abnormalities.	Safe. Small amounts in breast milk. Consider timing feeds to 4 hours post administration if high dose (e.g methylprednisolone) and monitor neonate.	Benediktsson et al., 1997; van Runnard Heimel et al., 2005; Tata et al., 2008; Hviid and Mølgaard-Nielsen, 2011; LactMed, 2006-
Hydroxychloroquine	Safe.	Safe.	Withdrawal may precipitate lupus flare. Indicated throughout pregnancy if patient has a history of lupus nephritis.	Placental transfer. No increase in miscarriage or congenital abnormality. May reduce risk of congenital heart block if maternal anti-SSA (Ro) and or anti-SSB (La) antibodies.	Safe.	Moroni et al., 2016; Izmirly et al., 2012; Wallace et al., 2012; Kaplan et al., 2016; Clowse et al., 2006; Marmor et al., 2016; LactMed, 2006-
Azathioprine	Safe.	Safe.	Recommend check TPMT status before dosing.	Placental transfer. No association with congenital abnormalities.	Safe. Low concentration in breast milk.	Francella et al., 2003; Flint et al., 2016; Götestam Skorpen et al., 2016; Sau et al., 2007; LactMed, 2006-
Ciclosporin	Safe.	Safe.	Monitor pre-dose levels more frequently in pregnancy and immediately post partum. Avoid medications that interfere with metabolism e.g. macrolides. Screen for gestational diabetes.	Placental transfer. No association with congenital abnormalities.	Safe.	Bar Oz et al., 2001; Chakkera et al., 2017; LactMed, 2006-
Tacrolimus						Kim et al., 2015, Aktürk et al., 2015; Kainz et al., 2000; LactMed, 2006-

Mycophenolate mofetil	Unsafe. Effective contraception during treatment and for 6 weeks after. Ensure disease/transplant stability prior to conception.	Unsafe.	None.	Placental transfer. Teratogenic causing ear, heart, eye, lip/palate, kidney, and bone abnormalities, tracheoesophageal fistula, congenital diaphragmatic hernia. Increased miscarriage.	Insufficient data: avoid.	Flint et al., 2016; Götestam Skorpen et al., 2016; Sifontis et al., 2006; LactMed, 2006-
Cyclophosphamide	Unsafe. Effective contraception during and for 3 months after treatment. Dose- and age-related risk of infertility.	Unsafe.	None.	Placental transfer. Teratogenic. Congenital abnormalities of the skull, ear, face, limb and visceral organs. Increased risk of miscarriage.	Excreted in breast milk. Discontinue breast-feeding during and for 36 hours after treatment.	Flint et al., 2016; Götestam Skorpen et al., 2016; Ioannidis et al., 2002; Zemlickis et al., 1992; LactMed, 2006-
Rituximab	Unclear: limited data. Treatment decision depends on indication and alternative options.	Unclear: limited data.	If indicated for severe disease, aim to give dose before, or in early, pregnancy to minimise the risk of neonatal B-cell depletion.	Active placental transfer in 2nd and 3rd trimester. Potential risk of neonatal B-cell depletion. Avoid unless potential benefit to mother outweighs risk. Long term effects unknown.	Insufficient data data. Possible excretion of trace amounts, neonatal absorption unlikely.	Flint et al., 2016; Götestam Skorpen et al., 2016; FDA, 2010a; Chakravarty et al., 2011; LactMed, 2006-
Sirolimus / Everolimus	Unsafe. Fetal toxicity in rats. Effective contraception during and for 3 months after.	Unsafe	Impaired wound healing. Proteinuria.	Likely placental transfer. Toxicity in animal studies.	Limited data: avoid.	FDA, 2003; FDA, 2010b; LactMed, 2006-
Eculizumab	Unclear: limited data. Depends on indication and alternative options.	Unclear: limited data	Morbidity of underlying condition may mean treatment required. Monitor for increased dosage requirements.	Active placental transfer in 2nd and 3rd trimester. No congenital abnormality reported in 20 infants. Long-term effects unknown.	Insufficient data data. Possible excretion of trace amounts, neonatal absorption unlikely.	Bruel et al., 2017; Kelly et al., 2015; LactMed, 2006-

Other						
Aspirin (75–150mg) (see Section 1.6.6.1)	Safe.	Safe.	Reduced incidence of pre-eclampsia in general obstetric population when taken from early pregnancy. No evidence of haemorrhagic complications. Insufficient data on optimum dose (i.e. 75mg versus 150mg).	No association with congenital abnormalities.	Safe.	NICE, 2011; NICE, 2019; Henderson et al., 2014; Rolnik et al., 2017; LactMed, 2006-
Iron	Safe.	Safe.	Intravenous preparations may offer better bioavailability in CKD.	Safety data available in 2nd and 3rd trimesters but limited data on exposure on the first trimester. Expert consensus is not to withhold IV iron if indicated in the first trimester.	Safe.	Albaramki et al., 2012; Tariq et al., 2015; Kriplani et al., 2013; Al et al., 2005; al-Momen et al., 1996; LactMed, 2006-
Low-molecular-weight heparin	Safe	Safe	Level of proteinuria with significant risk of VTE in pregnancy unknown.	No placental transfer.	Safe.	RCOG, 2015; LactMed, 2006-
Erythropoietin	Safe.	Safe.	Monitor blood pressure.	No placental transfer.	Safe.	McMullin et al., 2003; Sienas et al., 2013; Sanchez-Gonzalez et al., 2016; LactMed, 2006-
Metformin	Safe	Safe	Use contraindicated outside of pregnancy if eGFR <30ml/min/1.73m^2.	None.	Low levels in milk, infants receive <0.5% of maternal weight-adjusted dosage. No reported adverse effects.	NICE, 2015b; LactMed, 2006-

1.6 Pre-eclampsia and superimposed pre-eclampsia

1.6.1 Diagnostic criteria in women with and without chronic kidney disease

Pre-eclampsia is a multi-system disorder of pregnancy that affects 3-5% of pregnancies (Mol et al., 2016). It is a clinical diagnosis characterised by endothelial dysfunction occurring after 20 weeks' gestation leading to systemic features, which are non-specific in isolation. There is consensus between professional bodies that new onset hypertension is essential for diagnosis (Brown et al., 2018; ACOG, 2019). In the absence of additional features, this is termed gestational hypertension. In the presence of evidence of multi-organ features including proteinuria, maternal organ impairment or uteroplacental dysfunction a diagnosis of pre-eclampsia is made (Table 1.7). Therefore, pre-eclampsia can be diagnosed in the absence of proteinuria, if other disease features exist. Haemolysis, elevated liver enzymes, low platelet (HELLP) syndrome is a severe variant of pre-eclampsia. However, traditional sub-classification of pre-eclampsia and 'severe pre-eclampsia' is misleading due to the potential for sudden and rapid clinical deterioration across the disease spectrum. The terminology, 'pre-eclampsia with severe features' or 'pre-eclampsia without severe features' are now preferentially used (Brown et al., 2018).

Meta-analysis and contemporary cohort data show that women with CKD have ten times the risk of pre-eclampsia compared to women without CKD. Pre-eclampsia occurs in up to 40% of pregnancies in women with CKD, with increased prevalence at higher stages of pre-pregnancy CKD (Zhang et al., 2015; Bramham et al., 2016). However, epidemiological data are limited in the absence of defined diagnostic criteria for women with pre-pregnancy hypertension and/or proteinuria. The clinical interpretation of relative increases in blood pressure and proteinuria is complicated by physiological gestational variation, meaning these parameters are insufficient in isolation for a diagnosis of pre-eclampsia (Brown et al., 2018). Modifications of diagnostic criteria from international guidelines for women with CKD are outlined in Table 1.7.

Table 1.7 Diagnostic criteria for pre-eclampsia: diagnosis requires one essential and one additional clinical feature. Adapted from (ACOG, 2019) and (Brown et al., 2018)
*=severe features, [a]=from (Brown et al., 2018), [b]=from (ACOG, 2019). ALT=serum alanine transferase, AST=serum aspartate transferase, BP=blood pressure, CKD=chronic kidney disease, sBP=systolic blood pressure, dBP=diastolic blood pressure, uPCR=urinary protein:creatinine ratio, uACR=urinary albumin:creatinine ratio

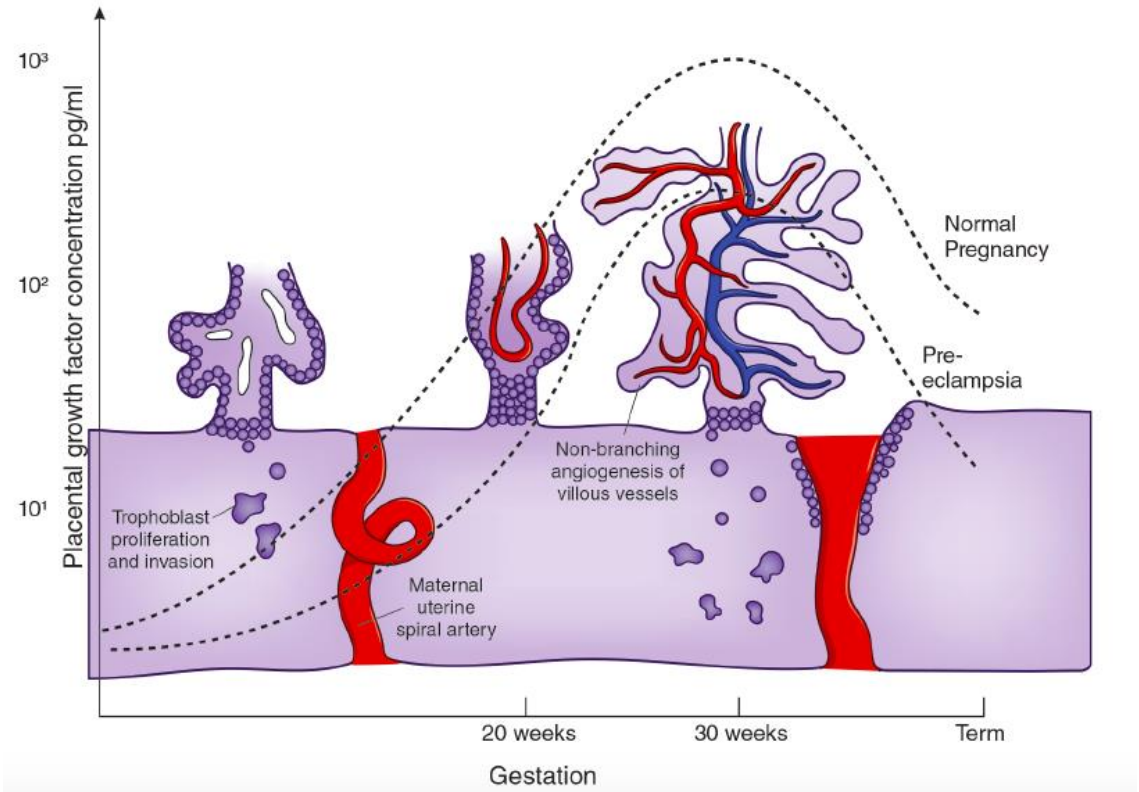
Diagnostic criteria	Pre-eclampsia	Pre-eclampsia in women with CKD
Essential	>20 weeks' gestation	
	Hypertension: New hypertension: systolic BP ≥140mmHg or diastolic BP ≥90mmHg on 2 occasions	Hypertension: • In women without chronic hypertension: as pre-eclampsia • In women with chronic hypertension: no diagnostic threshold • De novo severe BP (systolic BP>160 or diastolic BP >110mmHg) or increase in treatment to maintain BP <160/110mmgHg in research cohorts (Bramham et al., 2016)
Additional	Proteinuria: • uPCR >30mg/mmol • >300mg/24 hour (not indicated if uPCR available) • Dipstick >2+ (if other methods unavailable) • uACR >8mg/mmol (Waugh et al., 2017; NICE, 2019)	Proteinuria: • In women with non-proteinuric CKD: as pre-eclampsia • In women with proteinuric CKD: no diagnostic threshold • >100% increase and uPCR >30mg/mmol in research cohorts (Bramham et al., 2016)
	Serum creatinine: • Serum creatinine >90[a] - 100µmol/L[b]* • Doubling of serum creatinine below 100µmol/L[b]*	Serum creatinine: • In women with CKD and preserved excretory function: as pre-eclampsia • In women with abnormal pre-pregnancy excretory function: no consensus on diagnostic threshold for creatinine, >50% increase within 7 days in research cohorts (Bramham et al., 2016)

	Haematological complications: • platelets <100[b]-150[a] x10[9]/L* • haemolysis* • disseminated intravascular coagulation*
	Liver complications: • AST or ALT >40 IU/L[a] or double normal reference limit[b]* • epigastric/right upper quadrant pain (not attributable to alternate diagnosis)*
	Neurological complications: • eclampsia* • altered mental status* • blindness, persistent visual scotomata* • stroke* • clonus • new onset headache not attributable to alternate diagnosis*
	Respiratory complications: • pulmonary oedema*
	Uteroplacental dysfunction: • Fetal growth restriction, abnormal umbilical artery Doppler waveform, stillbirth

1.6.2 The role of the placenta

The placenta is a highly vascular organ containing an estimated 550km of capillaries, with a surface area of 15m^2 (Burton and Jauniaux, 1995). A complex process including pro-angiogenic and anti-angiogenic factors regulates the vasculogenesis required for normal placental function. Placental growth factor (PlGF) is a member of the vascular endothelial growth factor (VEGF) family, which stimulates endothelial cell activation and placental angiogenesis by binding to a membrane anchored receptor, fms-like tyrosine kinase 1 (Flt-1). In normal pregnancy PlGF is produced in large quantities by the placenta leading to measurable maternal plasma concentrations. PlGF concentrations rise with placental angiogenesis and maturation of uteroplacental vessels in the second trimester, with peak concentrations seen at approximately 30 weeks' gestation (Saffer et al., 2013) (Figure 1.6).

Figure 1.6 Circulating placental growth factor (PlGF) concentrations in normal pregnancy. PlGF concentrations gradually increase during pregnancy coinciding with non-branching angiogenesis of feto-placental vessels and maturation of the uteroplacental circulation to reach a peak at approximately 30 weeks' gestation. Adapted from (Chau et al., 2017, Wiles et al., 2020). PlGF concentrations (log scale) are based on median values using the Triage® PlGF test (previously Alere, now Quidel) (Saffer et al., 2013).



PlGF additionally binds to a circulating receptor, soluble Flt-1 (sFlt-1). sFlt-1 therefore has anti-angiogenic properties: reducing PlGF bioavailability, increasing maternal endothelium sensitivity to inflammatory cytokines (Cindrova-Davies et al., 2011) and causing vasoconstriction due to reduced levels of nitric oxide (Burton et al., 2019). Placental sFlt-1 production leads to rising concentrations throughout normal pregnancy. A decrease in PlGF production from the senescent placenta, in conjunction with increased binding by sFlt-1, is thought to be a trigger for delivery at term. Gestational balance between angiogenic and anti-angiogenic factors is fundamental to the understanding of normal placental function, and by default, pre-eclampsia pathophysiology.

1.6.3 Pre-eclampsia and angiogenesis

The pathogenesis of pre-eclampsia is a multistage process, which begins with disordered placental implantation. Small studies of placental bed biopsies demonstrate defective trophoblast invasion and impaired spiral artery remodelling in pre-eclampsia (Lyall et al., 2013), hypothesised to be due to a partial failure of maternal immune tolerance (Redman and Sargent, 2010). Historically, the disease was considered to remain silent until the clinical syndrome of pre-eclampsia developed in the latter half of pregnancy. However, new data over recent decades demonstrate that impaired placentation leads to a dysfunctional, stressed uteroplacental circulation, which releases inflammatory cytokines and anti-angiogenic factors (such as sFlt-1) into the maternal circulation (Burton et al., 2019). An abnormal balance between angiogenic (PlGF) and antiangiogenic (sFlt-1) factors is therefore quantifiable in maternal blood before the clinical syndrome of pre-eclampsia manifests.

Women with pre-eclampsia have lower PlGF (Levine et al., 2004) and higher sFlt-1 (Maynard et al., 2003; Hertig et al., 2004) concentrations compared to pregnant women without pre-eclampsia. Following extensive evaluation through prospective cohort studies (Rana et al., 2012; Chappell et al., 2013), and a randomised controlled trial (Duhig et al., 2019a), PlGF based testing is now implemented in UK clinical practice as a diagnostic adjunct in women with suspected pre-eclampsia (Table 1.8).

Table 1.8 Angiogenic markers in the prediction and diagnosis of pre-eclampsia in singleton pregnancies in general obstetric cohorts. Adapted from (Stepan et al., 2015) (Duhig et al., 2019a)* or another form of placental insufficiency e.g. fetal growth restriction. PlGF=placental growth factor, sFlt-1=soluble fms-like tyrosine kinase receptor 1

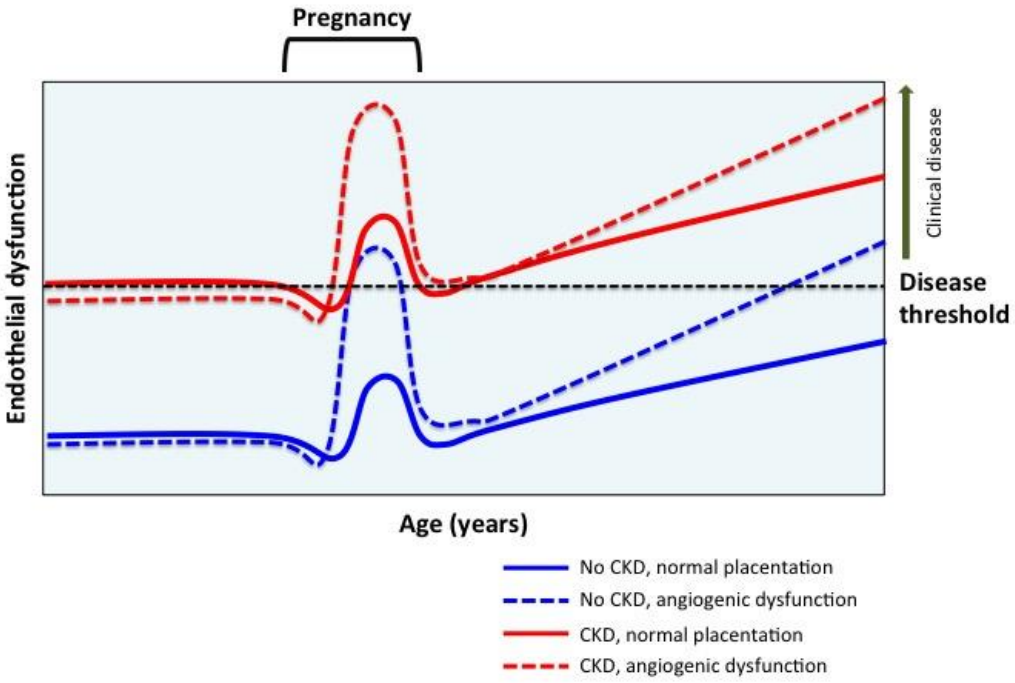
Angiogenic marker	Gestation used	Unlikely to develop pre-eclampsia* in the next week	At risk of developing pre-eclampsia* within 1-4 weeks	Assess as pre-eclampsia*
PlGF (Triage, Alere/Quidel)	20 to <37 weeks	>100pg/ml	12-100pg/ml	<12pg/ml
Ratio sFLT-1:PlGF (Elecsys, Roche)	24 to <34 weeks	<38	38-85	>85

Before 35 weeks' gestation, a PlGF concentration lower than 100pg/ml has been shown to rule out the need for delivery due to pre-eclampsia within the next two weeks with 98% probability in a general obstetric cohort, with better predictive power than other clinical parameters including blood pressure, transaminitis and dipstick proteinuria (Chappell et al., 2013). Although this cohort included 19 of 287 (7.1%) women with known kidney disease, median and interquartile ranges for serum creatinine were 51µmol/L and 44-62µmol/L respectively. More recently, a randomised controlled trial of revealed versus concealed PlGF testing was shown to reduce the time to pre-eclampsia diagnosis and maternal adverse event rate, with no difference in perinatal outcomes (Duhig et al., 2019a), at a cost saving of £149 per patient per patient compared to usual surveillance, including test cost of £70 (Duhig et al., 2019b). Only 4% of women in this trial had CKD.

When PlGF was combined with sFlt-1 to generate the ratio of sFlt-1:PlGF, a value lower than 38 had a negative predictive value of 99% for the development of pre-eclampsia within one week, and 95% for the development of pre-eclampsia within the next four weeks in a cohort of women presenting with suspected disease (Zeisler et al., 2016). Although the proportion of women with CKD was not described, only 1% (12/1050) had pre-existing proteinuria (Zeisler et al., 2016). Similarly, other studies do not report numbers of women with CKD, including the cohorts used to establish the diagnostic threshold of 85 for the sFlt-1:PlGF ratio (Verlohren et al., 2014).

Pre-eclampsia encompasses a spectrum of clinical disease including early and late forms, requiring delivery before or after 34 weeks' gestation respectively (Burton et al., 2019). Early onset pre-eclampsia, which typically has fetal involvement, is driven by placental pathology, evidenced by an angiogenic imbalance. However, when pre-eclampsia develops at later gestations, angiogenic dysregulation is less pronounced (Soto et al., 2012), not exhibited by all women (Noori et al., 2010; Rana et al., 2012; Moore et al., 2012), and the predictive and diagnostic accuracy of angiogenic markers are reduced (Soto et al., 2012; Zeisler et al., 2016). Thus, late pre-eclampsia has been proposed to be due to an imbalance between placental perfusion and metabolic demand, rather than angiogenic dysfunction. This occurs in the context of placental senescence, in the absence of substantial fetal growth restriction and is exacerbated by a predisposition to metabolic and cardiovascular disease (McLaughlin et al., 2018). When there is pre-existing endothelial dysfunction such as CKD, the physiological stress-test of pregnancy may therefore be sufficient for development of pre-eclampsia, even in the absence of substantial angiogenic dysregulation (Roberts and Catov, 2008) (Figure 1.7).

Figure 1.7 Threshold model of disease in women with (red) and without (blue) CKD.
Physiological changes in angiogenesis at the end of pregnancy trigger delivery, but do not manifest as clinical pre-eclampsia in women without CKD (blue line). Women with CKD can manifest pre-eclampsia without significant angiogenic dysfunction (red line) as endothelial dysfunction due to CKD places them closer to the threshold for clinical disease. Women with and without CKD who have an abnormal placenta resulting in pathological angiogenic dysfunction (dash) can both develop pregnancy-related disease (pre-eclampsia or fetal growth restriction). Women without CKD who have pre-eclampsia are more likely to develop cardiovascular and kidney disease later in life. The increased risk of accelerated endothelial disease in the lifetime of women with CKD following superimposed pre-eclampsia (red dash) is hypothesised. Adapted from (Sattar and Greer, 2002, Wiles et al., 2020).



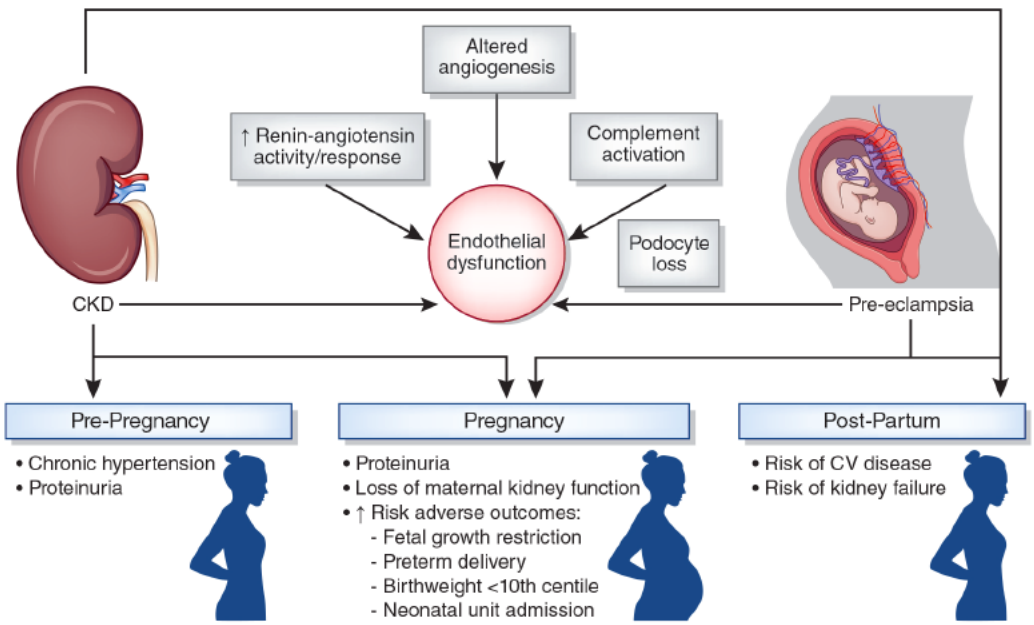
1.6.4 Pre-eclampsia and the kidney

1.6.4.1 Pathological mechanisms

There is an intimate relationship between pre-eclampsia and kidney disease manifest by a shared phenotype including hypertension, proteinuria, impaired excretory kidney function and increased cardiovascular risk (Stillman and Karumanchi, 2007; Leon et al., 2019); an increased incidence of pre-eclampsia in women with both previous acute

kidney injury (Tangren et al., 2017) and underlying kidney disease (Piccoli et al., 2015; Zhang et al., 2015; Williams and Davison, 2008); and an elevated lifetime risk of CKD and end-stage kidney disease in women with previous pre-eclampsia (Vikse et al., 2008; Wang et al., 2013; Kattah et al., 2017; Kristensen et al., 2019). Endothelial dysfunction is a common pathophysiological mechanism underlying both pre-eclampsia and CKD. Putative pathological processes contributing to endothelial dysfunction in both CKD and pre-eclampsia include altered angiogenesis, renin angiotensin system (RAS) activation, complement activation and podocyte loss (Figure 1.8).

Figure 1.8 The relationship between CKD and pre-eclampsia. There is a shared phenotype of endothelial dysfunction, including chronic hypertension and proteinuria. CKD increases the risk adverse pregnancy outcomes, and pre-eclampsia is associated with an increased risk of CKD, including end-stage kidney failure. Common pathophysiological mechanisms include endothelial and angiogenic dysfunction, podocyte loss, complement activation and renin-angiotensin system activation. Adapted from (Wiles et al., 2020). CV=cardiovascular.



As with pre-eclampsia, dysregulation of angiogenesis is described in CKD, although cohort heterogeneity, sample size, and the variable quantification of angiogenic

markers in both kidney tissue and the circulation mean that translation to clinical practice is limited (David et al., 2012; Yuan et al., 2013; Lindenmeyer et al., 2007; Agarwal et al., 2014; Dessapt-Baradez et al., 2014; Anderson et al., 2018).

Changes in RAS activity and/or responsiveness are common to both pre-eclampsia and CKD. Despite the hypertensive phenotype of pre-eclampsia, levels of renin, angiotensinogen, angiotensin I, and angiotensin II are all measurably lower in pre-eclampsia than in normotensive pregnancy (Irani and Xia, 2008; Rodriguez et al., 2012). This points to an exaggerated pressor response to RAS in pre-eclampsia thought to be mediated via an activating autoantibody, which stimulates the AT1 receptor (AT1-AA). Small cohort studies both suggest (Siddiqui et al., 2010) and refute (Stepan et al., 2006) an association between AT1-AA and sFlt-1 indicating that RAS may also contribute to pre-eclampsia independently of angiogenic dysfunction. The role of RAS in CKD progression is better defined, with therapeutic inhibition of RAS recommended for the prevention of progression of proteinuric CKD outside of pregnancy (Levin and Stevens, 2014). Whether the increased RAS response in pre-eclampsia contributes to pregnancy associated kidney injury and/or post-partum disease progression in women with CKD remains unknown.

Concentrations of complement products are higher in pregnant cohorts compared to non-pregnant women (Richani et al., 2005). This increase in complement activity is hypothesised to be a physiological compensation for the gestational reduction in adaptive immunity and facilitates clearance of fetoplacental debris from the maternal circulation. Complement regulatory proteins in the placenta are therefore required to ensure this complement response does not extend to the fetus. In pre-eclampsia, a pathological increase in complement activity and impaired control of complement activation are described in isolated case reports and small cohorts (Soto et al., 2010; Burwick et al., 2013; Regal et al., 2017). Complement activity is similarly hypothesised to play a role in chronic inflammation, vascular endothelial dysfunction and the progression of CKD (Fearn and Sheerin, 2015). Although rare, pregnancy is a recognised trigger for atypical haemolytic uraemic syndrome. This typically presents as

complement mediated kidney disease and typically develops in late pregnancy or in the post-partum period, coinciding with a decline in placental function (Fakhouri et al., 2010; Fakhouri, 2016). A pathological disruption to placental function in pre-eclampsia can therefore be similarly hypothesised to be a trigger for dysfunctional complement-mediated immune regulation, and peri-partum complement activation may contribute to the decline in kidney function that is recognised in women with CKD in relation to pregnancy (Nevis et al., 2011; Piccoli et al., 2015).

1.6.4.2 Kidney pathology

As a disease affecting approximately 5% of pregnancies worldwide, pre-eclampsia is likely to be one of the most prevalent conditions to affect the glomerulus, yet it is diagnosed and managed in the majority of cases without the involvement of a nephrologist. Although glomerular changes are considered pathognomonic of pre-eclampsia, diagnosis is made on the basis of clinical features and kidney biopsy is not indicated.

When kidney biopsy has been performed for historical or research purposes, the predominant change is that of increased glomerular volume and endothelial cell swelling (endotheliosis), leading to narrowing and occlusion of glomerular capillaries. Although mild endotheliosis has been described in normal pregnancies, mesangial interposition distinguishes hypertensive women (Strevens et al., 2003). Duplication of the glomerular basement membrane may be evident in severe disease. Thrombosis of arterioles is unusual, and if evident, non-pre-eclamptic thrombotic microangiopathy should be excluded. Prominent podocytes with vacuolisation, and endocapillary foam cells are a consequence of proteinuria, although foot process effacement is limited suggesting an alternative mechanism for proteinuria in pre-eclampsia. Fibrin deposition may be prominent, with low-level immunoglobulin staining due to non-immune mediated accumulation. Electron-dense deposits are not a feature of pre-eclampsia and warrant exclusion of an immune-mediated glomerulonephritis (Stillman and Karumanchi, 2007; Penning et al., 2014; Han et al., 2014).

Kidney conditions presenting in pregnancy may mimic both normal gestational physiology and pre-eclampsia (Table 1.5). Although rare, kidney biopsy may therefore be indicated in pregnancy for the diagnosis of new or recurrent kidney disease. The risks of kidney biopsy are higher in pregnancy (7%) than outside of pregnancy (1%), with meta-analysis data showing peak bleeding risk at 23-26 weeks (Piccoli et al., 2013a). Expert consensus is therefore that kidney biopsy should only be considered in the first and early second trimester, when histological diagnosis will change management (Wiles and Lightstone, 2018).

1.6.5 Superimposed pre-eclampsia

1.6.5.1 Diagnosis

There is no consensus terminology for pre-eclampsia in women with underlying conditions. Superimposed pre-eclampsia is most commonly used to describe pre-eclampsia in women with chronic hypertension. Chronic hypertension is prevalent in pregnant women with CKD with rates in contemporary cohorts of 27-49% (Piccoli et al., 2015; Bramham et al., 2016) and is an independent risk factor for adverse pregnancy outcome (Bramham et al., 2014). Similarly, proteinuria has been associated with loss of maternal kidney function in women with CKD (Imbasciati et al., 2007). This heterogeneity within CKD is often not considered, with confounding due to chronic hypertension and/proteinuria accounted for in a minority of studies (Zhang et al., 2015). This prevents independent assessment of risk associated with abnormal kidney function from that due to chronic hypertension and proteinuria. Superimposed pre-eclampsia remains an inadequate term in CKD that includes pre-eclampsia with abnormal kidney function, and/or chronic hypertension, and/or proteinuria, or any combination of such features (Table 1.9).

Table 1.9 The terminology of superimposed pre-eclampsia showing possible clinical features (+) with diagnostic utility in superimposed pre-eclampsia with underlying conditions.
BP=blood pressure, CHT=chronic hypertension, CNS=central nervous system symptoms, Cr=serum creatinine, FGR=fetal growth restriction/evidence of uteroplacental insufficiency, Plts=platelet count, uPCR=urinary protein:creatinine ratio

Underlying condition	Pre-pregnancy features	Potential diagnostic features						
		⇑BP	⇑uPCR	⇑Cr	⇑ALT/ AST	CNS	⇓Plts	FGR
CHT	CHT		+	+	+	+	+	+
CKD	1. CHT		+	+	+	+	+	+
	1. Proteinuria	+		+	+	+	+	+
	1. Reduced kidney excretory function	+	+		+	+	+	+
	1. CHT 2. Proteinuria			+	+	+	+	+
	1. CHT 2. Reduced kidney excretory function		+	+	+	+	+	+
	1. CHT 2. Proteinuria 3. Reduced kidney excretory function				+	+	+	+

A diagnosis of superimposed pre-eclampsia requires distinction from physiological variations in blood pressure and kidney function, and de novo and recurrent kidney disease. An assessment of the clinical utility of angiogenic profiling in women with CKD is therefore warranted, yet published data remain limited. The sFlt-1:PlGF ratio has been shown to distinguish CKD (in the absence of pre-eclampsia) from pre-eclampsia (in the absence of CKD), although this distinction does not address the challenge of diagnosing superimposed pre-eclampsia (Rolfo et al., 2015). In two small cohort studies of women with chronic glomerulonephritis, lower PlGF and higher sFlt-1 concentrations were demonstrated in superimposed pre-eclampsia compared to proteinuria in the absence of hypertension, and CKD with a normal pregnancy course; although these studies only included five (Masuyama et al., 2006) and ten (Masuyama et al., 2012) women with superimposed pre-eclampsia. Bramham and colleagues later demonstrated high diagnostic accuracy for angiogenic markers in superimposed pre-eclampsia in a mixed cohort of 165 women with chronic hypertension or CKD or both

(Bramham et al., 2016). The sensitivity, specificity, and positive and negative predictive values of a PlGF concentration <5th centile for predicting the need for delivery within two weeks specifically in women with CKD were 90%, 80%, 47% and 98% respectively although these data included only 19 women with CKD, and ten women with CKD and superimposed pre-eclampsia.

PlGF is known to undergo elimination by the kidney, leading to its detection in the urine of women with pre-eclampsia (Levine et al., 2005). Published data are insufficient to assess whether reduced kidney clearance in women with CKD affects the diagnostic and/or predictive capacity of PlGF quantification, either in isolation or as part of sFlt-1:PlGF ratios. In the cohorts of Masuyama and colleagues, angiogenic dysfunction was measurably reduced with worsening kidney function, although absolute numbers were small (Masuyama et al., 2006, Masuyama et al., 2012). In the larger cohort study by Bramham *et al*., the women with CKD had a median serum creatinine of 71µmol/L (IQR: 51-118µmol/L), thereby preventing an assessment of diagnostic performance in advanced kidney dysfunction (Bramham et al., 2016). Pre-existing endothelial disease in CKD may also mean that pre-eclampsia presents with less angiogenic dysfunction (i.e. at a higher PlGF concentration), compared to women without CKD (Figure 1.7).

1.6.5.2 Management

1.6.5.2.1 Aspirin

Originally trialled due to a hypothesis that an imbalance in prostacyclin and thromboxane A_2 metabolism was involved in the pathogenesis of pre-eclampsia, low-dose aspirin has been shown to be beneficial for reducing risk of pre-eclampsia in high-risk women (Askie et al., 2007; Henderson et al., 2014; Meher et al., 2017; Roberge et al., 2017). For women with CKD, prophylactic use of low-dose aspirin from early pregnancy is extrapolated from these general obstetric cohorts.

The optimum gestation at which aspirin should be commenced is ambiguous with meta-analysis data both suggesting (Roberge et al., 2017) and refuting (Meher et al., 2017) improved pregnancy outcomes when aspirin is commenced prior to 16 weeks' gestation. Current guidelines advise use from 12 weeks' gestation in women with one high-risk indicator (including chronic kidney disease) or two moderate risk indicators (NICE, 2019). The ethics of medication exposure during fetal organogenesis mean that safety data are limited for all drugs prior to 12 weeks' gestation. However, there is no evidence that aspirin is teratogenic and low dose aspirin in not withheld before 12 weeks in women with an indication for treatment.

Optimal aspirin dose is unclear. The most commonly prescribed doses in the UK and US are 75mg and 81mg respectively. Meta-analysis data demonstrate no benefit in the prevention of pre-eclampsia when 60mg is used, with most significant benefit evident at 100mg (Roberge et al., 2017), which is unavailable in the UK. A recent randomised controlled trial demonstrated a 62% reduction in preterm pre-eclampsia in women taking 150mg aspirin from 11-14 weeks' gestation compared to placebo (following identification by a screening algorithm), with no increase in adverse events including kidney injury (Rolnik et al., 2017). Despite absence of data comparing doses of 75-81mg with 150mg, this trial has been sufficient for many clinicians to switch to prescribing 150mg for pre-eclampsia prophylaxis. It is noteworthy that in a secondary analysis, no reduction in pre-eclampsia was seen in women with chronic hypertension (Poon et al., 2017), although it is not clear whether this is a true phenomenon or reflects the clinical challenge of diagnosing pre-eclampsia in women with pre-existing hypertension. The number of women with CKD in this trial was not reported and the benefits and risks of 150mg of aspirin in women with CKD remain unknown.

1.6.5.2.2 Calcium

Meta-analysis demonstrates that calcium supplementation (≥1g/day) is associated with reduced risk of maternal hypertension and pre-eclampsia, though this effect is only demonstrable in cohorts with low calcium intake (Hofmeyr et al., 2018). Calcium

supplementation is therefore not routinely advocated to reduce pre-eclampsia risk in either the US or UK (ACOG, 2019; Webster et al., 2019).

1.6.5.2.3 Management of blood pressure

Historical guidance avoided strict blood pressure control in pregnancy due to largely theoretical concerns that treatment of maternal hypertension leads to compromise of the fetal circulation and therefore impacts on fetal growth. A randomised controlled trial of 'tight' (target diastolic 85mmHg) with 'less tight' (100mmHg) blood pressure control in pregnancy was designed to address this concern. Although achieved blood pressure differences between groups were less than that intended (139/90mmHg versus 133/85mmHg), tighter control was associated with a significant reduction in the incidence of severe maternal hypertension (28% versus 41%) (Magee et al., 2015). A secondary analysis showed that severe hypertension was associated with an increased risk of adverse maternal and fetal outcomes in women with less tight control (Magee et al., 2016). A recent systematic review including 59 trials and 4,723 pregnant women with blood pressures between 140-169/90-109mmHg demonstrated that antihypertensive treatment halved the risk of severe maternal hypertension, with no adverse effects on other maternal and fetal outcomes (Abalos et al., 2018).

In 2019, guidance on hypertension in pregnancy was updated in both the UK and US. In the UK, evidence of a reduction in severe maternal hypertension, in the absence of adverse fetal and neonatal consequences, was sufficient to lead to a recommendation to reduce the treatment threshold for hypertension in pregnancy to 140/90mmHg (Webster et al., 2019). In contrast, a reduction in severe maternal hypertension was deemed insufficient to change US guidance in the absence of a measurable benefit on other maternal outcomes. Treatment thresholds in the US are 160/110mmHg for women with gestational hypertension or pre-eclampsia, and 150/100mmHg in women with end-organ damage, both higher than treatment recommendations outside of pregnancy (ACOG, 2013; ACOG, 2019). In contrast, expert consensus in the UK is that women with gestational hypertension should be offered treatment for blood pressures

greater than 140/90mmHg, with a treatment target of 135/85mmHg or below, and that antihypertensive treatment should not be withdrawn unless blood pressure is consistently less than 110/70mmHg (NICE, 2019). There are insufficient data to determine the risks and benefits of specific blood pressure targets in women with CKD in pregnancy.

The choice of antihypertensive agent in pregnancy is likely to be determined by licensing, availability and clinician experience with no high-level evidence that one agent is beneficial over another (NICE, 2019; Webster et al., 2017b). Labetalol, nifedipine and methyldopa are all considered safe for oral use in pregnancy. Labetalol and hydralazine can also be used intravenously if needed for severe hypertension. Fewer safety data are available for amlodipine and doxazosin, although no adverse fetal effects are reported (NICE, 2011; Vigil-De Gracia et al., 2014; Morgan et al., 2017). Angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists are contraindicated in pregnancy due to fetotoxicity in the second and third trimesters.

1.6.5.2.4 Peripartum management

Intravascular volume contraction with extracellular fluid overload complicates fluid balance assessment in pre-eclampsia. Capillary leak, reduced plasma oncotic pressure, and a variable cardiac output contribute to the risk of pulmonary oedema (Brown and Gallery, 1994; Melchiorre et al., 2013; Dennis and Castro, 2014), with associated maternal morbidity and mortality. In the absence of other haemodynamic insults (e.g. haemorrhage, sepsis) fluid intake should be restricted to insensible losses (30ml/hour) plus anticipated urinary losses (0.5ml/kg/hour), whilst limiting intake to no more than 85-100ml/hour to avoid the risk of pulmonary oedema (Brown et al., 2018; NICE, 2019). There is no role for diuretics in the prevention of pre-eclampsia (Churchill et al., 2007), although they may be required for the treatment of symptomatic fluid overload.

Intravenous magnesium sulfate is indicated in the treatment of eclampsia, for eclampsia prophylaxis in pre-eclampsia with severe features when delivery is anticipated within 24 hours, and for fetal neuroprotection when delivery occurs before 34 weeks (ACOG, 2019; NICE, 2011). In women with reduced kidney function, a loading dose of 4g can be given but maintenance treatment should be reduced, with clinical monitoring for toxicity. Although there is poor correlation between serum concentrations and clinical toxicity, monitoring is advocated in women with either acute kidney injury and/or CKD, with infusions stopped if serum magnesium concentrations are above 3.7mmol/L (9mg/dL) (ACOG, 2019).

Timing of delivery in pre-eclampsia balances the risks of maternal and fetal morbidity against those of prematurity. For pre-eclampsia presenting after 37 weeks, delivery is indicated. Prior to 34 weeks, it is usual to attempt expectant management in order to reduce neonatal morbidity associated with preterm delivery. Decision-making between 34 and 37 weeks was aided by a recent trial in which women between 34 and 37 weeks' gestation with pre-eclampsia were randomised to expectant management or planned delivery. Planned delivery was associated with reduced maternal morbidity, with three-quarters of women treated expectantly progressing to severe pre-eclampsia. Although neonatal admission was higher in those with planned delivery, this occurred without excess of neonatal morbidity (Chappell et al., 2019). The trade-off between a reduction in adverse maternal outcomes and greater neonatal unit admissions (without additional morbidity) should be discussed with women to allow shared decision making on timing of delivery. Women with CKD, including those with kidney transplants, can have a vaginal delivery.

1.6.5.2.5 Post-partum management

Pre-eclampsia is associated with an increased risk of kidney disease later in life in women not known to have CKD prior to pregnancy (Vikse et al., 2008; Wang et al., 2013; Kristensen et al., 2019; Khashan et al., 2019). However, accurate assessment of the impact of superimposed pre-eclampsia on future kidney health in women with CKD

is challenging due to heterogeneity of CKD, variation in definitions of superimposed pre-eclampsia, and the limitations of a binary diagnosis that does not consider pre-eclampsia or CKD severity. Women with CKD and superimposed pre-eclampsia should have close post-partum follow-up of blood pressure and kidney function. The therapeutic value of renin-angiotensin inhibition in post-partum regression of proteinuria is unknown. Safety data for angiotensin converting enzyme inhibitor use in lactation are limited to isolated cases and small case series of women taking enalapril (n=5) (Redman et al., 1990) and captopril (n=11) (Devlin and Fleiss, 1981).

1.6.5.2.6 Future treatments

The pathogenic role of angiogenic dysfunction in pre-eclampsia has led to a focus on targeted therapies that either increase PlGF or block the action of s-Flt1. Animal models include the therapeutic provision of VEGF (Gilbert et al., 2010; Siddiqui et al., 2011) and antagonists of sFlt-1 (Bergmann et al., 2010). sFlt-1 is positively charged and can therefore be selectively removed by apheresis. This technique was described in 11 women with pre-term pre-eclampsia, leading to a reduction in sFlt-1 concentrations, and an increase in gestation by eight days after one treatment and 15 days following multiple treatments, compared to three days in untreated women (Thadhani et al., 2016). A proof-of-concept trial is currently underway examining safety, dosing and efficacy of sFlt-1 apheresis in preterm pre-eclampsia (ClinicalTrials.gov identifier: NCT02923206).

1.7 Conclusions

Due to the physiological changes of pregnancy, eGFR formulae derived from non-pregnant cohorts underestimate kidney function in pregnancy and are not valid for use. Assessment of kidney function in pregnancy therefore uses serum creatinine concentrations, yet reference ranges for serum creatinine in pregnancy have not been established. This complicates the diagnosis of CKD in pregnancy, which is estimated to be a new diagnosis in up to one-third of women with CKD in pregnancy.

CKD is associated with reduced fertility due to mechanistic effects on the hypothalamic-ovarian axis and the cytotoxic treatment of kidney disease, in combination with the psychological implications of a life-long and potentially life-limiting disease. Yet, there are very little data on the assessment and management of fertility in women with CKD.

Women with CKD have an increased risk of adverse maternal and neonatal outcomes including superimposed pre-eclampsia, preterm delivery, small-for-gestational-age infants, neonatal unit admission and perinatal death. Absolute rates of adverse outcome vary between studies and are affected by cohort size, measure of kidney function and variance in clinician thresholds for iatrogenic pre-term delivery and neonatal admission. Although an increment in all complications with worsening kidney function has been shown, contemporary data on pregnancy outcomes in women with moderate and severe CKD (CKD stages 3-5) are limited. The biggest recent cohort includes only 47 women with CKD stages 3-5, with outcomes in larger cohorts reflective of historical renal and obstetric practice. There is a need for robust contemporary data to inform pre-pregnancy counselling and appropriate antenatal and post-natal surveillance in women with CKD, with a particular focus on those with moderate and severe CKD in whom counselling and clinical decision-making is most complex.

Pre-eclampsia and CKD have shared a shared phenotype, rendering standard diagnostic criteria for pre-eclampsia redundant in women with CKD and hypertension and/or proteinuria that predate pregnancy. Yet pre-eclampsia remains a key determinant of adverse pregnancy outcome, contributing to preterm delivery and maternal and neonatal morbidity. The disease trajectory and associated morbidity of pre-eclampsia requires distinction from gestational change and from kidney disease warranting alternative therapeutic intervention. Yet unless systemic or fetal complications of pre-eclampsia arise, discrimination of superimposed pre-eclampsia from CKD remains challenging.

The pathophysiological processes by which CKD confers an increased risk of superimposed pre-eclampsia remain poorly understood. Putative processes, which offer a mechanistic link and the potential for diagnostic discrimination, include endothelial dysfunction, renin-angiotensin system activation and complement dysregulation.

Pre-eclampsia is a disease of placentation, which leads to a dysfunctional balance between angiogenic (PlGF) and antiangiogenic (sFlt-1) proteins that is measurable prior to clinical presentation. Although quantification of angiogenic dysfunction is recommended as a diagnostic adjunct for pre-eclampsia in the general obstetric population, there are limited data on the diagnostic and predictive performance of angiogenic markers in women with CKD in whom the effects of pre-existing endothelial dysfunction and reduced glomerular clearance remain unknown.

Reproductive health issues in women with CKD are increasingly important given the population prevalence of CKD in conjunction with trends in women's health, including increasing maternal age and obesity. Evidence-based and expert guidance are warranted to improve the standard of, and to reduce regional variation in, the care of women with CKD who are pregnant, planning a pregnancy or in the post-partum period.

2 HYPOTHESES AND AIMS

The objective of this thesis was to understand physiological and pathophysiological factors that influence outcomes in reproductive health and pregnancy for women with chronic kidney disease (CKD) before, during and after pregnancy. The hypotheses and aims for each piece of work are outlined below.

2.1 Hypotheses

1. Published serum creatinine concentration data in pregnancy can be synthesised to produce a reference range for pregnancy as a percentage of non-pregnant concentrations, thereby eliminating variation due to assay method and ethnicity.
2. Ovarian reserve is lower in women with CKD compared to women without CKD, with implications for fertility assessment and intervention.
3. In women with moderate and severe CKD (pre-pregnancy CKD stages 3-5):
    a. Knowledge of contemporary maternal and neonatal outcome data will inform pre-pregnancy counselling and antenatal and post-natal surveillance.
    b. The impact of pregnancy upon maternal kidney function can be quantified relative to kidney function prior to pregnancy, generating a measure of pregnancy as equivalent years of kidney disease prior to pregnancy.
4. Endothelial dysfunction, renin-angiotensin system activation, complement activity and kidney injury are involved in the pathogenesis of superimposed pre-eclampsia and may be useful for diagnostic distinction.
5. Endothelial dysfunction and reduced renal clearance alter the diagnostic and prognostic performance of placental growth factor (PlGF) and sFlt-1:PlGF in women with CKD and suspected superimposed pre-eclampsia.
6. A clinical guideline on reproductive health and pregnancy in women with CKD will improve standards and reduce regional variations in the care of women with CKD who are pregnant, planning a pregnancy or post-partum.

2.2 Aims

2.2.1 Systematic review and meta-analysis of serum creatinine concentrations in healthy pregnancy compared to a matched non-pregnant cohort or local non-pregnant reference interval (Chapter 3)

The aim of this work was to compare serum creatinine concentrations in pregnancy ('exposed' cohort) with non-pregnant ('unexposed') and generate trimester-specific ratios of serum creatinine in pregnancy, in women without comorbid conditions and a normal pregnancy course. The intention was to produce trimester-specific pregnant:non-pregnant serum creatinine ratios that can be used to derive normal reference intervals for serum creatinine concentrations in pregnancy, generalisable for different assays and ethnicities.

2.2.2 Prospective cohort study of serum anti-Müllerian hormone concentrations in reproductive-age women with CKD (Chapter 4)

The aim of this work was to investigate serum anti-Müllerian hormone (AMH) concentrations in women across the spectrum of CKD severity, including women on dialysis and with renal transplants, using an automated assay and age-specific normal ranges to facilitate the interpretation of serum AMH concentrations in women with CKD.

2.2.3 Retrospective cohort study of pregnancy and renal outcomes in women with pre-pregnancy CKD stages 3-5 (Chapter 5)

The aims of this work were to describe contemporary maternal and neonatal outcomes in women with pre-pregnancy CKD stages 3-5 (including women with renal transplants), to delineate risk factors for adverse maternal and neonatal outcomes, and to define the impact of pregnancy on maternal renal function by examination of kidney disease trajectory before and after pregnancy.

2.2.4 Nested case-control study of diagnostic indicators of superimposed pre-eclampsia in women with chronic kidney disease (Chapter 6)

This aims of this work were to explore mechanistic links and investigate potential diagnostic indicators for superimposed pre-eclampsia in women with CKD, including markers of the renin-angiotensin system (active renin, angiotensinogen), endothelial glycocalyx dysfunction (hyaluronan, intercellular adhesion molecule (ICAM), vascular cell adhesion molecules (VCAM), P-selectin, E-selectin), complement activation (C3a, C5a, complement factor H, C5b-9) and kidney injury (kidney injury molecule-1, urinary lipocalin-2).

2.2.5 Prospective multicentre study of the predictive accuracy of placental growth factor (PlGF), soluble fms-like tyrosine kinase-1 (sFlt-1), hyaluronan and vascular cell adhesion molecule (VCAM) in women with CKD in pregnancy (Chapter 7)

The aims of this work were to evaluate the predictive performance of maternal PlGF, sFlt-1, the sFlt-1:PlGF ratio and other novel biomarkers for the development of superimposed pre-eclampsia requiring delivery within 14 and 28 days of testing in women with CKD.

2.2.6 A clinical practice guideline on pregnancy and renal disease (Appendix 1)

The aim of this work was to produce an evidence-base guide, including qualitative data describing the patient experience, for women with CKD planning a pregnancy, pregnant, or in the post-partum period in order to improve standards of care and reduce regional variation in the UK.

3 SYSTEMATIC REVIEW AND META-ANALYSIS OF SERUM CREATININE CONCENTRATIONS IN PREGNANCY

3.1 Abstract

3.1.1 Background

Standard assessment of renal function in pregnancy is by measurement of serum creatinine concentrations yet normal gestational ranges have not been established. The aim of this systematic review was to define the difference in serum creatinine in healthy pregnancy compared to concentrations in non-pregnant women to facilitate identification of abnormal kidney function in pregnancy.

3.1.2 Methods

Medline, PubMed, Embase, Web of Science™, theses, key obstetric texts and conference proceedings were searched to July 2017. Eligible studies included quantification of serum creatinine concentrations in a pregnant cohort, with either a reported local laboratory reference range or quantification in a matched, non-pregnant cohort. The outcomes of interest were the mean and upper reference limits for creatinine in pregnancy, measured as a ratio of pregnant:non-pregnant values. Study heterogeneity was examined by meta-regression analysis. PROSPERO registration: CRD42017068446.

3.1.3 Results

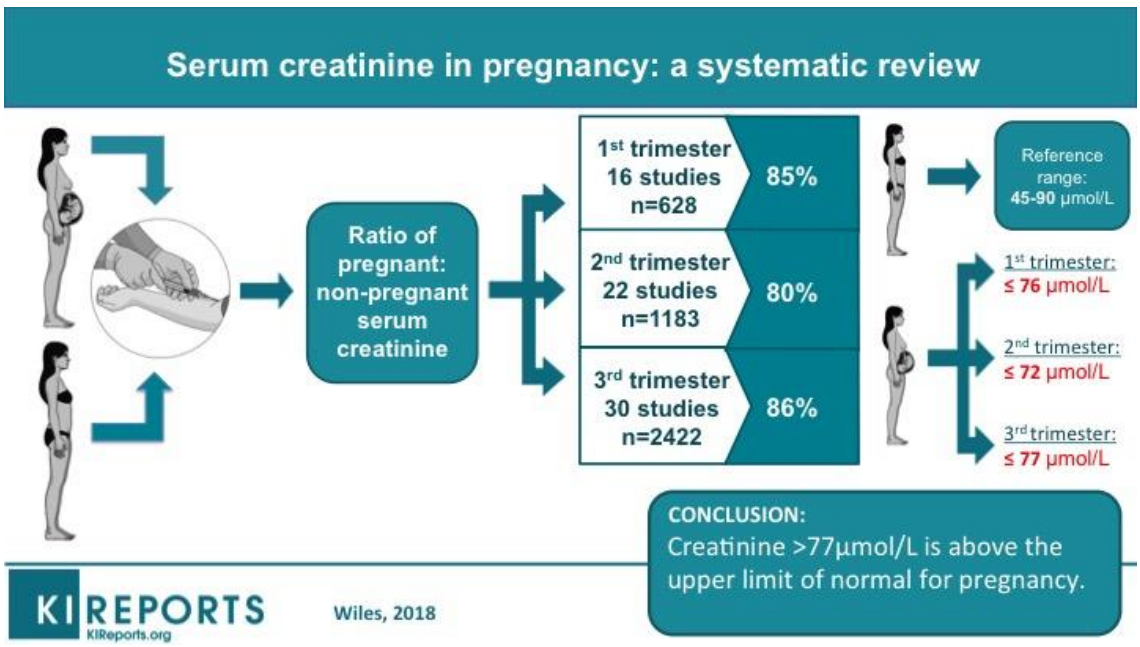
Forty-nine studies were identified. Data synthesis included 4421 serum creatinine values in pregnancy, weighted according to study cohort size. Mean values for serum creatinine in pregnancy were 84%, 77% and 80% of non-pregnant mean values during the first, second and third trimesters respectively. The 97.5th centiles (upper limit of

the 95% reference range) for serum creatinine in pregnancy were 85%, 80% and 86% of the non-pregnant upper limit in sequential trimesters.

3.1.4 Conclusions

Based on a non-pregnant reference interval of 45-90µmol/L, a serum creatinine of >77µmol/L should be considered outside the normal range for pregnancy. Future work can use this value to explore correlation of adverse pregnancy outcomes with serum creatinine concentrations.

3.2 Graphical Abstract



3.3 Introduction

Outside of pregnancy, glomerular filtration rates are routinely estimated from serum creatinine concentrations using standardised equations, facilitating the diagnosis of chronic kidney disease (CKD) and grading of kidney disease severity. Such equations use demographic and clinical variables to correct for physiological factors that affect

serum creatinine. However, in pregnancy, estimated glomerular filtration rates (eGFR) inconsistently underestimate renal function and cannot be used (Koetje et al., 2011). eGFR calculations based on the Modified Diet in Renal Disease (MDRD) formula underestimate GFR in pregnancy by up to 41ml/min/1.73m^2 compared with inulin clearance (Smith et al., 2008). Even in women with pre-eclampsia and contracted maternal plasma volume, eGFR remains inaccurate when derived by both MDRD and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) methods, compared to inulin and creatinine clearance (Smith et al., 2008; Alper et al., 2010).

Serum creatinine concentration therefore remains the only standard, single-point assessment for kidney function in pregnant populations, yet a normal range for serum creatinine in pregnancy has not been established. The upper limit (95th-97.5th centile) of creatinine concentration in healthy pregnancy varies between published cohorts. Reference range limits include values of 72µmol/L (Larsson et al., 2008), 80µmol/L (Abbassi-Ghanavati et al., 2009), 89µmol/L (Girling, 2000) and 95µmol/L (Lokitch, 1993). Such data have limited generalizability without correction for factors known to cause variance in serum creatinine including ethnicity, gestation, and the use of different creatinine assay methods. The most widely cited study of trimester-specific creatinine concentrations includes only 29 healthy pregnant women (Lokitch, 1993). Contemporaneous statements regarding creatinine concentration in pregnancy are largely based on expert opinion including a 'normal' range of 35-71µmol/L (Fischer, 2007; Maynard and Thadhani, 2009), an 'average' creatinine in pregnancy of 53µmol/L (August, 2013), and a recommendation that serum creatinine in pregnancy greater than 75µmol/L should raise suspicion of kidney injury (Lightstone, 2015).

We report here a systematic review of studies including serum creatinine concentrations in healthy pregnancy. Serum creatinine concentrations measured in pregnant cohorts were compared with either a local laboratory reference interval or with creatinine concentrations derived from a matched non-pregnant cohort. The objective of the study was to compare serum creatinine concentration in pregnancy

('exposed' cohort) with non-pregnant ('unexposed') via calculation of a ratio of pregnant:non-pregnant serum creatinine. The hypothesis of the study was that serum creatinine concentrations in pregnancy can be estimated as a proportion of matched non-pregnant values, thereby eliminating variation due to assay method and ethnicity, and allowing generation of generalisable normal reference ratios for serum creatinine concentration in pregnancy.

3.4 Methods

Data sources and searches were conducted by two authors with training in (KW, KB), and experience of (KB), systematic review methodology. Medline, PubMed and Embase were searched from first publication to July 2017. Search terms included creatinine, glomerular filtration, GFR, MDRD, Cockcroft, renal function, kidney function, biochemistry, and clinical chemistry in combination with pregnan$, trimester, gestat$. Specific search strategies are detailed in Box 3.1. A search of conference proceedings specific to the field of obstetrics and gynaecology, as classified by Web of Science™, was also completed. A hand search was undertaken of key English obstetric textbooks for creatinine reference ranges in pregnancy and the sources for these data were included where available. A search for academic theses relevant to pregnancy was performed via proquest.com and ethos.bl.uk.

Citations were independently screened by two authors (KW, KB) based on the title and abstract. Non-English language articles were included if a translation of the abstract into English was available. A full text review was carried out on all eligible studies, and where eligibility was uncertain from the title or abstract. If a control population was not reported, study authors were contacted to provide the relevant local laboratory reference range for the creatinine assay used at the time of their study.

Box 3.1: Database search terms

Ovid Medline (1946 to present), Embase (1974-2017 Week 26)

1. creatinine.tw.
2. creatinine.mp. or exp creatinine/
3. kidney function.mp.
4. function.mp.
5. exp glomerular filtration rate/ or glomerular filtration.mp.
6. GFR.mp.
7. kidney function.tw.
8. renal function.tw.
9. glomerular filtration.tw.
10. GFR.tw.
11. MDRD.tw.
12. Cockcroft.tw.
13. exp biochemistry/ or biochemistry.mp.
14. exp clinical, chemistry/ or clinical, chemistry.mp.
15. or/1-14
16. exp pregnancy/
17. exp pregnancy trimester, first/ or exp pregnancy trimester, second/ or exp pregnancy trimester, third/
18. pregnan$.tw.
19. trimester.tw.
20. gestat$.tw.
21. exp gestation/
22. pregnan$.mp.
23. gestat$.mp.
24. or/16-23
25. exp reference range/
26. normal range.tw
27. reference range.mp.
28. reference interval.tw.
29. exp reference values/
30. reference values.mp.
31. reference values.tw
32. or/25-31
33. 15 and 24 and 32
34. remove duplicates from 33
35. limit 34 to english language
36. limit 35 to "all adult (19 plus years)"
37. limit 36 to adult <18 to 64 years>
38. limit 37 to humans

PubMed (to July 2017)

((((((pregnan*[Title/Abstract]) AND (serum[Text Word] AND creatinine[Text Word]) OR ((renal[Title/Abstract] AND function[Title/Abstract]) OR (serum[Title/Abstract] AND creatinine[Title/Abstract]) OR chemistry[Title/Abstract] OR glomerul*[Title/Abstract] OR GFR[Title/Abstract] OR MDRD[Title/Abstract] OR Cockcroft[Title/Abstract]) AND pregnan*[Title/Abstract])) OR ((reference[Title/Abstract] AND range[Title/Abstract]) AND pregnan*[Title/Abstract])) AND Humans[Mesh]) NOT Review[Publication Type]) NOT "case reports"[Publication Type]

Only studies reporting a local laboratory serum creatinine concentration reference interval or cohort data from a non-pregnant population, and including a measure of data spread across the cohort (standard deviation, standard error, interquartile range, centile, or normal range) were eligible. Gestational age at the time of serum creatinine measurement was required for analysis of data according to trimester. Studies that included pregnant women with kidney disease (upper reference range for creatinine in control population >125µmol/L), vascular disease, diabetes and adverse pregnancy outcomes including pre-eclampsia were excluded. Any study that did not adequately describe the health of the population was excluded, as 'normality' in the population could not be presumed. Studies were also excluded if serum creatinine concentrations were assessed in the non-pregnant cohort within 6 weeks of delivery.

Methodological quality of the studies was scored using the Newcastle-Ottawa scale for observational cohort studies (Higgins and Green, 2011). This included measures of how representative both pregnant and non-pregnant cohorts were of 'average' women of reproductive age in the community, the exclusion of CKD, and whether data were adequately controlled for pregnancy pathology including pre-eclampsia.

Data were extracted in duplicate by two authors (KW, KB) working independently using a proforma based on the study inclusion criteria. Author, publication year, study type (longitudinal/cross sectional), ethnicity, laboratory method for determination of serum creatinine, definition of control population, definition of normal pregnancy, gestation in weeks, and creatinine values including measure of data spread (standard deviation/error or centile) were recorded. Where ethnicity was not recorded, black and non-black ethnicity was assigned based upon the population demographic of the country in which the study took place. Disagreements were resolved by discussion between two authors (KW, KB), with arbitration from a third author (LC).

We defined exposure as pregnancy, and gestation at sample collection was recorded. To enable comparison, creatinine measures were converted from mg/dL to µmol/L using a conversion factor of 88.42.

A normal distribution of serum creatinine concentrations was assumed based on previously published cohort data in non-pregnant (Mussap et al., 2002; Pottel et al., 2008; Huang et al., 2013; Pottel et al., 2015) and pregnant (Girling, 2000, Kristensen et al., 2007a) cohorts. Mean creatinine concentrations in the pregnant and non-pregnant groups were extracted from the raw data, or derived from the median or reference range on the assumption of a normal distribution. Similarly, creatinine reference intervals for both pregnant and non-pregnant cohorts were obtained from the available raw data or a 97.5th centile (upper limit of the 95% reference range) was calculated as the mean value + 1.96 standard deviations.

Data were divided by trimesters of pregnancy (<13 weeks, 13-26 weeks, >26 weeks gestation). Where a range of gestation was included, data were allocated to the trimester for which the gestational range was most representative. If studies included more than one measure of creatinine in the same trimester, mean values for each trimester were calculated. Mean and upper reference values for creatinine concentrations in pregnancy were converted to a proportion (percentage) of the equivalent value from either the matched non-pregnant cohort, or the mean and upper reference limit of the given local reference range. A bootstrapping method (described below) was then used to provide a combined estimate for each trimester.

We used the calculation of the I^2 statistic (Higgins and Thompson, 2002; Higgins et al., 2003) to test for heterogeneity in the pregnant:non-pregnant ratio between studies. Where heterogeneity was found, meta-regression was used to assess whether the differences were due to the use of cross-sectional data, year of publication, the specific exclusion of renal disease, Jaffe and enzymatic methods of creatinine measurement, or black ethnicity. This was done by separate linear regression of each

variable, in each trimester, with impact on the pregnant:non-pregnant creatinine ratio measured as a coefficient value. Year of publication was analysed as a continuous measure and by conversion to decade. Statistical analysis was performed using Stata version 14.2. Analytic weights were defined by Stata.

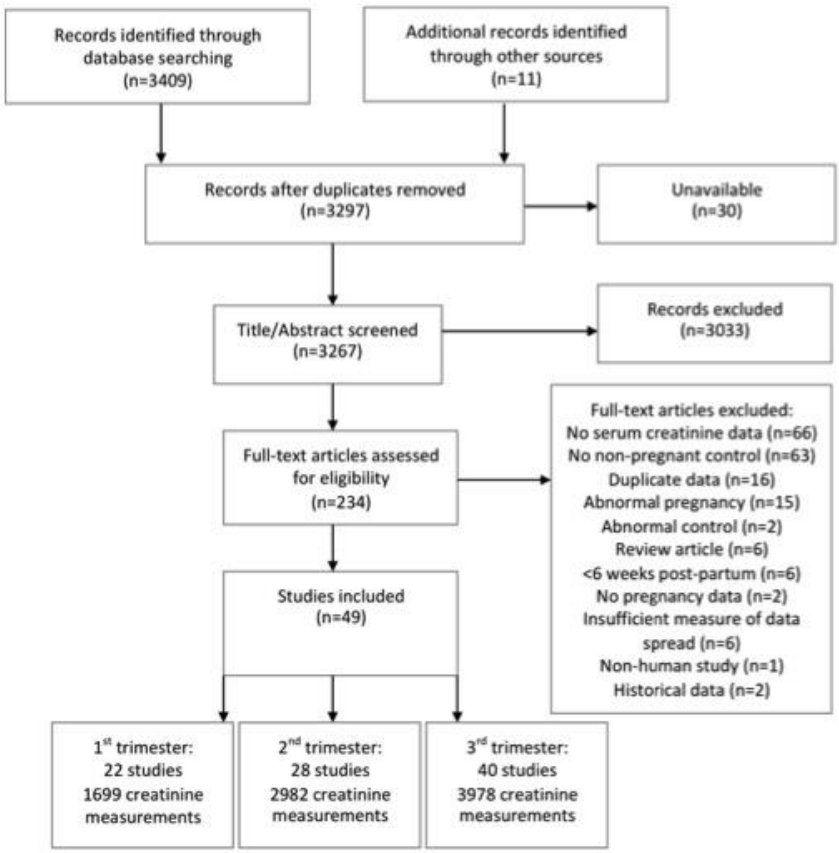
The calculation of pregnant:non-pregnant creatinine ratios meant that standard error measurements were not available, with no accepted method to estimate this quantity from summary data. The complexity of determining the variance and distribution of a ratio value meant we were unable to use most standard meta-analysis techniques including DerSimonian and Laird estimates of the combined effect, Forest plots, and an assessment of publication bias (Scott and Wu, 1981). Data were therefore synthesised using a bootstrapping technique. This involved repeat sampling (10,000 repetitions) with each study acting as a single observation. Bootstrapping was informed by the assessment of heterogeneity and the results of the meta-regression. Heterogeneity between studies was high (I^2>99%). The inclusion of studies using a reference range as the non-pregnant comparator revealed an irreconcilable heterogeneity of data, which prevented meaningful synthesis. Heterogeneity was however reduced (I^2=12.3) when the pregnant:non-pregnant ratio was examined using studies with a large (>100 women) non-pregnant cohort. Meta-regression supported the importance of pregnant cohort size. The bootstrapping technique therefore included all studies with a non-pregnant cohort, weighted according to the product of the geometric mean of pregnant and non-pregnant cohort size. Bias-corrected confidence intervals were generated using an automatic algorithm, which estimates and corrects for bias in the sampling process (DiCiccio and Efron, 1996).

This systematic review was registered on the PROSPERO database with registration number CRD42017068446.

3.5 Results

Electronic searching identified 3297 unique citations including 11 sources identified by hand searching of textbooks. Of the 3267 available sources, we excluded 3033 sources on the basis of title and abstract review. The majority of excluded papers were studies of urinary creatinine concentration in pregnancy usually performed as part of a urinary protein:creatinine ratio in relation to pre-eclampsia, and did not include serum creatinine measurements. Studies of amniotic, fetal or neonatal creatinine measurement were also excluded. A further 185 sources were excluded after full-text review (Figure 3.1). Four studies were included after contacting the authors to provide local laboratory reference ranges at the time of their study.

Figure 3.1 Flow diagram of the identification process for eligible studies.



Forty-nine studies were included in the analysis. Study characteristics including reference details, ethnicity, study type, sample size, trimester specific creatinine measurements, creatinine assay method, assessment of normal pregnancy and the Newcastle-Ottawa assessment of study quality are reported in Table 3.1.

Table 3.1 Study characteristics. Creatinine values are given as μmol/L.
[a]=Data distribution in pregnancy: C=cross-sectional, L=longitudinal
[b]=Assessment of pregnancy normality in control: 1=limited data, 2=exclusion of comorbidity associated with abnormal renal function including pre-eclampsia, diabetes, vascular disease, 3=specific exclusion of renal disease
[c]=but no record that additional data was excluded from study
[d]=provided by study author/centre or available from an alternative source and appropriate for date of study
[e]=women with emesis excluded from extracted data
[f]=includes 2 study cohorts at different altitude
[g]=Total 131 pregnant women, distribution between trimesters not recorded
[h]=mean creatinine data only, upper limit data not derived from interquartile range
Cr=creatinine, NA=not available/stated, ULN=upper limit of normal, LRR=laboratory reference range, WE=white European, AC=Afro-Caribbean, Med=Mediterranean

1st author	Year	Country/ Ethnicity	Data[a]	Control			Trimester 1			Trimester 2			Trimester 3			Assay	Control score[b]	Normal pregnancy outcome confirmed	Newcastle -Ottowa grade
				n	Mean Cr	ULN	n	Mean Cr	ULN	n	Mean Cr	ULN	n	Mean Cr	ULN				
Afolabi	2011	Nigeria	C	15	58	80				9	61	93	3	57	104	Jaffe	1		6
Akbari	2005	Canada	C	13	74	86				68	52	69	68	54	78	NA	2		7
Al Kuran	2012	Jordan	L	LRR	70	96	797	67	97	797	64	100	797	72	132	Jaffe	2		6
Babay	2005	Saudi Arabia	C	40	58	71	54	56	75	53	57	81	50	52	70	NA	3	Yes	8
Babu	2013	India	C	LRR	71	78							25	52	70	NA	3		4
Chapman	1998	WE 10:AC 1	L	13	71	88	10	65	77	8	53	73	8	49	68	Jaffe	3		8
Collins	1981	Canada	C	65	71	88							350	53	71	Jaffe	1		6
Davison	1980	UK	L	10	69	104							10	60	104	Enzyme	3	Yes	9

Davison	1981	UK	L	9	72	85	9	64	77	9	57	69				Enzyme	3	Yes[c]	8
Djordjevic	2004	Serbia-Montenegro	L	30	61	83	30	65	91							NA	1		7
Duvekot	1995	Netherlands	L	10	56	63	10	53	68							NA	1	Yes	6
Fasshauser	2008a	Germany	C	LRR[d]	76	104							20	55	79	NA	1		5
Fasshauser	2008b	Germany	C	LRR[d]	76	104							20	54	79	NA	3		5
de Flamingh	1984	South Africa	C	16	74	88	10	61	75	10	55	71	40	54	93	NA	3		4
Girling	2000	47% WE, 21% AC, 10% Med	C	LRR[d]	88	120	20	68	84	271	63	125	68	54	97	Jaffe	3		6
Guo	2012	China	L	LRR[d]	89	115				96	42	52	96	54	70	Jaffe	3		4
Hanna	2009	Iraq	C	40	84	121	40	83	118	40	75	94	40	54	92	Jaffe	3		7
Heguilén	2007	Argentina	C	8	82	102				5	66	88				NA	3		4
Iqbal	2003	Pakistan	C	26	72	89	18	65	95	22	70	94	23	69	94	Jaffe	1		6
Järnfelt-Samsioe[e]	1985	Sweden	C	LRR	80	110				37	68	94	34	66	94	NA	2	Yes[c]	4
Jaing	2013	Italy	C	19	53	66							29	42	58	NA	1	Yes	7
Kametas[f]	2003	Peru	C	13-15	55-63	68-80				77-80	47-56	58-74				Jaffe	2	Yes	6
Klajnbard	2010	Denmark	L	LRR	70	90				532	58	73	358	62	84	Enzyme	2	Yes	7
Knopp	1985	USA (WE)	C	77	67	88							546	51	78	Jaffe	1		5
Koetje	2011	Netherlands	C	44	69	91	44	58	74							Jaffe	2		4
Kristensen	2007a	Sweden	C	58	65	82	94	53	70	107	51	64	88	54	70	Enzyme	3	Yes[c]	6
Kristensen	2007b	Sweden	C	58	65	82							218	53	68	Enzyme	3	Yes	6
Lain	2005	USA	L	63	50	92	63	51	92	63	44	99	63	50	92	Enzyme	2	Yes	9
Larsson	2008	Sweden	L	51	67	86	50	49	62	51	46	62	52	47	72	Jaffe	2	Yes[c]	6
Lockitch	1993	Most WE	L	121	73	94	29	52	77	29	50	73	29	56	87	Enzyme	2	Yes	6

Lohsiriwat	2008	Thailand	L	26	72	90							26	64	84	Jaffe	3	Yes	9
Mahendru	2014	91% WE	L	54	68	88	54	53	69							NA	2	Yes	7
Majewska	2010	Poland	L	40	72	94	40	50	63	40	46	60	40	52	75	NA	3	Yes	8
Makuyana	2002	Zimbabwe	C	LRR	78	121							72	52	70	Jaffe	3		6
Matteucci	1997	Italy	L	18	82	102	18	64	82	18	62	78	18	65	77	Jaffe	2	Yes	4
Milman	2007	Denmark	L	164	75	96				394	55	71	521	58	81	Jaffe	2	Yes	7
Milne	2002	UK (WE)	L	11	65	95							11	75	78	NA	3	Yes	9
Miri-Dashe	2014	Nigeria	C	127	79	118	43[g]	46	68	43[g]	46	59	43[g]	65	94	Enzyme	1		6
Ogueh	2011	UK	L	13	88	107	12	78	96	13	77	105	12	74	106	Jaffe	1	Yes	8
Pahl	2001	USA	C	15	67	83				16	64	76				Enzyme	3		7
Roberts	1996	UK (WE)	L	11	74	88				16	54	66	11	53	63	Jaffe	3	Yes	9
Saxena	2012	USA	L	12	71	101				12	53	77	12	62	80	Jaffe	1	Yes	8
Schoenmaker	2013	Gambia	C	10	59	89							10	74	68	Enzyme	1		5
Siddiqui	1993	Pakistan	C	30	69	88							35	49	58	Jaffe	3		7
Strevens	2002	Sweden	C	12	61	83							14	48	66	Enzyme	3		6
Van Buul	1995	Netherlands	L	LRR	70	90	66	59	70	66	59	70	66	59	75	Jaffe	3	Yes	8
Vural	1998	Turkey	C	15	63	95							20	61	73	Jaffe	2		4
de Weerd[h]	2003	Netherlands	L	96	70		188	62								Jaffe	2	Yes[c]	6
Weissberg	1991	Israel	C	9	77	92							32	61	71	Jaffe	1		5

Median pregnant cohort sizes were 40, 40 and 35 in the first, second and third trimesters respectively (interquartile range 17-67). Of the 49 included studies, only nine had creatinine concentrations from more than 100 women within the same trimester. Detail regarding the specific exclusion of renal disease was made in 22 studies.

Non-pregnant control cohorts were the 'unexposed' comparator in 39 studies. The median non-pregnant cohort size was 19 women (interquartile range 13-52). Only three studies included more than 100 non-pregnant women in the control cohort. Serum creatinine in pregnancy was compared to a laboratory reference interval in 10 studies. No details were available regarding how these laboratory reference intervals had been derived and whether they were specific to a female population.

Most studies had limited reporting of creatinine assay methods. Creatinine was quantified using the Jaffe reaction in 24 studies and by a kinetic enzymatic reaction in 11 studies. Assay method was not available for 14 studies. Inter-assay precision was reported in only 10 studies. No studies documented whether creatinine assay methods were traceable to an isotope dilution mass spectrometry (IDMS) reference, according to current recommendation (Myers et al., 2006).

Study quality was variable. In 19 of the 49 studies 'normal' pregnancy was confirmed after completion of the pregnancy, with exclusion of data from women who experienced an abnormal pregnancy. However quality scores ranged from 4-9 on the Newcastle-Ottawa scale based on selection, comparability and outcome. Based on previously described thresholds for quality assessment (McPhetters et al., 2012), only 11 of the 49 studies were classified as 'good' quality for this systematic review.

Meta-regression demonstrated that the size of the pregnant cohort had a significant impact on the pregnant:non-pregnant creatinine ratio across all three trimesters. The

use of cross-sectional data, year and decade of publication, the specific exclusion of renal disease, creatinine assay method, and black ethnicity showed no significant effect on the ratio result (Table 3.2).

Table 3.2 Meta-regression showing impact of each variable on the pregnant:non-pregnant serum creatinine ratio in the second trimester. The coefficient is a measure of the difference in the pregnant:non-pregnant ratio between studies that can be attributed to that variable. [[a]=per 100 women]

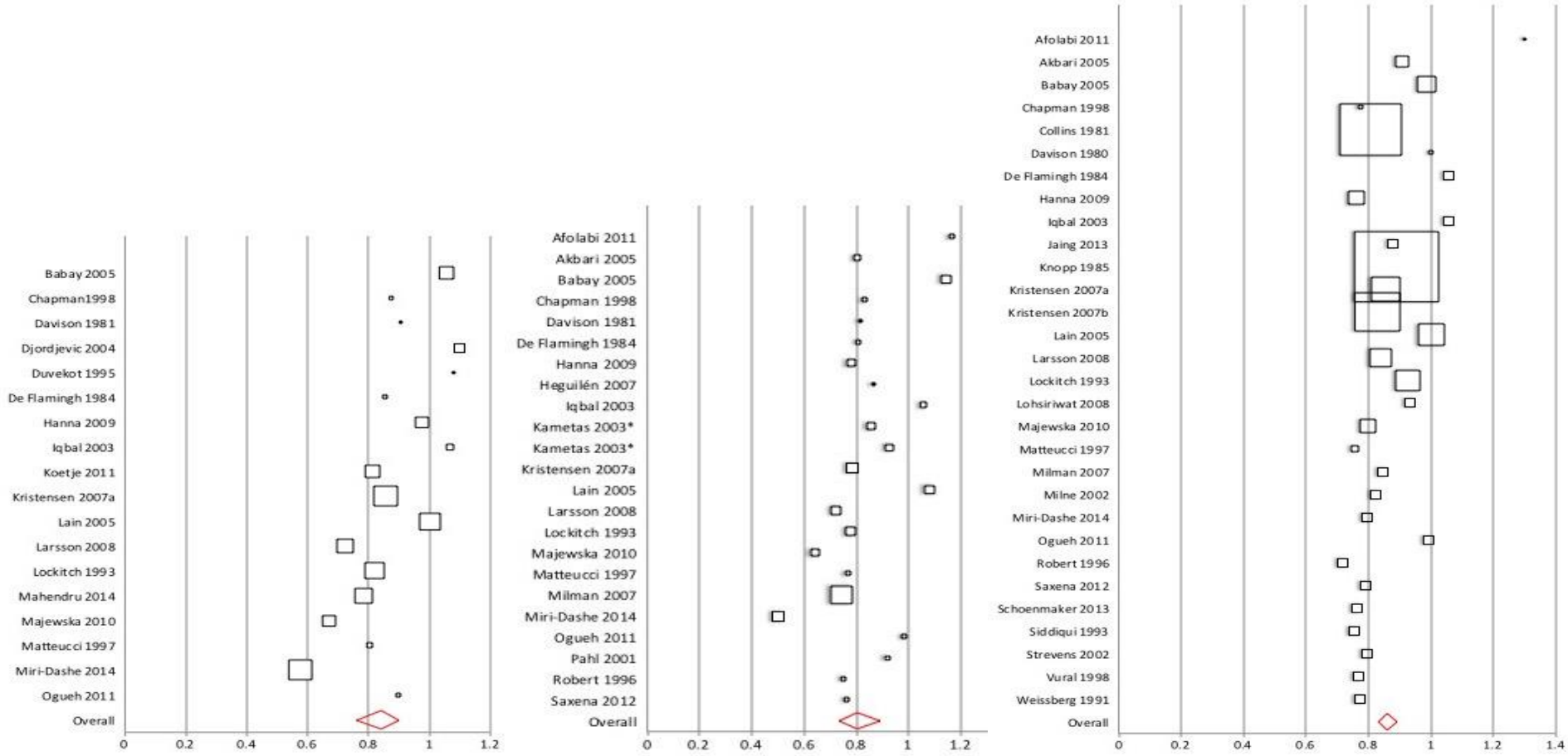
Variable	**Coefficient (95% confidence interval)**	**p-value**
Pregnant cohort size[a]	0.026 (0.002 to 0.049)	0.03
Cross sectional data	0.064 (-0.082 to 0.211)	0.38
Year of publication	-0.003 (-0.013 to 0.007)	0.52
Decade of publication (compared to 2010-17): • 1980 • 1990 • 2000	 0.218 (-0.333 to 0.377) -0.044 (-0.300 to 0.211) 0.059 (-0.096 to 0.214)	 0.90 0.72 0.44
Exclusion of renal disease	0.094 (-0.198 to 0.386)	0.52
Enzymatic method for creatinine (compared to Jaffe method)	-0.069 (-0.286 to 0.319)	0.91
Black ethnicity	-0.266 (-0.592 to 0.061)	0.11

Data synthesis included all studies that had a matched non-pregnant control cohort as the non-pregnant comparator. This included 816 creatinine values (19 studies) from the first trimester, 1183 creatinine values (22 studies) from the second trimester, and 2422 creatinine values (30 studies) from the third trimester. Mean values for serum creatinine in pregnancy were 84% (95% confidence interval 76%-90%), 77% (72%-83%), and 80% (77%-84%) of mean values outside of pregnancy during the first, second and third trimesters respectively. Using the 97.5th centile (upper limit of the 95% reference range), serum creatinine in pregnancy was 85% (76%-93%), 80% (73%-89%), and 86% (83%-89%) of the upper reference limit for non-pregnant females in sequential trimesters (Table 3.3, Figure 3.2).

Table 3.3 Creatinine in pregnancy as a percentage of non-pregnant concentrations according to trimester.
[a]=Example creatinine concentrations are based on a typical value for non-pregnant females of 67.5µmol/L and an upper limit of 90µmol/L (Mazzachi et al., 2000).
[b]=19 studies (816 creatinine measures) inform the mean value and 18 studies (628 creatinine measures) inform the upper limit.
CI=confidence interval.

Trimester	**1st**	**2nd**	**3rd**
Number of included studies	19[b]	22	30
Number of creatinine measures in pregnancy	816[b]	1183	2422
Mean creatinine in pregnancy as % of non-pregnant mean value (95% CI)	84% (76-90)	77% (72-83)	80% (77-84)
Example mean creatinine[a]	**56**	**52**	**54**
Upper limit creatinine as % of non-pregnant upper limit based on a 95% reference range (95% CI)	85% (76-93)	80% (73-89)	86% (83-89)
Example upper limit creatinine[a]	**76**	**72**	**77**

Figure 3.2 Pregnant:non-pregnant ratio values for the upper limit of serum creatinine in the first (left), second (middle) and third (right) trimesters, according to study. Squares represent the point estimate of the ratio for each study, sized according to the study weight (geometric mean product of pregnant and non-pregnant sample size). Confidence intervals are not available due to the complexity of determining the precision of a ratio value. Overall (red) is the summary value and 95% confidence interval generated by the bootstrapping technique for each trimester.



3.6 Discussion

Data synthesis from this systematic review produces mean and upper reference limit values for serum creatinine in pregnancy, compared to non-pregnant values. Mean serum creatinine in pregnancy is 77-84% of mean values outside of pregnancy, and the reference limit for serum creatinine is 80-86% of that in non-pregnant women. Based on a normal female range for serum creatinine of 45-90µmol/L (Mazzachi et al., 2000), this equates to mean serum creatinine values of 56µmol/L, 52µmol/L and 54µmol/L in sequential trimesters, whilst serum creatinine values greater than 76µmol/L in the first trimester, 72µmol/L in the second trimester, and 77µmol/L in the third trimester should be considered to be outside the upper limit of normal for pregnancy. A serum creatinine greater than 77µmol/L in pregnancy should raise the possibility of either acute kidney injury or undiagnosed CKD predating the pregnancy.

As far as we are aware, this is the only study published to date that attempts to offer a value for serum creatinine in pregnancy that is generalizable and not limited to a specific population or creatinine assay technique. The strength of this study is that, through the use of a ratio of pregnant to non-pregnant values, it provides a synthesis of published creatinine data from multiple normal pregnant cohorts, across different ethnicities and assay techniques. Previous reports of creatinine concentrations according to gestation are limited by small numbers of women, diverse methodology and insufficient information about disease states in 'normal women'.

The main limitation of this study is the amount of heterogeneity in the included data. This is likely to be due to a combination of both study design and clinical factors. The complexity of generating standard deviation or standard error values for a ratio value (Scott and Wu, 1981) means that the precision of each study is not considered in the meta-analysis. In addition, creatinine data are summarised as single value for each trimester, which may fail to adequately represent the true variation in serum

creatinine for individual pregnant women, including a progressive physiological adaption to both early pregnancy and parturition (Davison et al., 1980; Davison and Noble, 1981; Roberts et al., 1996; Chapman et al., 1998).

Heterogeneity was reduced when the ratio of pregnant:non-pregnant creatinine used a matched non-pregnant cohort, compared to ratios generated from laboratory reference intervals. This is likely due to quantification in a control population being performed over the same time period as the samples taken during pregnancy, conferring less analytical variance and better reproducibility of values (Ross et al., 1998). In contrast, heterogeneity when using a laboratory reference range as the non-pregnant comparator may have arisen due to baseline differences between the reference and pregnant cohorts including gender, age and ethnicity; although there was insufficient information on the generation of the reference intervals in the included studies to allow assessment of this.

Meta-regression showed no significant difference in the pregnant:non-pregnant creatinine ratio related to the use of alkaline picrate (Jaffe) or enzymatic assay method. This suggests that either the two techniques are affected by pregnancy equally, or that differences between assay techniques are insignificant relative to the effect of pregnancy on serum creatinine concentrations. However, dichotomisation by assay technique may be overly simplistic. This review includes internationally diverse studies, performed over a 34-year period. Although the majority of studies used a Jaffe method, this is known to lack standardisation, resulting in significant methodological variation, which is not measurable in this study (Delanghe and Speeckaert, 2011). Confirmation of the findings of this systematic review using IDMS traceable creatinine assay methods (Myers et al., 2006) is warranted.

The results of this study concur with the known physiological changes of pregnancy; namely a fall in serum creatinine due to gestational hyperfiltration resulting in a 50% increase in creatinine clearance by the second trimester (Davison and Noble, 1981;

Roberts et al., 1996; Chapman et al., 1998), followed by a decrease in creatinine clearance during the third trimester (Davison et al., 1980) leading to an increase in serum creatinine concentrations towards term. This study suggests that the normal range for creatinine in pregnancy is either comparable to (Larsson et al., 2008), or lower (Abbassi-Ghanavati et al., 2009; Girling, 2000; Lokitch, 1993) than that derived from other published cohorts, which are limited by assay method, ethnic differences in creatinine, and small cohort sizes.

The synthesis of data in this study generated a mean value and upper reference range limit for creatinine in pregnancy as a relative proportion of a matched non-pregnant cohort. In practice, clinicians have access to a laboratory reference range for creatinine, rather than a matched control value. For example, at the authors' institution (Guy's and St. Thomas NHS Foundation Trust), the female-specific reference interval for serum creatinine is 45-90μmol/L. This was derived from 269 healthy, Red Cross blood donors (Mazzachi et al., 2000). Although gender specific, this reference interval is not specific to reproductive age women as the reference population was aged 18-70 years. However, the use of this reference interval to derive values for child-bearing age women can be justified on the basis that an increased prevalence of silent chronic kidney disease with age is potentially counterbalanced by a simultaneous age-related decline in creatinine synthesis (Shlipak et al., 2009), with minimal effect on absolute serum creatinine values. Indeed, serum creatinine concentrations have been shown to be stable in female, white European populations between the ages of 20 and 70 years (Pottel et al., 2008). However, the generation of an upper limit for serum creatinine in pregnancy through conversion of a local reference range will always be subject to the limitations under which that reference range was generated, and whether that reference interval is appropriately matched for gender and ethnicity.

Pregnancy-associated acute kidney injury (AKI) occurs most commonly in the third trimester, predominantly due to the development of hypertensive disorders and puerperal pathologies including sepsis and haemorrhage (Prakash et al., 2016;

Gopalakrishnan et al., 2015; Hildebrand et al., 2015; Liu et al., 2015). Diagnostic criteria for AKI do not exist in pregnancy and up to 40% of pregnancy-associated AKI may be missed by clinicians in the UK (Wiles and Banerjee, 2016). In this study, the upper reference limit for serum creatinine in the third trimester is based on data from 30 studies including 2422 pregnant women. Based on a non-pregnant upper limit for creatinine of 90µmol/L (Mazzachi et al., 2000), a new serum creatinine of >77µmol/L should trigger investigation for underlying AKI.

This study generated a mean and upper reference limit for creatinine in pregnancy, as a percentage of that outside of pregnancy. In the absence of both a valid measure of eGFR and practical measure of true GFR in pregnancy, the assessment of renal function in pregnant women remains limited to serum creatinine despite confounders, insensitivity, and inter-assay variability. However, the use of creatinine thresholds of 85%, 80% and 86% of the upper limit of the non-pregnant reference range for the first, second and third trimesters respectively, represents a new and clinically relevant diagnostic parameter, which is potentially generalisable across different cohorts and creatinine assays methods.

A clinically relevant reference interval distinguishes physiology from pathology. The clinical utility of the pathological threshold suggested by this systematic review now requires prospective studies which correlate a creatinine in pregnancy that is >86% of the upper limit for non-pregnant females with adverse maternal and/or neonatal outcomes. Whether a similar percentage change in serum creatinine in pregnancy is seen in women with chronic kidney disease remains unknown, although a failure of serum creatinine to fall in the first trimester of pregnancy is hypothesised to represent a failure of the renal system to adapt in pregnancy and is used anecdotally as a poor prognostic indicator (Fitzpatrick et al., 2016). Future research is required into patterns of serum creatinine change in women with chronic kidney disease who do and do not develop adverse pregnancy outcomes.

3.7 Addendum

This systematic review was completed prior to the publication of a retrospective cross-sectional, population study from Canada, which included serum creatinine concentrations in almost 250,000 women (Harel et al., 2019). These data are comparable to the results of this systematic review, demonstrating a second trimester nadir of 47µmol/L (compared to 52µmol/L in this study) and a 95th centile value of 76-81µmol at the time of delivery (compared to a 97.5th centile of 77µmol/L in the third trimester reported here). The Canadian data are derived from women with a least two measures of serum creatinine in pregnancy. Although women with known CKD, pre-pregnancy albuminuria, gestational hypertension and pre-eclampsia were excluded; the indication for serum creatinine testing, which is not routine in pregnancy in Canada, was unknown. The possibility of an underlying condition, rather than routine screening of normal women cannot therefore be excluded. In addition, details of the creatinine assay and race are not provided, limiting generalisability.

4 PROSPECTIVE COHORT STUDY OF SERUM ANTI-MÜLLERIAN HORMONE CONCENTRATIONS IN REPRODUCTIVE-AGE WOMEN WITH CKD

4.1 Abstract

4.1.1 Background

Serum anti-Müllerian hormone (AMH) is a biomarker of ovarian reserve. There are limited data to guide the clinical interpretation of AMH in women with CKD. The purpose of this study was to examine AMH concentrations in women with chronic kidney disease compared to women without chronic kidney disease.

4.1.2 Methods

We conducted a prospective cohort study of serum AMH concentrations in 163 non-pregnant women with CKD. Serum AMH concentrations were compared to age-specific AMH centiles from 887 healthy female controls.

4.1.3 Results

Participants included 30 women with stage 1 CKD, 37 women with stage 2 CKD, 26 women with stage 3a CKD, 31 women with stage 3b CKD, and 39 women with stages 4-5 CKD. Median eGFR was 51 (IQR 31-80) ml/min/1.73m^2. Serum AMH concentrations were lower in all CKD stages compared to women without CKD. Women with CKD aged 20-24 years had comparable serum AMH concentrations (median 1.959ng/ml) to women aged 35-39 years without CKD (median 1.995ng/ml). There was no evidence that glomerular filtration rate was an independent modifier of serum AMH concentrations. More than half of women with CKD (58%) were predicted to have a low response to gonadotrophin stimulation.

4.1.4 Conclusions

Women with CKD have a lower ovarian reserve compared women without CKD of a similar age. Women with CKD who fail to conceive within six months of regular unprotected intercourse should be considered for fertility assessment and intervention. More than half of women with CKD are predicted to have a lower ovarian response to gonadotrophin stimulation based on AMH concentrations. In addition to serum AMH concentrations, age and the clinical implications of intravascular fluid depletion should inform gonadotropin dosing in women with CKD.

4.2 Introduction

Anti-Müllerian hormone (AMH) is expressed in the granulosa cells of developing follicles. Serum concentrations of AMH therefore reflect the number of small antral follicles and are considered to be the best currently available biomarker of ovarian reserve (Broer et al., 2014). AMH is proposed to be clinically superior to other biomarkers because serum concentrations are unaffected by the growth of a dominant follicle in the latter half of the menstrual cycle meaning that intra- and inter cycle variability is limited (van Disseldorp et al., 2010). AMH concentrations can be used to predict response to fertility treatment and individualise dosing for ovarian stimulation (Dewailly et al., 2014; Iliodromiti et al., 2015; NICE, 2013), and there is evolving evidence demonstrating its use in the assessment of iatrogenic gonadotoxicity and prediction of the female reproductive lifespan (Broer et al., 2014; Iwase et al., 2018).

CKD is estimated to effect 3% women of reproductive age (Piccoli et al., 2010). The mechanistic effects of chronic kidney disease (CKD) upon fertility include inhibition of the hypothalamic-pituitary axis due to low oestrogen levels, loss of the normal cyclical variation in luteinising hormone concentration, and hyperprolactinaemia (Wiles et al., 2018). Sexual dysfunction, voluntary childlessness and the use of cyclophosphamide, which is known to be gonadotoxic (Ioannidis et al., 2002; Boumpas et al., 1993),

contribute to the complex clinical scenario in which women with CKD present for fertility advice and investigation. Yet the interpretation of circulating AMH concentrations in women with CKD remains poorly understood. Published data regarding the assessment of ovarian reserve in women with CKD are limited to three small cohort studies (Sikora-Grabka et al., 2016; Stoumpos et al., 2018; Szydłowska et al., 2018), which report higher AMH concentrations in haemodialysis patients compared to other stages of CKD. These studies are limited by manual methods of AMH quantification and the absence of assay-specific normal ranges (Sikora-Grabka et al., 2016; Szydłowska et al., 2018). To date, no analysis of AMH according to stage of CKD has been published. Serum AMH concentrations in women with early stage CKD (eGFR >60ml/min/1.73m^2) have never been described, yet these women represent the majority of women with CKD presenting for pre-pregnancy advice in the UK (Wiles et al., 2015).

The aim of this study was to investigate serum AMH concentrations in women across the spectrum of CKD severity, including women on dialysis and with renal transplants, using an automated assay and age-specific normal ranges, to facilitate the interpretation of serum AMH concentrations in women with CKD.

4.3 Materials and methods

Non-pregnant women were recruited from specialist pre-pregnancy and general nephrology clinics at two UK centres (Guy's and St. Thomas' NHS Foundation Trust and King's College Hospital NHS Trust) between 2015 and 2017. Inclusion criteria were reproductive age with a known diagnosis of CKD based on Kidney Disease: Improving Global Outcomes (KDIGO) criteria (Levin and Stevens, 2014).

Participants were enrolled prospectively. Collected demographic data included age, ethnicity, renal disease aetiology, menstrual cycle and pregnancy history, mode of dialysis, medication and contraceptive use. Estimated glomerular filtration rates

(eGFR) were calculated from serum creatinine concentrations using the CKD-EPI formula, with classification according to CKD stage: 1 (eGFR>90ml/min/1.73m^2), 2 (eGFR 60-89ml/min/1.73m^2), 3a (eGFR 45-59ml/min/1.73m^2), 3b (eGFR 30-44 ml/min/1.73m^2), 4-5 (eGFR<30ml/min/1.73m^2).

Serum samples were collected at routine outpatient attendance or prior to dialysis in women receiving regular dialysis treatment. Samples were stored on ice before being centrifuged at 1500xg for 10 minutes at 4^{o}C. The separated supernatant was aliquoted and stored at -80^{o}C. Serum AMH was quantified using a fully automated AMH electrochemiluminescence assay (Elecsys® AMH assay, Roche diagnostics) (Anckaert et al., 2016). The inter-assay and intra-assay coefficients of variation were 1.4 % and 2.4% respectively.

Differences across CKD stages were assessed using a Chi-square test for categorical variables and a Kruskal-Wallis test for continuous variables. The relationship between AMH concentrations and eGFR was examined using non-parametric Spearman correlation. In order to remove age as a confounding factor, AMH concentrations were converted from pmol/l to ng/ml using a multiplication factor of 0.14. Age-specific AMH centiles were then generated from data derived from 887 healthy women aged 20-50 with regular menstrual cycles (Anckaert et al., 2016) using polynomial interpolation from percentile point estimates at 1-5% intervals provided by Roche Diagnostics. Mann-Whitney tests were used to examine for differences in age-corrected AMH centile between women with and without CKD. As study participants were recruited from tertiary centres that may not provide routine renal care, a history of cyclophosphamide use was not always available. To exclude cyclophosphamide use as a confounder of serum AMH concentrations (Mok et al., 2013; Morel et al., 2013), analyses were repeated with the exclusion of women with a diagnosis of lupus, non-lupus vasculitis, and transplantation where the aetiology of renal failure was unknown. An assay specific cut-off of ≤5.4pmol/l was used to predict a low response to gonadotropins in accordance with National Institute of Health and Care Excellence

recommendation (NICE, 2013). Single linear regression was used to assess the effect on AMH centile attributable to CKD (compared to healthy controls), and to examine the effect of age, serum creatinine, eGFR, ethnicity, chronic hypertension, renal disease aetiology, transplantation, dialysis, regular menstruation (in the absence of oestrogen and progesterone use), and the use of oestrogen or progesterone containing medication within three months of sample collection in women with CKD. Statistical analysis was performed using GraphPad Prism 7 XML and Stata 15.1.

Approval was provided by the UK Research Ethics Service and the Health Research Authority (15/WA/0009). The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

4.4 Results

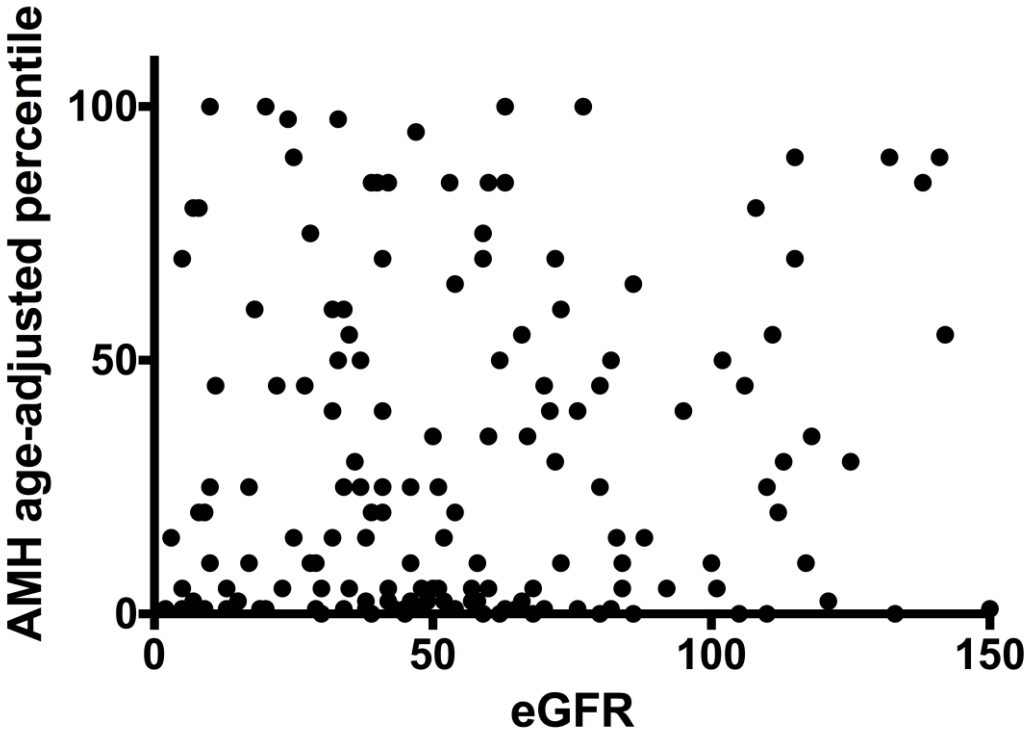
Serum AMH concentrations were measured in 163 women with CKD including 30 women with stage 1 CKD, 37 women with stage 2 CKD, 26 women with stage 3a CKD, 31 women with stage 3b CKD, and 39 women with stage 4-5 CKD. Median eGFR was 51 ml/min/1.73m^2 (IQR 31-80). The most common cause of renal disease was non-lupus glomerulonephritis (26%), with reflux nephropathy more prevalent amongst women with higher stages of CKD. There were 37 (23%) women with a functioning renal transplant and 10 (6%) receiving dialysis therapy. Cohort demographics according to CKD stage are shown in Table 4.1. Women with more advanced CKD were older but there were no other measurable demographic differences across CKD stages.

Table 4.1 Cohort demographics, serum AMH concentrations and age-corrected AMH centiles according to CKD stage. Values are median (interquartile range) unless stated.
[a]=AMH ≤5.4pmol/l (Beckman-Coulter assay) is used to predict a low ovarian response to gonadotrophin stimulation (NICE, 2013). eGFR = estimated glomerular filtration rate, AMH = anti-Müllerian hormone

CKD Stage	**All**	**1**	**2**	**3a**	**3b**	**4-5**
n	163	30	37	26	31	39
Age	36.5 (29.9-42.9)	33.2 (25.9-36.8)	38.3 (30.0-44.8)	38.0 (30.6-42.3)	34.8 (30.7-44.1)	41.7 (34.5-44.9)
Ethnicity (%):						
• White European	84 (62)	16 (64)	17 (63)	16 (67)	17 (63)	18 (55)
• Black	30 (22)	5 (20)	5 (19)	6 (25)	5 (19)	9 (27)
• South-East Asian	22 (16)	4 (16)	5 (19)	2 (8)	5 (19)	6 (18)
eGFR (ml/min/1.73m^2)	51 (31-80)	116 (109-140)	72 (65-80)	52 (48-56)	38 (34-41)	15 (9-23)
Aetiology (%)						
• Non-lupus GN	42 (26)	11 (37)	9 (24)	6 (23)	9 (29)	7 (18)
• Lupus/vasculitis	28 (17)	10 (33)	3 (8)	4 (15)	3 (10)	8 (21)
• Hereditary/congenital	21 (13)	2 (7)	11 (30)	1 (4)	2 (6)	5 (13)
• Reflux	14 (9)	0 (0)	3 (8)	2 (8)	4 (13)	5 (13)
• Diabetic nephropathy	13 (8)	2 (7)	1 (3)	2 (8)	4 (13)	4 (10)
• BP/renovascular	8 (5)	0 (0)	2 (5)	3 (12)	2 (6)	1 (3)
• Other	15 (9)	0 (0)	4 (11)	3 (12)	2 (6)	6 (15)
• Unknown	22 (13)	5 (17)	4 (11)	5 (19)	5 (16)	3 (8)
Renal transplant (%)						
• Functioning	37 (23)	1 (3)	3 (8)	10 (38)	14 (45)	9 (23)
• Non-functioning	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)
Current dialysis (%)	10 (6)	0 (0)	0 (0)	0 (0)	0 (0)	10 (56)
• Haemodialysis	7 (4)	0 (0)	0 (0)	0 (0)	0 (0)	7 (39)
• Peritoneal dialysis	3 (2)	0 (0)	0 (0)	0 (0))	0 (0)	3 (17)
Regular menstruation (%)	35/51 (69)	8/11 (73)	5/8 (64)	5/8 (64)	8/12 (67)	9/12 (75)
Oestrogen containing drug use (%)	9/133 (7)	2/24 (8)	5/30 (17)	0/20 (0)	0/25 (0)	2/34 (6)
Progesterone containing contraceptive use (%)	25/131 (19)	4/24 (17)	5/29 (17)	3/20 (15)	7/25 (28)	6/33 (18)
Serum AMH pmol/l	6.33 (1.90-15.65)	10.06 (4.62-20.73)	6.02 (1.79-12.85)	4.27 (1.44-8.79)	8.89 (4.99-19.36)	5.29 (1.27-14.77)
Serum AMH ng/ml	0.88 (0.27-2.19)	1.41 (0.65-2.90)	0.84 (0.25-1.80)	0.60 (0.20-1.23)	1.25 (0.70-2.71)	0.74 (0.18-2.07)
AMH centile	19 (8-53)	30 (4-55)	28 (10-53)	11 (4-31)	24 (14-59)	15 (7-60)
AMH ≤5.4pmol/l[a]	95 (58)	9 (30)	18 (47)	17 (65)	8 (26)	20 (51)

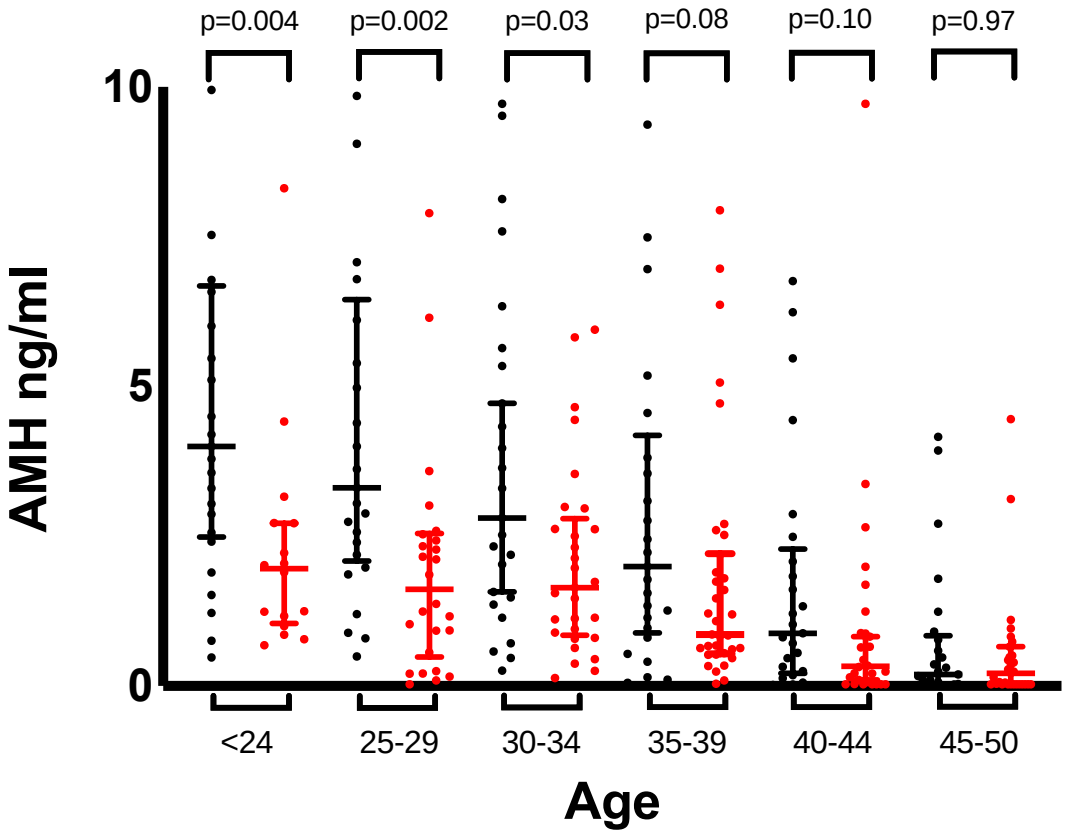
AMH concentrations were lower and maternal age was higher with increasing CKD stage (Table 4.1). However, there was no measurable difference in age-corrected AMH centiles across CKD stages, or correlation between eGFR and AMH centile (Figure 4.1).

Figure 4.1 Scatter plot of age corrected AMH centiles against eGFR in women with CKD.



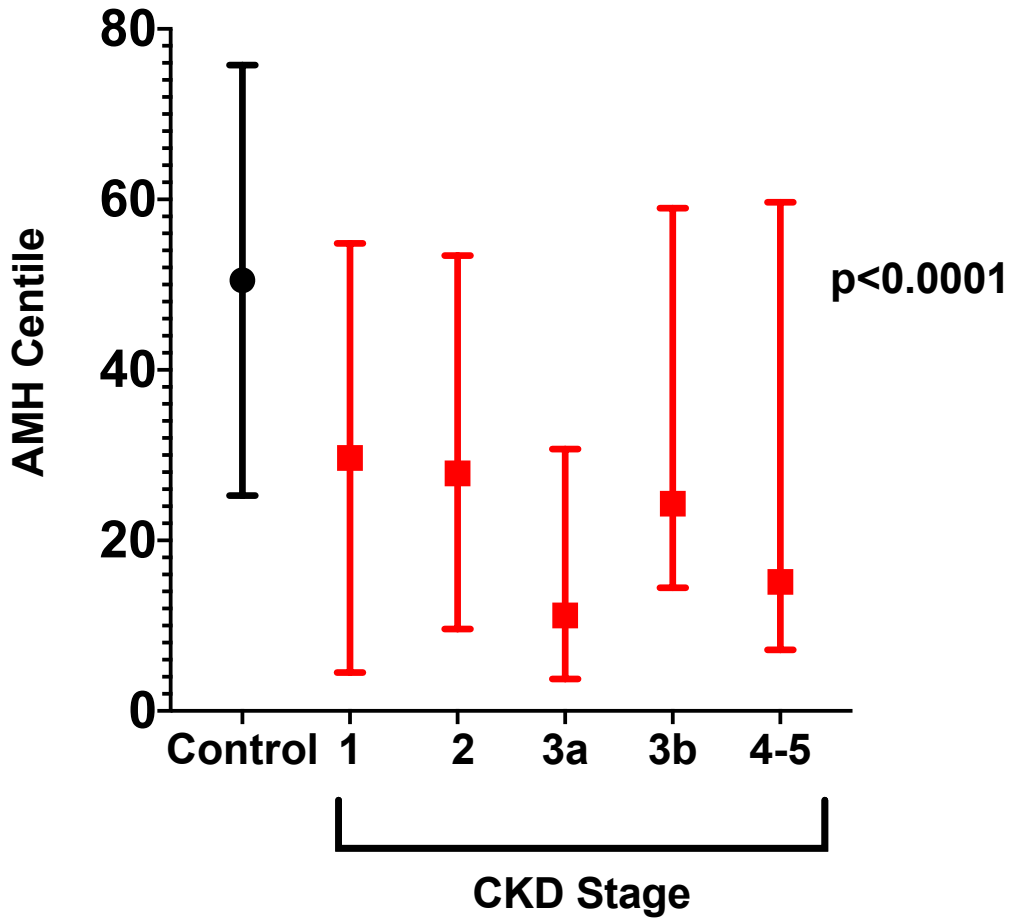
For women aged under 35 years, serum AMH concentrations were lower in women with CKD compared to those without CKD (Figure 4.2). Women aged 20-24 with CKD had comparable AMH concentrations (median 1.959ng/ml, interquartile range 1.126 to 2.717ng/ml) to women aged 35-39 without CKD (median 1.995ng/ml, interquartile range 0.889 to 4.185ng/ml, p=0.741). For women aged 35 years and over, age was a more important determinant of AMH concentrations than CKD.

Figure 4.2 Serum AMH concentrations in women with CKD (red) compared to age matched women without CKD (black). Bars show median ± interquartile range values. Serum AMH concentrations for women without CKD were obtained from Anckaert *et al*., 2016 (Anckaert et al., 2016).



AMH centiles were lower in both early and late stages of CKD compared to concentrations in women without CKD (Figure 4.3). This difference was apparent even with the exclusion of women with a confirmed or possible history of previous cyclophosphamide exposure including women with lupus, non-lupus vasculitis, and transplantation where the aetiology of renal failure was unknown (p=0.004).

Figure 4.3 AMH centiles in women without CKD (control, black) and in women with CKD stages 1-5 (red). Bars show median centile value ± interquartile range. p<0.001 is a measure of the difference in AMH centile across all groups shown.



A low ovarian response to gonadotrophin stimulation was predicted in 95 (58%) of women with CKD, with no significant difference detectable between CKD stages (Table 4.1).

Amongst women with CKD, there was no measurable relationship between AMH centile and serum creatinine concentration, eGFR, CKD stage, ethnicity, chronic hypertension, glomerular disease, transplantation, dialysis, regular menstruation, or oestrogen and progesterone containing drug use (Table 4.2).

Table 4.2 Linear regression analysis of age-corrected AMH centiles in women with CKD. The coefficient is a measure of the difference in AMH centile that can be attributed to that variable.
[a] compared to women without CKD
[b] White European/Black/South-East Asian
[c] in the absence of oestrogen and progesterone use

Variable	Simple linear regression coefficient (95% confidence interval)	p-value
CKD[a]	-17.82 (-25.42 to -10.21)	<0.001
Serum creatinine	-0.01 (-0.03 to 0.01)	0.424
eGFR	0.016 (-0.112 to 0.145)	0.803
CKD stage	-1.16 (-5.18 to 2.87)	0.570
Ethnicity[b]	2.08 (-2.21 to 6.38)	0.339
Black ethnicity	-7.82 (-20.23 to 4.58)	0.215
Chronic hypertension	3.27 (-6.53 to 13.06)	0.511
Renal transplantation	1.08 (-10.40 to 12.56)	0.853
Glomerular disease	-2.53 (-13.04 to 7.98)	0.635
Regular menstruation[c]	2.94 (-36.04 to 41.91)	0.872
Oestrogen-containing drug use	-4.070 (-25.752 to 17.611)	0.711
Progesterone-containing drug use	-9.560 (-23.401 to 4.281)	0.174

4.5 Discussion

Serum AMH concentrations in women aged less than 35 years with CKD are substantially lower than in women without CKD. For example, women with CKD aged 20-24 years have comparable serum AMH concentrations to women aged 35 years and over without CKD. Lower serum AMH concentrations are evident across all CKD stages, even with the exclusion of women exposed to cyclophosphamide therapy. There is no evidence that glomerular filtration rate is an independent modifier of serum AMH concentrations, or that serum AMH concentrations are higher in women on dialysis. More than half of women with CKD would be anticipated to have a low ovarian response to gonadotrophin stimulation.

To my knowledge, following a literature search, this is largest study to date examining serum AMH concentrations in women with CKD and the first to assess serum AMH across the spectrum of CKD severity including both mild and severe disease. This study uses a fully automated, precise, sensitive AMH assay (Anckaert et al., 2016), which avoids the variability and poor reproducibility encountered in historic studies (Rustamov et al., 2012), is unaffected by complement activity (Anckaert et al., 2016) and provides an accurate and validated quantification on samples previously stored at -80^{O}C (Gassner and Jung, 2014). A strength of this study is the use of assay specific, age–specific centiles, as age is a known confounder of both low serum AMH concentrations (Lanham et al., 2017) and impaired renal function (Hill et al., 2016).

This study shows a reduction in age-corrected AMH centiles in women with CKD including those on dialysis. This is consistent with the molecular size of AMH, which at 140kDa is too large to be substantially influenced by glomerular filtration or dialytic clearance. Despite this, previous published cohorts reported higher serum AMH concentrations in 26 women receiving dialysis compared to women with earlier stage CKD (Stoumpos et al., 2018), and a reduction in serum AMH concentrations after the successful renal transplantation of 10 women previously on dialysis (Sikora-Grabka et al., 2016). These results are based on limited control data (Sikora-Grabka et al., 2016) and a small number of age-corrected values (Stoumpos et al., 2018). Whether there are modality-specific effects in haemo- and peritoneal dialysis remains unknown and a larger study is needed.

Reliable menstrual history was available for only 31% (51/163) of women with CKD in this study. However, this is unlikely to have impacted on the study findings given that menstrual irregularity is thought to lead to an increase in AMH via impaired folliculogenesis and polycystic ovarian syndrome (Anckaert et al., 2016), and therefore cannot explain the lower AMH concentrations in women with CKD compared to women without CKD. Hormonal contraceptives were used by 24% (32/131) of women

in this cohort. The impact of hormonal contraceptive use upon AMH concentrations remains unclear (D'Arpe et al., 2016), with studies both suggesting (Kristensen et al., 2012, van den Berg et al., 2010) and refuting (Streuli et al., 2008, Li et al., 2011b) an association with AMH concentrations. Our study provides no evidence that oestrogen-containing or progesterone-only contraceptive use in the three months prior to the study sample were significant modifiers of age-specific AMH centile in women with CKD.

The finding of a reduction in serum AMH concentrations in women with CKD is similar to the AMH profile described in other chronic diseases including Crohn's disease (Şenateş et al., 2013), coeliac disease (Cakmak et al., 2018), chronic viral hepatitis (Karampatou et al., 2018), psoriasis (Aydogan Mathyk et al., 2019), multiple sclerosis (Graves et al., 2018) and neuromyelitis (Thöne et al., 2018). Lower AMH concentrations in women with chronic inflammatory disease can be hypothesised to be an appropriate physiological response, reducing fertility where pregnancy may be detrimental to maternal health and/or the survival of the offspring, and this may be relevant to women with CKD.

The clinical implications of lower AMH concentrations in women with CKD are uncertain. Although serum AMH is utilised as quantitative marker of ovarian reserve, it does not measure the quality of ovarian follicles and cannot be used in isolation to determine likely reproductive success. Women with low circulating concentrations of AMH can and do conceive (Pacheco et al., 2017). AMH concentration is a variable predictor of both time to conception (Depmann et al., 2017; Hagen et al., 2012; Steiner et al., 2011) and time to menopause (de Kat et al., 2016; Tehrani et al., 2009; Broer et al., 2011). Age, rather than biomarker quantification, is advocated as the initial predictor of the likelihood of reproductive success (NICE, 2013). The clinical significance and predictive value of a lower measured AMH in young women with CKD remains unclear.

AMH concentrations are used to predict the response to ovarian stimulation in women undergoing assisted reproduction (NICE, 2013). More than half of women with CKD in this cohort (58%) would be predicted to have a low response. Further work is needed to determine how these data should be used to inform gonadotropin dosing in women with CKD given the clinical implications of intravascular fluid depletion and superimposed acute kidney injury which may result from hyperstimulation.

CKD impacts on mechanistic, functional and psychological components of fertility and is associated with lower serum AMH concentrations compared to age-matched women without CKD. Although the trajectory of AMH decline across the reproductive lifespan shows marked inter-individual variation (de Kat et al., 2016), these data suggest that women with CKD who fail to conceive within six months of regular unprotected intercourse should be considered for fertility assessment and treatment. This mirrors guidelines for women aged over 36 years without CKD (NICE, 2013) in whom serum AMH concentrations are comparable, although consideration of the risks of ovarian stimulation in women with CKD is warranted. These findings have potential implications for planning timing of pregnancy for women with CKD, although prospective studies on natural reproductive success are needed.

5 RETROSPECTIVE COHORT STUDY OF PREGNANCY AND RENAL OUTCOMES IN WOMEN WITH PRE-PREGNANCY CHRONIC KIDNEY DISEASE STAGES 3-5

5.1 Abstract

5.1.1 Background

Contemporaneous data are required for women with chronic kidney disease stages 3-5 (CKD 3-5) to inform pre-pregnancy counselling and institute appropriate antenatal and post-natal surveillance.

5.1.2 Methods

A retrospective cohort study in women with pre-pregnancy CKD stages 3-5 after 20 weeks' gestation was undertaken in six UK tertiary renal centres in the UK between 2003 and 2017. Factors predicting adverse outcomes and the impact of pregnancy in accelerating the need for renal replacement therapy were assessed.

5.1.3 Results

There were 178 pregnancies in 159 women. The live birth rate was 98%, but 56% of babies were born before 37 weeks' gestation. Chronic hypertension was the strongest predictor of delivery before 34 weeks' gestation. Of 121 women with known pre-pregnancy hypertension status, the incidence of delivery before 34 weeks was 36% (31/96) in women with confirmed chronic hypertension, compared to 0% (0/25) in normotensive women. The risk of delivery before 34 weeks doubled in women with chronic hypertension from 20% (95% CI: 9-36%) to 40% (95% CI: 26-56%) if the gestational fall in serum creatinine was less than 10% of pre-pregnancy concentrations. Women with a urinary protein:creatinine ratio >100mg/mmol prior to pregnancy or before 20 weeks' gestation had an increased risk for birthweight below the 10th centile (OR 2.57, 95% CI: 1.20-5.53). There was a measurable drop in estimated glomerular

filtration rate (eGFR) between pre-pregnancy and post-partum values (4.5ml/min/1.73m^2), which was greater than the annual decline in eGFR prior to pregnancy (1.8ml/min/1.73m^2/year). The effect of pregnancy was therefore equivalent to 1.7, 2.1 and 4.9 years of pre-pregnancy renal disease in CKD stages 3a, 3b and 4-5 respectively. The pregnancy-associated decline in renal function was greater in women with chronic hypertension and in those with a gestational fall in serum creatinine less than 10% of pre-pregnancy concentrations. At one-year post-partum, 46% (58/126) of women had lost 25% or more of their pre-pregnancy estimated glomerular filtration rate, or required renal replacement therapy.

5.1.4 Conclusions

Contemporary pregnancies in women with CKD 3-5 are complicated by preterm delivery, low birthweight and loss of maternal renal function. Chronic hypertension, pre- or early pregnancy proteinuria, and a gestational fall in serum creatinine of less than 10% of pre-pregnancy values are more important predictors of adverse obstetric and renal outcomes than CKD stages 3-5. Pregnancy in women with CKD stages 3-5 advances the need for dialysis or transplantation by 2.5 years.

5.2 Introduction

Chronic kidney disease (CKD) is estimated to complicate 3% of pregnancies, with 1 in 750 pregnancies in women with CKD stages 3-5 (Piccoli et al., 2018). CKD is a risk factor for adverse outcomes including preterm delivery, fetal growth restriction, and a decline in maternal renal function (Jones and Hayslett, 1996; Imbasciati et al., 2007; Williams and Davison, 2008; Piccoli et al., 2015). However, the interplay between hypothesised predictors of adverse pregnancy outcomes including chronic hypertension (Bramham et al., 2014; Bramham et al., 2016), proteinuria (Imbasciati et al., 2007; De Castro et al., 2017) and advanced renal disease (Imbasciati et al., 2007; Piccoli et al., 2015), remains unclear, limiting the information available for contemporary risk counselling prior to pregnancy (Piccoli et al., 2018). In view of the

predicted rise in CKD prevalence in women of reproductive age as a consequence of population trends in obesity (MacLaughlin et al., 2015) and diabetes (Wu et al., 2016b), the impact of CKD on pregnancy is increasingly relevant to contemporary practice.

Although CKD has been shown to increase the risk of adverse pregnancy outcomes compared to women without CKD (Zhang et al., 2015), the incidence of adverse outcomes in women with moderate to severe CKD is derived from small (Piccoli et al., 2015; He et al., 2018) and historical (Jones and Hayslett, 1996; Trevisan et al., 2004; Imbasciati et al., 2007) cohorts, and by non-systematic review of published data (Williams and Davison, 2008). The largest published cohort, which included 82 pregnancies from 1971-1993, predated the use of estimated glomerular filtration rate (eGFR) and does not reflect contemporary standards of obstetric and renal care (Jones and Hayslett, 1996). The impact of pregnancy upon maternal CKD remains unclear with published data suggesting (Jones and Hayslett, 1996; Trevisan et al., 2004) and refuting (Piccoli et al., 2015; He et al., 2018) an association between CKD stage and loss of maternal renal function. These studies are limited by small numbers and do not examine the trajectory of renal function decline prior to pregnancy. Thus, there is a need for larger, contemporaneous datasets in women with clinically significant chronic kidney disease using pre-pregnancy staging of CKD for risk stratification and an analysis of renal function prior to as well as following pregnancy, in order to inform pre-pregnancy counselling and appropriate surveillance during pregnancy and in the postpartum period.

We report on neonatal and maternal outcomes of pregnancies in women with CKD stages 3-5 (eGFR <60ml/min/1.73m^2) who were not receiving dialysis at conception. The aims of this work were to investigate the impact of CKD 3-5 on pregnancy, to delineate risk factors for adverse maternal and neonatal outcomes and to define the impact of pregnancy on maternal renal function by examination of renal disease trajectory before and after pregnancy in women with and without renal transplants.

5.3 Materials and Methods

5.3.1 Study design

This retrospective cohort study included women from six specialist obstetric-nephrology centres in the UK to which all women with CKD stages 3-5 in those regions are referred in pregnancy. Women were included if they conceived a pregnancy between January 2003 – June 2017 and had an eGFR <60ml/min/1.73m^2 calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levin and Stevens, 2014), or a creatinine >125μmol/L prior to 20 weeks' gestation in the absence of a precipitant for kidney injury. Women on dialysis at the time of conception were excluded, as were those with spontaneous fetal loss prior to 20 weeks' gestation. Conception date was calculated as 280 days before the estimated date of delivery by dating scan or from last menstrual period if scan details were not available.

Serum creatinine concentrations were recorded at up to nine time-points: 12-24 months prior to conception, 6-12 months prior to conception, closest value prior to conception, early pregnancy, pre-delivery, first postpartum value, 3-6 months postpartum, 1-year post-partum and the latest value postpartum. For women who had more than one baby during the study period, postpartum creatinine values were recorded up until the next calculated date of conception. All recorded creatinine concentrations were representative values selected by consultant nephrologists, with consideration of previous values where available. Creatinine concentrations were not recorded once renal replacement therapy was commenced.

A diagnosis of chronic hypertension was assigned if there was a requirement for antihypertensive treatment prior to pregnancy, a diastolic blood pressure >85mmHg before 16 weeks' gestation (Macdonald-Wallis et al., 2015), or a documented diagnosis in the hospital record. A diagnosis of chronic hypertension was not made if there was isolated use of renin-angiotensin blockade, unless confirmed by clinical information.

Birthweight was converted to a gestation-related optimal weight (GROW) centile (Version 8.0.3)(Gardosi et al, 2018). For twin pregnancies, the larger birthweight was used in the summary outcome data.

A diagnosis of pre-eclampsia could not be reliably made due to inter-clinician variation in diagnosis and documentation in patients with renal disease, and changing definitions over the study period.

5.3.2 Statistical Analysis

Kruskal-Wallis and Chi-square tests were used to compare demographic and outcome data across CKD stages as appropriate. Age, black ethnicity, chronic hypertension, pre-pregnancy CKD stage, proteinuria, renal transplantation, glomerulonephritis and a fall in gestational creatinine compared to pre-pregnancy values (Fitzpatrick et al., 2016) were tested as predictors of adverse outcomes. A proteinuria threshold of PCR >100mg/mmol pre-pregnancy, or in early pregnancy if no pre-pregnancy value was available, was used (Imbasciati et al., 2007). Adverse renal outcomes were defined at 1-year post-partum as either a 25% loss in eGFR compared to pre-pregnancy or progression to renal replacement.

Simple and multivariable logistic regression were used to determine demographic and clinical predictors of clinically important adverse obstetric outcomes, defined as gestational age <34 weeks (Manuck et al., 2016) and birthweight <10^{th} centile (Mendez-Figueroa et al., 2016). Risk estimates were generated using probabilities and exact binomial confidence intervals.

The trajectory of change in maternal renal function in relation to pregnancy was examined using regression modelling of pre- and postpartum CKD-EPI eGFR values,

using a maximum likelihood model. Models included the overall trend in eGFR, the step-loss in eGFR in relation to pregnancy, and the trajectory of eGFR decline both pre- and postpartum. The optimum model was selected using information criterion comparison and linear regression. eGFR modelling was used to generate a measure of eGFR decline in pregnancy according to pre-pregnancy CKD stage, converted to years of background disease based on the calculated pre-pregnancy trajectory of eGFR. To assess that this trajectory modelling was not distorted by single unconfirmed creatinine concentrations or by outlying data, the trajectory of renal decline was additionally examined in women with at least two creatinine measures both prior to, and following pregnancy. Linear regression with case-wise deletion was used to examine the impact of clinical variables on the step-change in eGFR during pregnancy.

Multifetal pregnancies were excluded from logistic and linear regression analyses and the regression modelling of maternal renal function. Statistical analyses were performed using GraphPad Prism 8 and Stata 15.1.

5.3.3 Ethics

The direct-care clinical team collated anonymised, retrospective data collected as part of usual patient care (Guy's and St. Thomas' NHS Foundation Trust, Imperial College Healthcare NHS Trust, King's College Hospital NHS Foundation Trust and Nottingham University Hospitals NHS Trust). Imperial College Healthcare NHS Trust and University Hospitals of Leicester NHS Trust collected data as part of registered clinical audits. Women who conceived after February 2014 at Guy's and St. Thomas' NHS Foundation Trust, Imperial College Healthcare NHS Trust and King's College Hospital NHS Foundation Trust gave consent for access to their medical records, approved by the Research Ethics Service and the Health Research Authority (15/WA/0009).

5.4 Results

There were 178 pregnancies in 159 women, including two twin pregnancies and 19 sibling infant pairs. Median pre-pregnancy creatinine was 140μmol/l (interquartile range (IQR) 123-167μmol/l, range 104-457μmol/l). Pre-pregnancy CKD was stage 3a in 79 (47%) women, stage 3b in 63 (38%) women and stage 4-5 in 25 (15%) women. Pre-pregnancy CKD stage was unclassified for eleven women. In ten women there was no pre-pregnancy value available but creatinine concentrations in pregnancy were greater than 125μmol/L (median 163μmol/l, IQR 145-190). One pregnancy was included in a woman diagnosed with stage 3a CKD prior to her first pregnancy, but without a serum creatinine measurement being done in the period between her pregnancies.

There were no measurable differences in age, ethnicity, BMI, nulliparity, renal disease aetiology or renal transplantation between women of different CKD stages. The presence or absence of chronic hypertension was confirmed in 121 (68%) of pregnancies. The prevalence of chronic hypertension was lower in women with CKD stage 3a compared to women with stages 3b and 4-5. Pre-pregnancy quantification of proteinuria was available in 102 (57%) women, with early pregnancy values available for an additional 38 women (median gestation 13.4 weeks, IQR 9.0 to 17.6 weeks). Pre-pregnancy proteinuria was significantly higher in women with stages 4-5 CKD compared to stage 3 CKD. The most common renal diagnoses were glomerulonephritis in 49 (28%) and reflux nephropathy in 47 (26%) of women (Table 5.1).

Table 5.1 Maternal characteristics prior to conception. Values are median ± interquartile range unless specified. If information was not available a different denominator is shown.

[a=]includes 11 pregnancies unclassified by pre-pregnancy eGFR: serum creatinine in pregnancy >125µmol/L (n=10) and known CKD stage 3a prior to a previous pregnancy with no inter-partum measure (n=1).

[b]=pre-pregnancy (n=102) or early pregnancy (n=38).

CKD = chronic kidney disease, CKD-EPI = chronic kidney disease epidemiology collaboration equation, uPCR = urinary protein:creatinine ratio.

CKD stage pre-pregnancy (CKD-EPI eGFR ml/min/1.73m^2)	**All (<60)**	**CKD 3a (45-59)**	**CKD 3b (30-44)**	**CKD 4-5 (<30)**	**p-value across CKD stages**
n (%)	178[a]	79 (47)	63 (38)	25 (15)	
Age at conception, years	32.8 (30.1-35.9)	33.2 (30.7-36.4)	33.1 (30.5-37.5)	32.5 (27.4-35.3)	0.2526
Black ethnicity (%)	31/176 (18)	17/78 (22)	5/62 (8)	8/25 (32)	0.8713
Body mass index, kg/m^2	26.2 (22.3-30.9)	26.4 (22.4-32.0)	24.9 (21.6-31.5)	25.5 (22.6-27.9)	0.2706
Nulliparity (%)	61/155 (39)	31/75 (41)	18/50 (36)	8/21 (38)	0.6913
Chronic hypertension (%)	96/121 (79)	39/55 (71)	33/38 (87)	16/17 (94)	0.0159
Pre-pregnancy uPCR[b], mg/mmol	63 (18-215)	29 (13-100)	54 (19-172)	188 (87-341)	0.0006
Functioning renal transplant %	43 (24)	23 (29)	16 (25)	3 (12)	0.1117
Aetiology of CKD (%)					
• **Glomerulonephritis**	49 (28)	25 (32)	16 (25)	8 (32)	0.0744
• **Reflux nephropathy**	47 (26)	19 (24)	19 (30)	8 (32)	0.3512
• **Diabetic nephropathy**	16 (9)	5 (6)	7 (11)	2 (8)	0.5537
• **Congenital/rare cause**	14 (8)	7 (9)	3 (5)	1 (4)	0.2897
• **Polycystic kidney disease**	8 (4)	5 (6)	2 (3)	0 (0)	0.1421
• **Other**	18 (10)	8 (10)	4 (6)	4 (16)	0.6682
• **Unknown**	26 (31)	10 (13)	12 (19)	2 (8)	0.9415

5.4.1 Obstetric Outcomes

Live birth rate was 98% (174/178), with 56% (99/178) of babies born preterm (<37 weeks' gestation) and 26% (47/178) delivering prior to 34 weeks' gestation. Gestational age and birthweight were lower, and the incidence of small-for-gestational-age babies (<10th and <3rd centile) higher, with increasing stage of CKD. Overall, 35% (58/167) of babies required neonatal unit admission with higher admission rates in the infants of women with CKD stage 3b or more. More than half of women (57%, 98/172) had a Caesarean delivery with no marked differences across CKD stages (Table 5.2).

Table 5.2 Obstetric and renal outcomes of women with CKD. Values are median ± interquartile range unless specified. If information was not available a different denominator is shown.

[a=]includes 11 pregnancies unclassified by pre-pregnancy eGFR: serum creatinine in pregnancy >125µmol/L (n=10) and known CKD stage 3a prior to a previous pregnancy with no interpartum measure (n=1).

CKD = chronic kidney disease, CKD-EPI = chronic kidney disease epidemiology collaboration equation, eGFR = estimated glomerular filtration rate, RRT = renal replacement therapy.

CKD stage pre-pregnancy (CKD-EPI eGFR ml/min/1.73m^2)	**All[a] (<60)**	**CKD 3a (45-59)**	**CKD 3b (30-44)**	**CKD 4-5 (<30)**	**p-value across CKD stages**
n	178	79	63	25	
Gestation at delivery, weeks	36.3 (33.3-37.7)	37.4 (34.7-38.1)	35.9 (33.4-37.1)	34.7 (32.4-36.2)	0.0003
Delivery <37 weeks (%)	99 (56)	32 (41)	39 (62)	22 (88)	<0.0001
Delivery <34 weeks (%)	47 (26)	16 (20)	16 (25)	10 (40)	0.0628
Caesarean delivery (%)	98/172 (57)	40/78 (51)	39/60 (65)	14/24 (58)	0.2566
Birthweight, grams	2495 (1856-2952)	2750 (2200-3120)	2490 (1860-2912)	1872 (1290-2474)	<0.0001
Birthweight <10th centile (%)	57/158 (36)	17/72 (24)	17/53 (32)	14/22 (64)	0.0013
Birthweight <3rd centile (%)	34/158 (22)	9/72 (13)	11/53 (21)	9/22 (41)	0.0049
Neonatal unit admission (%)	58/167 (35)	18/75 (24)	24/59 (41)	11/23 (48)	0.0139
Fall in serum creatinine in pregnancy <10% of pre-pregnancy creatinine (%)	86/162 (53)	36/76 (47)	33/62 (53)	14/24 (58)	0.0454
25% fall in eGFR or RRT at 1 year post-partum (%)	58/126 (46)	17/49 (34)	17/48 (35)	19/22 (86)	0.0003

Chronic hypertension was the strongest predictor of delivery before 34 weeks with 32% (31/96) of women with chronic hypertension delivering before 34 weeks' gestation (Table 5.3). In contrast there were no deliveries prior to 34 weeks in normotensive women (0/25). In women with chronic hypertension, the risk of delivery before 34 weeks doubled from 20% to 40% if the gestational fall in serum creatinine concentration was less than 10% of pre-pregnancy concentrations (Table 5.4). A urinary protein:creatinine ratio (uPCR) greater than 100mg/mmol prior to pregnancy or before 20 weeks' gestation increased the risk of a birthweight below 10th centile (OR 2.57; CI: 1.20 to 5.53, p=0.016) (Table 5.5). Chronic hypertension and pre-existing proteinuria were stronger determinants of the risk of adverse obstetric outcomes than CKD stages 3-5. Maternal age, black ethnicity, renal transplantation and glomerulonephritis were not independently associated with adverse obstetric outcomes (Tables 5.3 and 5.5).

Table 5.3 Odds ratios of delivery prior to 34 weeks' gestation in women with CKD stages 3-5.

[a]=the presence (n=96) or absence (n=25) of chronic hypertension was confirmed in 121 women. The absence of chronic hypertension predicted delivery after 34 weeks (i.e. all women without chronic hypertension delivered after 34 weeks). In women with confirmed chronic hypertension only one variable was significant therefore adjusted analysis was not undertaken.
[b]= median unbiased estimate of odds ratio by exact logistic regression.
[c]=compared to pre-pregnancy values.
[d]=pre-pregnancy (n=102) or early pregnancy (n=38).
[e]=pre-pregnancy CKD stage by CKD-EPI, compared to Stage 3a.
CKD = chronic kidney disease, uPCR = urinary protein:creatinine ratio.

Variable	Unadjusted odds ratio in all women (n=121)[a] (95% confidence interval)	p-value	Unadjusted odds ratio in women with chronic hypertension (n=96)[a] (95% confidence interval)	p-value
Chronic hypertension	16.45 (2.74 to ∞)[b]	<0.001		
Gestational fall in serum creatinine <10%[c]			2.67 (1.00 to 7.09)	0.049
uPCR[+] >100mg/mmol[d]			2.22 (0.86 to 5.74)	0.101
CKD stage 4-5[e]			1.89 (0.62 to 5.78)	0.267
Maternal age			0.97 (0.89 to 1.05)	0.430
Renal transplantation			1.36 (0.52 to 3.59)	0.529
Black ethnicity			0.80 (0.28 to 2.31)	0.680
CKD stage 3b[e]			0.96 (0.36 to 2.61)	0.943
Glomerulonephritis			1.00 (0.40 to 2.49)	0.996

Table 5.4 Probability of delivery prior to 34 weeks'gestation in women with CKD, according to presence or absence of chronic hypertension and a gestational fall in serum creatinine concentrations.

[a]=All pregnancies confirmed to be normotensive prior to pregnancy (n=25) and pregnancies with confirmed chronic hypertension with recorded pre-pregnancy and gestational serum creatinine concentrations (n=85).
[b]=one sided 97.5% confidence interval

Chronic hypertension	**Gestational fall in serum creatinine**	**Number of pregnancies (n=110)[a]**	**Delivery <34 weeks' gestation (%) (95% confidence interval)**
No	Any	25	0 (0 to 14)[b]
Yes	>10%	40	20 (9 to 36)
	<10%	45	40 (26 to 56)

Table 5.5 Odds ratios of birth weight <10th centile in women with CKD
[a]=Adjusted for all factors found to be significant in the unadjusted analysis.
[b]=Based on significance in the adjusted model.
[c]=pre-pregnancy (n=102) or early pregnancy (n=38).
[d]=pre-pregnancy CKD stage by CKD-EPI, compared to Stage 3a.
[e]=compared to pre-pregnancy values.
CKD=chronic kidney disease, uPCR=urinary protein:creatinine ratio.

Variable	**Unadjusted odds ratio (95% confidence interval)**	**p-value**	**Adjusted odds ratio[a] (95% confidence interval)**	**p-value**	**Final model[b] (95% confidence interval)**	p-value
uPCR+ >100mg/mmol[c]	3.00 (1.45 to 6.21)	0.003	1.71 (0.70 to 4.17)	0.238	2.57 (1.20 to 5.53)	0.016
CKD stage 4-5[d]	3.39 (1.35 to 8.52)	0.009	4.03 (1.24 to 13.09)	0.020	1.81 (0.63 to 5.24)	0.271
Gestational fall in serum creatinine <10%[e]	2.18 (1.08 to 4.41)	0.029	1.26 (0.54 to 2.94)	0.599		
Black race	1.88 (0.87 to 4.07)	0.111				
Chronic hypertension	1.65 (0.63 to 4.35)	0.309				
Glomerulonephritis	1.40 (0.71 to 2.79)	0.335				
Maternal age	0.98 (0.91 to 1.04)	0.450				
Renal transplantation	0.82 (0.39 to 1.72)	0.604				
CKD stage 3b[d]	0.85 (0.42 to 1.74)	0.662				

5.4.2 Renal Outcomes

In over half of women (86/162, 53%), the gestational fall in serum creatinine was less than 10% of pre-pregnancy serum creatinine concentrations. Renal replacement therapy was initiated during pregnancy in five (3%) women, including one woman with CKD 5 prior to conception (eGFR 13ml/min/1.73m^2), three women with CKD 4 (eGFR 21-27ml/min/1.73m^2), and one woman with CKD 3a (eGFR 48ml/min/1.73m^2) complicated by heavy pre-pregnancy proteinuria (uPCR 519mg/mmol) and refractory antenatal hypertension.

Post-partum serum creatinine concentrations beyond four weeks post-partum were available for 90% (160/178) of women. Median follow up was 23.5 months (IQR 13.5 to 26.0 months, range 43 days to 6 years). At one year postpartum, 46% (58/126) of women had lost 25% of their eGFR compared to pre-pregnancy values or required renal replacement therapy. This composite outcome was more common in women with pre-pregnancy CKD stage 4-5 compared to other stages.

Renal replacement therapy was initiated in 7% (9/134) of women within the first post-partum year. These women had a median pre-pregnancy eGFR of 24ml/min/1.73m^2 (range 19-50ml/min/1.73m^2). Median start time was 39 weeks postpartum (range 3 to 51 weeks). Haemodialysis was commenced in three women, peritoneal dialysis in five women, and one woman received a pre-emptive renal transplant in the first post-partum year. A further 19 women with a median pre-pregnancy eGFR of 41ml/min/1.73m^2 (range 24-50ml/min/1.73m^2) required renal replacement beyond the first year after delivery. Haemodialysis was commenced in ten women, peritoneal dialysis was initiated in four women, and five women received pre-emptive renal transplants at a median of 3.0 (IQR 2.0-4.8) years post-partum.

A total of 761 eGFR values were available from the 165 singleton pregnancies with pre-pregnancy eGFR data (mean 4.6 values per woman, range 1-7) (Figure 5.1). The

optimum statistical model of eGFR included the pre-pregnancy trend in eGFR and the step-decline between pre-pregnant and post-partum values, with adjustment for pre-pregnancy CKD stage (Table 5.6). The inclusion of the post-partum eGFR did not improve the model, with no measurable difference between pre-pregnancy and post-partum eGFR trajectory (Table 5.7).

Figure 5.1 eGFR prior to and following pregnancy according to pre-pregnancy CKD stage. Post-partum decline was not measurably different from pre-pregnancy decline and measurement of post-partum renal function did not improve a statistical model including pre-pregnancy data and the step in renal function between pre-pregnancy and post-partum values.

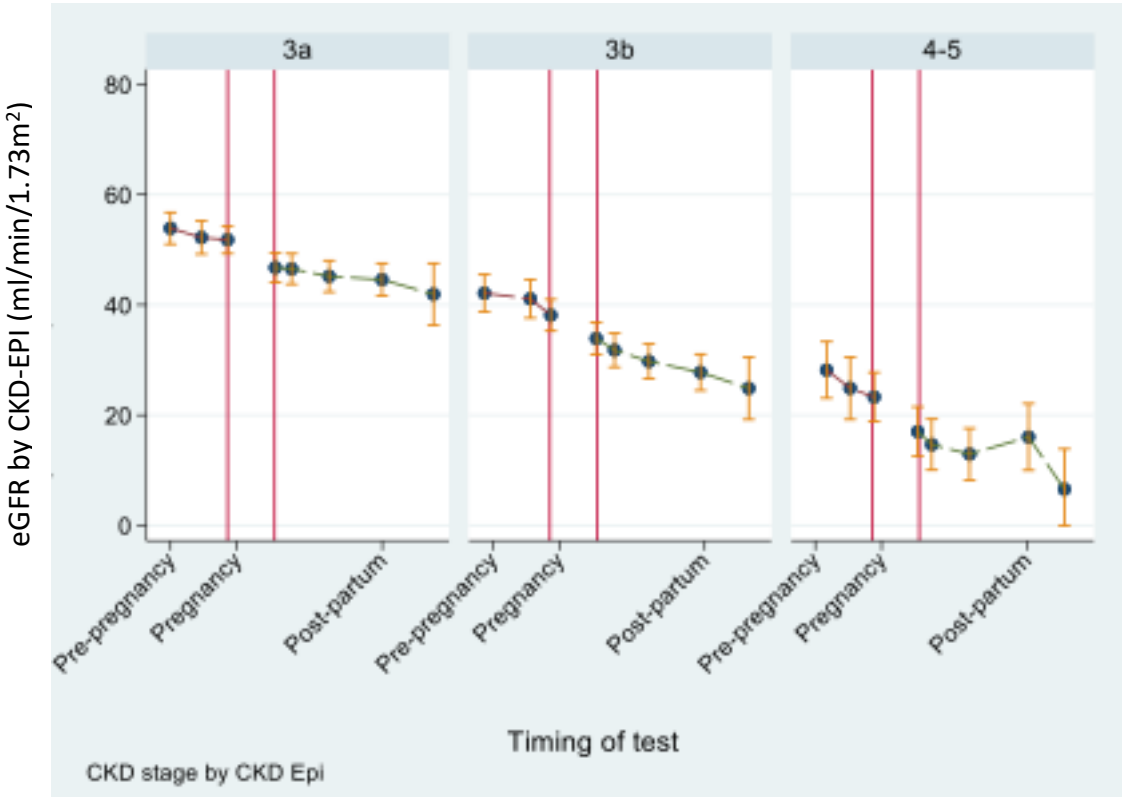


Table 5.6 Details of the statistical model of eGFR in relation to pregnancy. Optimum (lowest) information criterion was shown by model 3, with no addition information provided by model 4

[a]=between last value prior to conception and first available post-partum value.

Model	**Elements of model**	**Akaike's information criterion**	**Bayesian information criterion**	**Likelihood ratio test nested in model 3 (Chi^2, p-value)**
1	Overall change in eGFR	8458	8493	22.88, <0.0001
2	Pre-pregnant and post-partum change in eGFR	8448	8488	NA
3	Pre-pregnant change in eGFR and step-decline in eGFR during pregnancy[a]	8437	8477	-
4	Pre-pregnant change in eGFR, step-decline in eGFR during pregnancy[a] and post-partum change in eGFR	8438	8483	0.71, 0.401

Table 5.7 Regression analysis of eGFR. The coefficient is a measure of the effect of post-partum time in a model that includes pre-pregnant change in eGFR, step-decline in eGFR during pregnancy and post-partum change in eGFR.

CKD Stage	**Coefficient (95% confidence interval)**	**p-value**
3a	0.22 (-2.52 to 2.96)	0.876
3b	0.19 (-2.11 to 2.50)	0.869
4-5	0.18 (-3.25 to 3.61)	0.918

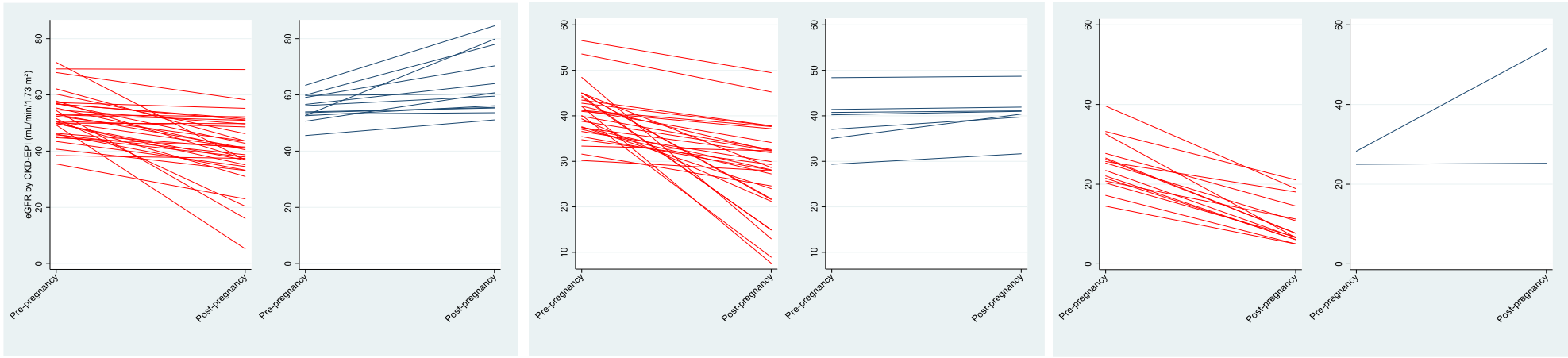
The step-decline between eGFR values taken before conception and post-partum was significant. Across the whole cohort, the mean decline in eGFR prior to pregnancy was 1.8 ml/min/1.73m^2/year. The step-decline in eGFR between pre-pregnancy and post-partum values was 4.5ml/min/1.73m^2, therefore equivalent to 2.5 years of renal disease prior to pregnancy. This effect differed according to pre-pregnancy CKD stage with pregnancy calculated to be the equivalent of 1.7, 2.1 and 4.9 years of pre-pregnancy renal disease in CKD stage 3a, 3b and 4-5 respectively (Table 5.8). Women with renal transplants had a lower step-decline of 3.7ml/min/1.73m^2 between pre- and post-pregnancy values compared to women without transplants (5.3 ml/min/1.73m^2). However, this loss converted into a higher number of equivalent years of pre-pregnancy disease (4.5 versus 2.5 years), as women with renal transplants also demonstrated more stable renal function prior to pregnancy compared to women with native CKD (0.9 versus 2.1ml/min/1.73m^2/year). It was not possible to examine the effect of CKD stage amongst women with renal transplants as the majority of women had CKD stage 3, with only 3 women with renal transplants undertaking pregnancy with pre-pregnancy stage 4-5. An overall decline in renal function in relation to pregnancy was confirmed in women with at least two pre-pregnancy and two post-partum eGFR values, with 80% (86/108) of women demonstrating a step-decline in eGFR (Figure 5.2).

Table 5.8 Loss of eGFR between pre-pregnancy and post-pregnancy values according to CKD stage

[a]= Multifetal pregnancies (n=2) excluded
[b]=CKD stage in women with transplants: 23 women with stage 3a, 16 women with stage 3b and 3 women with stage 4-5.
[c]= 2 twin pregnancies excluded
[d]= no confidence interval possible as the estimate for pre-pregnancy decline in women with CKD stages 4-5 includes zero.
eGFR = estimated glomerular filtration rate.

Pre-pregnancy CKD stage	**Number of pregnancies**	**Number of eGFR values**	**Pre-pregnancy decline in eGFR ml/min/1.73m^2/year (95% confidence interval)**	**eGFR loss in pregnancy ml/min/1.73m^2 (95% confidence interval)**	**Years of pre-pregnancy disease equivalent to eGFR loss in pregnancy (95% confidence interval)**
All (3-5)	165[a]	761	1.8 (0.9 to 2.6)	4.5 (2.0 to 7.1)	2.5 (0.0 to 5.1)
• **Transplants (3-5)[b]**	42	229	0.9 (0.7 to 2.4)	3.7 (0.7 to 8.1)	4.3 (0.0 to 7.9)
• **Native CKD (3-5)**	123	532	2.1 (1.0 to 3.1)	5.3 (2.2 to 8.3)	2.5 (0.0 to 5.2)
3a	79	360	1.7 (0.3 to 3.0)	2.9 (0.0 to 7.0)	1.7 (0.0 to 5.5)
3b	61[c]	283	2.2 (0.9 to 3.5)	4.6 (0.7 to 8.5)	2.1 (0.0 to 4.9)
4-5	25	118	1.6 (0.0 to 3.3)	7.9 (3.2 to 12.6)	4.9[d]

Figure 5.2 The trend in eGFR between pre-pregnancy and post-partum values according to CKD stage in women with at least two values prior to and two values after pregnancy. Stage 3a (left): Fall in eGFR in 36 women (red), stable eGFR in 13 women (blue); Stage 3b (middle): Fall in eGFR in 34 women (red), stable eGFR in 7 women (blue); Stage 4-5 (right): Fall in eGFR in 16 women (red), stable eGFR in 2 women (blue).



Examination of pre-pregnancy variables showed that chronic hypertension and uPCR greater than 100mg/mmol were significant determinants of the step-decline between pre-pregnant and post-partum eGFR. An apparent protective effect of renal transplantation was lost when data were adjusted for chronic hypertension and proteinuria. Adjusted analysis combining pre-pregnancy and post-pregnancy variables showed that chronic hypertension remained significant, though the measurable effect of proteinuria was lost when pregnancy outcomes were known. A gestational fall in serum creatinine of less than 10% of pre-pregnancy values was a more significant predictor of renal function decline in pregnancy than delivery before 34 weeks and birthweight less than the 10^{th} centile. Maternal age, black ethnicity and a diagnosis of glomerulonephritis had no measurable effect on the step-decline in eGFR in relation to pregnancy (Table 5.9).

Table 5.9 Predictors of the step decline in eGFR in relation to pregnancy.
Step decline is between eGFR pre-pregnancy the eGFR post-partum. Shaded variables are not known pre-pregnancy. The coefficient is a measure of the difference in eGFR between pre-pregnancy and post-partum eGFR values that can be attributed to that variable.
[a]=pre-pregnancy (n=123) or early pregnancy (n=50), [b]=pre-pregnancy CKD stage by CKD-EPI, compared to stage 3a. [c]=compared to pre-pregnancy values.

Variable	**Single linear regression coefficient (95% confidence interval)**	**p-value**	**Multiple linear regression of pre-pregnancy variables (95% confidence interval)**	**p-value**	**Multiple linear regression of all variables (95% confidence interval)**	**p-value**
Pre-pregnancy variables						
Chronic hypertension	-8.31 (-11.89 to -4.73)	<0.001	-6.63 (-10.53 to -2.72)	0.001	-5.67 (-9.52 to -1.82)	0.004
uPCR^{+} >100mg/mmol[a]	-8.72 (-11.27 to -6.19)	<0.001	-6.78 (-10.16 to –3.40)	<0.001	-2.43 (-5.64 to 0.77)	0.138
Renal transplantation	3.72 (1.26 to 6.18)	0.003	-1.03 (-4.38 to 2.32)	0.547		
Ethnicity: black versus non-black	-2.57 (-5.48 to 1.56)	0.084				
Glomerulonephritis	-1.26 (-3.78 to 1.26)	0.328				
Maternal age	0.11 (-0.14 to 0.36)	0.387				
Post-pregnancy variables						
Gestational creatinine fall <10%[c]	-8.04 (-10.52 to -5.56)	<0.001			--5.57 (-8.61 to -2.53)	<0.001
Preterm delivery <34 weeks	-8.04 (-10.52 to -5.56)	<0.001			-1.27 (-5.21 to 2.66)	0.527
Birth weight <10th centile	-4.29 (-6.78 to -1.81)	0.001			-0.94 (-4.25 to 2.37)	0.576

5.5 Discussion

Women with CKD stages 3-5 have a high live birth rate (98%) in pregnancies progressing beyond 20 weeks' gestation, but pregnancies are complicated by preterm delivery (56%) and birthweight below the 10th centile (36%). Chronic hypertension was the strongest predictor of the risk of delivery before 34 weeks with one third of women with chronic hypertension delivering before 34 weeks in this cohort. A gestational fall in serum creatinine that was less than 10% of pre-pregnancy values was associated with a doubling of the risk of delivery before 34 weeks from 20% to 40% in women with chronic hypertension. Pre- or early pregnancy proteinuria approximating to greater than 1g/24 hours was the strongest predictor of birthweight below the 10th centile. Chronic hypertension, pre- or early pregnancy proteinuria and a gestational fall in serum creatinine of less than 10% were stronger predictors of adverse obstetric outcomes than CKD stages 3-5. The trajectory of eGFR was not measurably different pre- and post-partum, but there was a step-decline in renal function in relation to pregnancy in 80% of women. This was equivalent to between 1.7 and 4.9 years of background renal disease depending on renal function prior to pregnancy and pre-pregnancy CKD stage. Overall, pregnancy was estimated to bring forward the need for renal replacement therapy by 2.5 years. Predictors of the risk of a decline in eGFR in relation to pregnancy were chronic hypertension and a gestational fall in serum creatinine that was less than 10% of pre-pregnancy creatinine.

The finding of a higher incidence of preterm delivery and low birthweight with increasing CKD stage confirms previous data (Imbasciati et al., 2007; Williams and Davison, 2008, Piccoli et al., 2015). However, CKD stage is confounded by an increased prevalence of both chronic hypertension and proteinuria, and this study is the first to demonstrate that chronic hypertension and pre- or early pregnancy proteinuria are stronger predictors of adverse obstetric outcomes than CKD stage in women with CKD stages 3-5. Overall rates of renal replacement therapy in this cohort were low, with 3% of women commencing dialysis during pregnancy and 7% within the first post-partum year. However, renal replacement was not limited to women with CKD 4-5. Although documentation of the clinical indicators for dialysis was insufficient to allow detailed

analysis, hypertension and proteinuria were considered to be clinically important in those with pre-pregnancy CKD stage 3 who progressed to dialysis during pregnancy or within the first year post-partum.

The novel conversion of renal function decline during pregnancy to 2.5 equivalent years of background renal disease is useful for both patients and clinicians in providing a tangible measure of the effect of pregnancy on renal function. The effect of pregnancy can be estimated to bring forward to need for renal replacement by 1.7, 2.1 and 4.9 years in stage 3a, 3b and 4-5 respectively. Women with CKD stages 4-5 and renal disease progression which, in the absence of pregnancy would be anticipated to lead to renal replacement within five years, should be advised that a decline in GFR is likely to precipitate the need for renal replacement therapy either in pregnancy or within the immediate post-partum period.

Although the loss of eGFR in relation to pregnancy was less in women with renal transplants, this effect was confounded by the majority having CKD stage 3a prior to pregnancy, and the apparent protective effect of renal transplantation on the decline in eGFR in relation to pregnancy was lost when data were corrected for chronic hypertension and proteinuria. Although there is a potential treatment paradox in women with renal transplants, with a lower threshold for iatrogenic pre-term delivery when there is a gestational increase in serum creatinine concentrations in transplants compared to native CKD, the finding that renal transplantation does not increase the risk of adverse obstetric outcomes is reassuring.

In women with normal renal function, physiological adaptation to pregnancy includes a 50% increase in creatinine clearance, and a gestational fall in serum creatinine concentration (Davison and Noble, 1981; Chapman et al., 1998). In the absence of published data, the failure of serum creatinine to fall in pregnancy has been interpreted as a sign of impaired renal adaptation to pregnancy and used anecdotally as a poor prognostic indictor (Fitzpatrick et al., 2016). Our study is the first to confirm that a failure of serum creatinine concentration to fall in pregnancy by 10% or more

compared to pre-pregnancy values is associated with both delivery prior to 34 weeks and a greater pregnancy-associated decline in eGFR. Although the absence of a gestational fall in serum creatinine in pregnancy could represent progressive kidney disease rather than a pathological response to pregnancy, the optimum statistical model of eGFR in this study required both the non-pregnant trajectory in eGFR and the step-decline in eGFR between pre-pregnancy and post-partum values suggesting that the gestational effect on renal function in women with CKD is more complex than a continuation of pre-pregnancy disease.

To my knowledge, this is the largest study of obstetric and renal outcomes in women with CKD 3-5, surpassing recent cohorts that included 15 and 47 women (Piccoli et al., 2010; Piccoli et al., 2015). The largest study available to date preceded CKD staging and included 82 pregnancies with serum creatinine concentrations >124µmol/L, delivering between 23 and 47 years ago (Jones and Hayslett, 1996). We therefore provide much needed contemporary data to inform pre-pregnancy counselling and the intra- and post-partum surveillance of women with moderate and severe pre-pregnancy CKD, staged by pre-pregnancy CKD-EPI according to current practice (NICE, 2015a).

A limitation of the study is the absence of pre-eclampsia coding as a modifier of both obstetric and renal outcomes. In the absence of defined diagnostic criteria for superimposed pre-eclampsia in women with chronic hypertension and/or pre-existing proteinuria, a reliable diagnosis of pre-eclampsia could not be determined by retrospective case-note review. Preterm delivery before 34 weeks and birthweight less than the 10th centile were used as important obstetric outcomes in this study. Although these outcomes may suggest the possibility of underlying pre-eclampsia, these surrogate markers are confounded by any pathology that impacts growth and delivery, as well as differences in clinician-threshold for iatrogenic preterm delivery. This study excluded spontaneous pregnancy loss prior to 20 weeks due to the possibility of miscoding error and information bias. The live birth rate of 98% therefore refers only to pregnancies which progress beyond 20 weeks' gestation. Predictors of early pregnancy loss in women with CKD 3-5 have not been identified and the effect of

early pregnancy loss on long-term maternal renal function is unknown. Evidence for low dose aspirin in the prophylaxis of pre-eclampsia coincided with the time period of this study, although use and adherence could not be confirmed in all women. There were insufficient data on the use of renin-angiotensin blockade, and whether there is benefit in the use of angiotensin converting enzyme inhibitors in the pre-and post-partum period outside of standard indications in CKD remains unknown.

Future work includes the generation of a prediction model for women with CKD, comparable to those available to women with hypertensive disorders of pregnancy (Ukah et al., 2019), in order to provide appropriate counselling and surveillance. Clinical indicators for the commencement of dialysis in pregnancy for the optimisation of maternal and neonatal outcomes are also warranted. Research into the contribution of superimposed pre-eclampsia in mediating adverse pregnancy outcomes may be informative. Prospective studies, including pre-defined diagnostic criteria, in conjunction with emerging biomarkers of placental dysfunction (Bramham et al., 2016), may offer valuable insight into pathophysiology of adverse outcomes in order to develop targeted interventions.

6 NESTED CASE CONTROL STUDY OF DIAGNOSTIC INDICATORS OF SUPERIMPOSED PRE-ECLAMPSIA IN WOMEN WITH CKD

6.1 Abstract

6.1.1 Background

Diagnosis of superimposed pre-eclampsia in women with chronic kidney disease (CKD) is complicated by the presence of hypertension and proteinuria due to renal disease. The aims of this study were to determine mechanistic links between superimposed pre-eclampsia and renin-angiotensin system activation, endothelial pathology, complement dysfunction and tubular injury; and to explore the role of diagnostic indicators of superimposed pre-eclampsia.

6.1.2 Methods

Plasma and urinary biomarkers derived from the renin-angiotensin system (active renin, angiotensinogen), endothelial glycocalyx (hyaluronan, intercellular adhesion molecule, vascular cell adhesion molecule, P-selectin, E-selectin), complement activation (C3a, C5a, complement factor H, C5b-9) and tubular injury (kidney injury molecule-1, urinary lipocalin-2) were quantified in 60 pregnant women with CKD, including 15 women at the time of superimposed pre-eclampsia diagnosis and 45 women who did not develop superimposed pre-eclampsia; 18 women with pre-eclampsia, and 20 normal pregnancies. Correlation with plasma placental growth factor was assessed.

6.1.3 Results

Plasma concentrations of hyaluronan (67.5ng/ml vs. 27.2ng/ml, p=0.0017, ROC area 0.79) and VCAM (1132ng/ml vs. 659ng/ml, p=<0.0001, ROC area 0.86) distinguished women with CKD and superimposed pre-eclampsia from those without superimposed pre-eclampsia, and correlated with plasma placental growth factor concentrations. The

diagnostic discrimination of markers of the renin-angiotensin system was reduced by adjustment for chronic hypertension, antihypertensive drug use and black ethnicity. Other markers offered limited or no diagnostic discrimination for superimposed pre-eclampsia.

6.1.4 Conclusion

This study suggests that endothelial dysfunction contributes to the pathophysiology of superimposed pre-eclampsia and a diagnostic role for plasma hyaluronan and vascular cell adhesion molecule is hypothesised.

6.2 Introduction

It is estimated that up to 3% of women who become pregnant have underlying chronic kidney disease (CKD) (Piccoli et al., 2018), which is associated with adverse pregnancy outcomes including pre-eclampsia, fetal growth restriction, preterm delivery, and decline in maternal renal function.

A diagnosis of pre-eclampsia is made on the basis of de novo hypertension developing after 20 weeks' gestation in conjunction with either new proteinuria or evidence of maternal organ or uteroplacental dysfunction (Brown et al., 2018). In women with CKD, the diagnosis of superimposed pre-eclampsia is complicated by chronic hypertension and/or proteinuria due to renal disease, estimated to be present in half and a third of pregnancies respectively (Piccoli et al., 2015; Bramham et al., 2016), thereby rendering standard diagnostic criteria redundant. In the absence of formal diagnostic criteria for superimposed pre-eclampsia, meta-analysis estimates a ten-fold increased risk for the development of superimposed pre-eclampsia in women with CKD compared to women without CKD (Zhang et al., 2015), with pre-eclampsia affecting 20-87% of pregnancies in women with CKD, depending upon the stage of pre-pregnancy disease and diagnostic criteria used (Piccoli et al., 2015; Williams and Davison, 2008).

Pre-eclampsia remains a key determinant of adverse pregnancy outcome, contributing to preterm delivery and maternal and neonatal morbidity in general obstetric populations (Mol et al., 2016) and in women with CKD (Bramham et al., 2016; Luders et al., 2018). The disease trajectory and associated morbidity of pre-eclampsia require distinction from gestational change in CKD, yet unless systemic or fetal complications of pre-eclampsia arise, discrimination of superimposed pre-eclampsia from CKD remains challenging. Although utilised (Piccoli et al., 2015; Bramham et al., 2016; Luders et al., 2018), the diagnostic value of relative changes in both blood pressure and proteinuria in pre-eclampsia remain unclear (Brown et al., 2018). Diagnostic utility has however been demonstrated in the use of angiogenic (placenta growth factor, PlGF) and anti-angiogenic (soluble fms-like tyrosine kinase-1, sFlt-1) biomarkers in pre-eclampsia in the general population (Chappell et al., 2013; NICE, 2016; Duhig et al., 2019a), with emerging data on their use as a diagnostic adjunct in pregnant women with CKD (Masuyama et al., 2006; Masuyama et al., 2012; Bramham et al., 2016).

The pathophysiological processes by which CKD confers an increased risk of superimposed pre-eclampsia remain poorly understood. Putative mechanisms, which offer a mechanistic link between renal disease and pre-eclampsia, include endothelial dysfunction (Obeidat et al., 2012; Padberg et al., 2014; Tomimatsu et al., 2017), renin-angiotensin system (RAS) activation (van der Graaf et al., 2012), complement dysregulation (Denny et al., 2013; Regal et al., 2015; Fearn and Sheerin, 2015) and kidney injury (Xiao et al., 2013; Tangren et al., 2017).

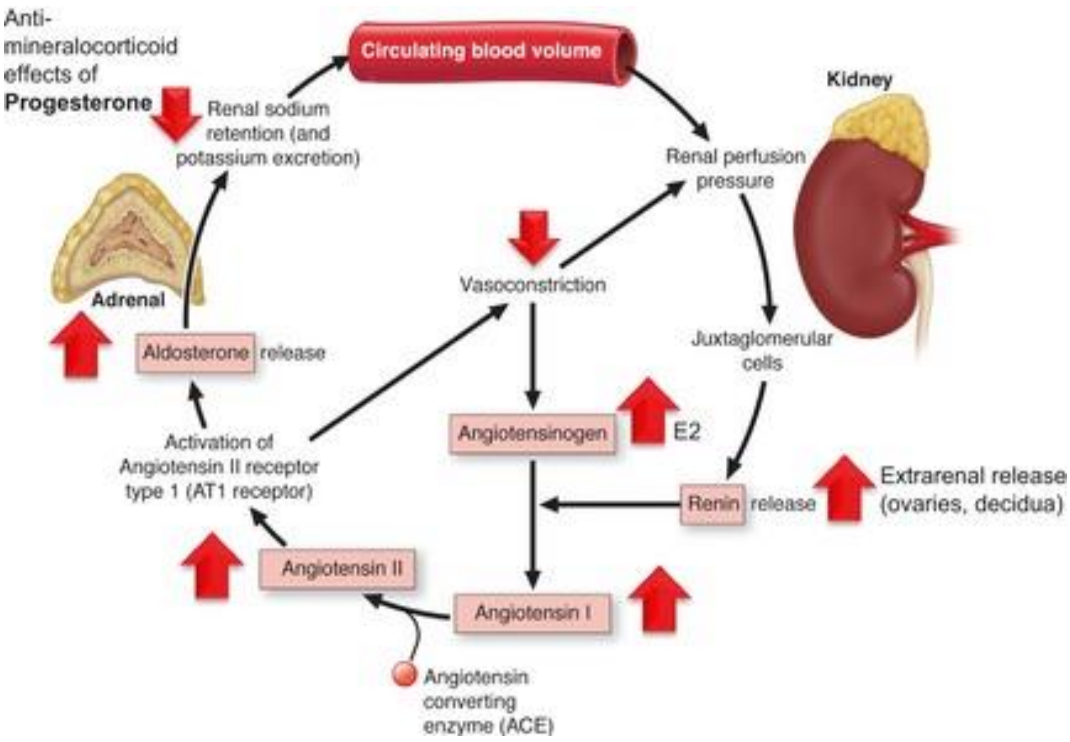
6.2.1 Renin-angiotensin system

The renin-angiotensin system regulates blood pressure, electrolyte balance and volume homeostasis. Synthesis and release of renin occurs in the juxta-glomerular apparatus of the kidney in response to a reduction in circulating volume. Renin and angiotensin converting enzyme (ACE) are sequential enzymes in the cleavage of angiotensinogen to biologically inactive angiotensin I, followed by production of biologically active angiotensin II (Figure 6.1). Angiotensin II acts primarily via the angiotensin II receptor type 1 (AT1) to induce a vasopressor response. In addition, non-

ACE angiotensin generating enzymes in mast cells, skin, heart, and the placenta contribute to the functional angiotensin II pool (Irani and Xia, 2008). The renin-angiotensin system is also thought to be more functionally diverse than solely a pressor regulator, with involvement demonstrated in growth and remodelling (Tamura et al., 2000), renal development (Terata et al., 2012), inflammation (Schieffer et al., 2000), and thrombosis (Brown and Vaughan, 2000).

The pregnant state results in major changes to the renin-angiotensin axis (Figure 6.1). All components of the renin-angiotensin system are increased with the exception of angiotensin converting enzyme (Merrill et al., 2002). Despite this, pregnancy is a state of relative hypotension, with a progressive rise towards pre-pregnancy blood pressure towards term (Loerup et al., 2019). Relative hypotension in the context of an increase in the renin-angiotensin components points to a relative insensitivity in pregnancy, which has been attributed to progesterone and prostacyclins (Gant et al., 1980), and an insensitive monomeric AT1 receptor (AbdAlla et al., 2001).

Figure 6.1 Schematic representation of the renin-angiotensin system in pregnancy. Measurable components of the renin-angiotensin system used in this work include renin (via plasma renin activity), angiotensinogen, and aldosterone. Figure modified from Arlt W, Disorders of the Adrenal Cortex, Harrison's Textbook Principles of Internal Medicine, 18th edition, McGraw Hill, 2011.



The changes to RAS in pre-eclampsia are counterintuitive. Despite the hypertensive phenotype, levels of renin, angiotensinogen, angiotensin I, and angiotensin II are lower than in normotensive pregnancy (Irani and Xia, 2008; Rodriguez et al., 2012). This points to an exaggerated pressor response to the renin-angiotensin system in pre-eclampsia compared to normal pregnancy, thought to be mediated by an activating agonistic autoantibody (AT1-AA) acting on the AT1 receptor. Correlations between maternal AT1-AA concentrations and pre-eclampsia severity and sFlt-1 concentrations have been shown (Siddiqui et al., 2010). There is also evidence for a reduction in the counter-regulation of angiotensin II by angiotensin-(1-7) (Ang(1-7)), which has vasodilatory and antihypertensive properties. Ang(1-7) is elevated in normal pregnancy but decreased in pre-eclampsia in a small cohort (Merrill et al., 2002). The uteroplacental role is less clear with increased local renin production in maternal decidua both described (Shah et al., 2000), and refuted (Herse et al., 2007) in pre-eclampsia.

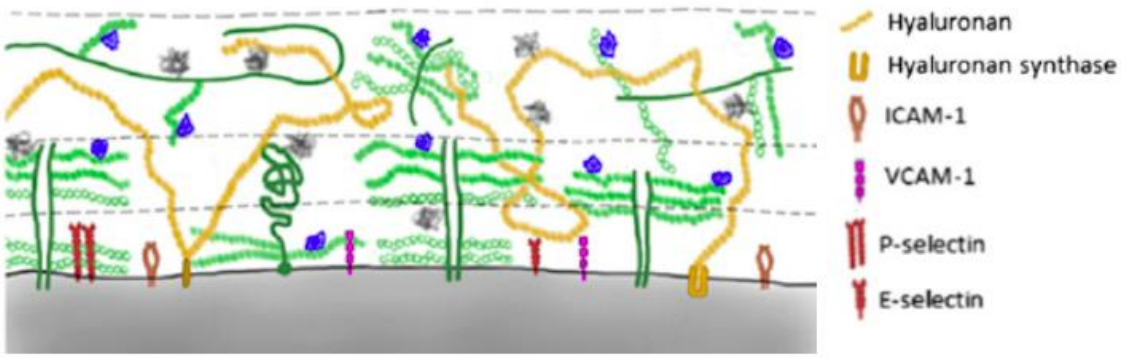
Plasma concentrations of renin (Shah, 2005; Irani and Xia, 2008; Malha et al., 2016) and angiotensinogen (Verdonk et al., 2015), and urinary concentrations of angiotensinogen (Yilmaz et al., 2015) and aldosterone (Buhl et al., 2012) are altered in pre-eclampsia compared to normal pregnancy in small cohorts including women with chronic hypertension (August et al., 1990; Mistry et al., 2015; Malha et al., 2016) thereby offering the potential for diagnostic distinction.

RAS dysfunction provides a mechanistic link between pre-eclampsia and renal disease, contributing to glomerular hyperfiltration, proteinuria and CKD (Brewster and Perazella, 2004). There is in-vitro evidence that the activation of AT1 receptor by AT1-AA leads to synthesis and secretion of plasminogen activator inhibitor-1 in the mesangium of the kidney, hypothesised to contribute to fibrin deposition, fibrosis and CKD progression (Xia et al., 2002, Xia et al., 2003; Bobst et al., 2005). Levels of urinary angiotensinogen have been shown to positively correlate with the histological severity of kidney disease (Urushihara et al., 2010; Kim et al., 2011; Kobori and Urushihara, 2012).

6.2.2 The glycocalyx and cell adhesion molecules

In non-stimulated conditions, the endothelial cell presents a negatively charged endothelial surface layer (glycocalyx) composed of membrane bound proteoglycans and glycoproteins anchored to the endothelium cell membrane. Circulating cells have equivalent surface layers, which under normal conditions repel the endothelial cell surface. Under inflammatory stimuli, both endothelial and circulating cells present and shed molecules that facilitate interaction, cell adhesion, cell migration, and an ensuing inflammatory response. The inflammatory change in surface layer expression includes the expression of cell adhesion molecules, selectins, and the cleavage of hyaluronan (Figure 6.2).

Figure 6.2 The vascular endothelium under inflammatory conditions. Components of the endothelial surface layer are shown including hyaluronan, intercellular cell adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), P-selectin, and E-selectin. Adapted from (Marki et al., 2015).



Hyaluronan is a principal component of the endothelial glycocalyx. The high molecular weight (>500kDa) 'native' form is immunologically inert and preserves normal endothelium function including permeability, tone, and coagulation. The intact glycocalyx acts as a transducer of mechanical signals to the endothelial cell leading to appropriate reorganisation of the cytoskeleton, nitric oxide synthesis and vasodilatory adaption to a mechanical load (Markos et al., 2013). In response to tissue injury, immune activation, and/or systemic inflammation, hyaluronan degrades to a lower molecule weight molecule (<500kDA) with activation of pro-inflammatory cytokines

and hypertension. Pre-eclampsia therefore represents a disease model in which destabilisation of the endothelial glycocalyx may be significant for pathogenesis (Ziganshina et al., 2016). Small cohorts studies of between 10 and 60 women demonstrate that concentrations of hyaluronan are increased in women with pre-eclampsia and HELLP compared to normotensive pregnant women (Osmers et al., 1998; Matejevic et al., 1999; Berg et al., 2001; Romão et al., 2013). Similarly higher concentrations of vascular cell adhesion molecule (VCAM), P-selectin and E-selectin are reported in pre-eclampsia compared to normal pregnancy (Chaiworapongsa et al., 2002; Kim et al., 2004) although this is not consistent across all studies (Lewis et al., 2010). Intercellular adhesion molecule (ICAM) concentrations are both positively (Anim-Nyame et al., 2003; Szarka et al., 2010; Farzadnia et al., 2013) and negatively associated with pre-eclampsia (Chaiworapongsa et al., 2002; Kim et al., 2004; Lewis et al., 2010).

6.2.3 Complement

Complement activity is increased in normal pregnancy (Richani et al., 2005). This is hypothesised to facilitate clearance of fetoplacental debris from the maternal circulation (Burwick et al., 2014), and to protect mother and fetus from microorganisms and antigen whilst adaptive immunity is physiologically suppressed (Richani et al., 2005). Simultaneously, the fetus is thought to be protected from increased complement activity by trophoblastic expression of complement regulatory proteins.

A pathological increase and impaired regulation of complement activity are described in pre-eclampsia (Buurma et al., 2012; Regal et al., 2015), quantifiable via concentrations of plasma and urinary complement activation products including C3a, C5a and C59-9 (Soto et al., 2010; Lynch et al., 2011; Burwick et al., 2014). Increased urine concentrations of C5a, C3a and C5b-9 have been shown to distinguish pre-eclampsia from chronic hypertension in a small cohort (Burwick et al., 2013). Although a correlation between serum complement factor H concentrations and severity of thrombocytopenia in HELLP is described, this was measured without a substantial

difference in complement concentrations between women who developed HELLP compared to those with a normal pregnancy (Ari et al., 2009).

Complement activation provides an alternative link between pregnancy and renal disease. Atypical haemolytic uraemic syndrome (aHUS) is a thrombotic microangiopathy (TMA) attributed to uncontrolled activation of complement. Pregnancy-associated HUS is well described and complement pathway mutations are detected in the majority (86%) of women who develop pregnancy-related disease. Renal disease in these women is severe (prior to the use of C5 monoclonal antibody therapy (Gupta et al., 2020)) with 81% requiring renal replacement therapy and 62% developing end-stage kidney disease (Fakhouri et al., 2010). Despite the underlying genetic susceptibility, most cases (80%) develop in the post-partum period suggesting the placenta confers protective regulation of complement. Pre-eclampsia, as the clinical manifestation of a failing placenta, may therefore be a trigger for complement mediated renal damage.

6.2.4 Kidney injury

Kidney injury molecule-1 (KIM-1) is a transmembrane protein, absent in healthy kidney tissue, but elevated in the proximal renal tubule apical membrane after renal injury (Waanders et al., 2010). Increased urinary KIM-1 concentrations have been described in small cohorts (n=25) of women with pre-eclampsia (Xiao et al., 2013), correlating with activated complement products (Burwick et al., 2014), suggesting a pathogenic role for proximal tubular damage in pre-eclampsia.

Lipocalin-2 (previously neutrophil gelatinase-associated lipocalin (NGAL)) is upregulated in response to a variety of inflammatory stimuli and is implicated as a modulator of inflammation, apoptosis, and metabolic homeostasis (Abella et al., 2015). In the kidney, lipocalin-2 is rapidly released from renal tubular cells after an injuring stimulus. Increased urinary lipocalin-2 levels have been measured in pre-eclampsia (Xiao et al., 2013), with correlation between serum concentrations and

blood pressure and proteinuria (D'Anna et al., 2010), although findings are not consistent (Burwick et al., 2014).

6.2.5 Aims

This aim of this study were to explore mechanistic links and investigate potential diagnostic indicators in superimposed pre-eclampsia linked to pathophysiology, including markers of the renin-angiotensin system (active renin, angiotensinogen), endothelial glycocalyx dysfunction (hyaluronan, ICAM, VCAM, P-selectin, E-selectin), complement activation (C3a, C5a, complement factor H, C5b-9) and kidney injury (kidney injury molecule-1, urinary lipocalin-2). Given the inherent complexity in diagnosing superimposed pre-eclampsia in women with CKD and the emerging diagnostic role of PlGF, a, correlation between the novel markers and plasma PlGF concentration was examined.

6.3 Methods

Pregnant women with and without CKD, and non-pregnant women with CKD were recruited at three London centres (Guy's and St. Thomas' NHS Foundation Trust, Imperial College Healthcare NHS Trust, King's College Hospital NHS Foundation Trust) between 2009 and 2015. Approval was provided by the Research Ethics Service and the Health Research Authority (11/LO/1776 and 15/WA/0009). Inclusion criteria were women of reproductive age with a known diagnosis of CKD based on Kidney Disease: Improving Global Outcomes (KDIGO) criteria (Levin and Stevens, 2014), in addition to pregnant women with a presumed diagnosis of CKD based on either a raised creatinine (>85μmol/L) in the absence of risk factors for acute kidney injury, or persistent proteinuria (urinary protein:creatinine ratio >30mg/mmol) prior to 20 weeks' gestation.

Pregnant women were enrolled prospectively. Plasma (EDTA) and urine samples were collected at routine outpatient attendance. Samples were stored on ice before being

centrifuged at 1500xg for 10 minutes at 4^{o}C. The separated supernatant was aliquoted and stored at -80^{o}C.

Outcomes were based on pre-determined criteria. In the absence of pre-pregnancy hypertension and proteinuria, standard diagnostic criteria were used for the diagnosis of superimposed pre-eclampsia (Brown et al., 2018). For women with pre-existing hypertension and proteinuria, in whom isolated rises in blood pressure and proteinuria are insufficient for a diagnosis of superimposed pre-eclampsia (Brown et al., 2018), predefined diagnostic criteria for the purposes of this study included either the development of severe hypertension (>160/110mmHg) or an increment in antihypertensive treatment in order to maintain BP <160/110mmHg, a doubling of proteinuria above the pathological threshold for pregnancy (urinary protein:creatinine ratio >30mg/mmol), or clinical features of pre-eclampsia including liver involvement (alanine transaminase >71 U/L, right upper quadrant or epigastric pain), platelet count <100,000/µl, pulmonary oedema, new onset cerebral or visual disturbance, and fetal growth restriction (Bramham et al., 2016). In addition, all complex cases were reviewed and a diagnosis confirmed by two senior clinical staff with expertise in renal disease in pregnancy (KB, LC, LL) assessing independently, and without access to study results.

Obstetric outcomes included mode of delivery, gestational age, preterm delivery defined as less than 37 and 34 weeks' gestation, neonatal unit admission, birthweight and birthweight centile assessed as a customized birth weight percentile calculated using the Gestation Related Optimal Weight method (www.pi.nhs.uk/download/graw/GRAWCentv1.xls (Gardosi et al., 2018)). Small for gestational age (SGA) was reported as less than 10th and 3rd centile.

A nested case-control group was retrospectively selected based on time of disease (pre-eclampsia/superimposed pre-eclampsia). This included all women with CKD who had biological samples taken at the time of a diagnosis of superimposed pre-eclampsia. These women were matched for CKD stage and week of gestation with

pregnant women with CKD who did not develop superimposed pre-eclampsia, and for week of gestation with pregnant women without CKD who did, and did not, develop pre-eclampsia. Additional analysis of discriminatory plasma biomarkers was carried out in non-pregnant women of reproductive age with advanced CKD to assess the effect of reduced renal clearance on biomarker concentration outside of pregnancy.

Given that chronic hypertension is known to recognised to be an independent modifier of RAS (Preston et al., 1998; Mulatero et al., 200; Malha et al., 2016), the case control group was extended to facilitate additional renin-angiotensin axis analysis in women with, and without, chronic hypertension. This extended group included biological samples at gestations that were unmatched between study subgroups.

6.3.1 Biomarker analysis

Plasma and urine samples were tested with masking of clinical outcomes. The selection of specific analytes was based upon hypothesised mechanistic links between renal disease and pre-eclampsia, feasibility in the context of sampling methodology and long-term storage of biological samples at -80^{o}C, and the authors' experience of biomarker research in pregnancy (Chappell et al., 2013; Mistry et al., 2015; Bramham et al., 2016; Webster et al., 2018). Hyaluronan, active renin, angiotensinogen and complement components (C3a, C5a, C5b-9, CFH) were quantified using specific enzyme linked immunosorbent assay (ELISA) kits according to manufacturers' protocols. Although the MIcroVue SC5b-9 ELISA is not validated for urine, quantification of urinary C5b-9 has been achieved (Morita et al., 2000; Gou et al., 2013). Pre-dilution of urine was not required to achieve quantification of urinary C5b-9 within the detectable range, and plate shaking at 80 revolutions/min was added to the manufacturer's protocol during both conjugate and substrate incubations in order to achieve satisfactory assay performance in urine, as previously described (Bottinger, 2015). Extraction of C5a in urine was insufficiently sensitive and analysis was not possible. Plasma concentrations of ICAM, VCAM, P-selectin, E-selectin, and Kidney Injury Molecule (KIM-1), and urinary concentrations of lipocalin-2 (NGAL) were

quantified simultaneously using a Luminex® Performance Assay multiplex kit according to the manufacturer's protocol and read by a Luminex® FlexMap3D analyser system. Urine creatinine was quantified in order to report urinary biomarker concentrations as a normalised ratio to urinary creatinine concentration. Plasma PlGF was quantified using the Triage PlGF Test by Alere/Quidel (Bramham et al., 2016, Saffer et al., 2013). Manufacturers' details and measures of precision are given in Table 6.1.

Table 6.1 Biomarker assay details

Analyte	**Assay kit**	**Detectable range**	**Intra-assay CV (%)**	**Inter-assay CV (%)**
Active renin	IBL GMBH RE53321	0.81-128pg/ml	4.0	11.6
Angiotensinogen	IBL GMBH REJP27412	0.31-20ng/ml	Plasma 4.2 Urine 4.8	Plasma 14.1 Urine 11.6
Hyaluronan	R&D DHYALO	0.625-40ng/ml	4.2	14.9
C3a	Hycult Biotech HK354	31.3-2000pg/ml	8.1	13.4
C5a	Hycult Biotech HK349	0.3-20ng/ml	6.4	12.0
CFH	Microvue SC5-9 Plus EIA	8.8ng/ml	8.1	11.8
C5b-9	Hycult Biotech HK342	3.9-250ng/ml	3.4	6.9
ICAM	R&D Human Adhesion Molecules LKT007	52.5-18716pg/ml	4.6	12.3
VCAM		10-9233pg/ml	5.0	9.0
P-selectin		135-23246pg/ml	5.8	17.7
E-selectin		123-23978pg/ml	5.0	11.7
KIM-1	R&D Kidney Biomarker Premixed Kit FCSTM16	159-116,000pg/ml	10.1	10.5
Lipocalin 2 (NGAL)		50-36,100pg/ml	3.8	8.8
Urine creatinine	Roche Diagnostics enzymatic creatinine method		0.8	2.1

6.3.2 Statistical analysis

Categorical data were examined by the use of Fisher's exact test. For continuous data, a Mann-Whitney test was used. As the biomarkers had log-normal distributions, t-tests of log transformed data were used to generate geometric mean ratios of biomarker concentrations, including interval regression as appropriate for concentrations

censored at the upper or lower limit of detection. Although the study subgroups were matched for pre-pregnancy CKD stage and sample gestation, interval regression was also used to examine for any significant effect due to these variables (Pearce, 2016). Non-parametric receiver operating characteristic (ROC) curve analyses examined the capacity of each biomarker to discriminate pre-eclampsia from normal pregnancy, in women with and without CKD. Optimal cut-points were determined for discriminatory biomarkers through the examination of the Youden Index (Faraggi, 2003). In order to correct for gestational variation, plasma PlGF concentrations between 20 and 37 weeks' gestation were transformed into PlGF centiles using data from 1366 samples from 247 women without pre-eclampsia (Saffer et al., 2013). Correlation between the biomarkers of interest and PlGF centile was measured using non-parametric Spearman correlation. Statistical analysis was performed using GraphPad Prism 7 XML and Stata 15.1.

6.4 Results

6.4.1 Study cohorts

The cases in the case-control group were 15 women with CKD with superimposed pre-eclampsia. The controls were: a) 45 women with CKD but without superimposed pre-eclampsia matched for gestation and pre-pregnancy CKD stage, b) 18 women without CKD but with pre-eclampsia matched for gestation, and c) 20 women without CKD or pre-eclampsia. Additionally, quantification of discriminatory biomarkers was carried out in 22 non-pregnant women with CKD stages 2-4 (median eGFR 35ml/min/1.72m^2, range 23-48ml/min/1.73m^2). Standard diagnostic criteria were used for the diagnosis of superimposed pre-eclampsia in 25% (15/60) of the women with CKD. Demographic (Table 6.2) and outcome data (Table 6.3) are shown.

Table 6.2 Nested case-control cohort demographics.
[a]=First blood pressure recorded in pregnancy or non-pregnant value for non-pregnant controls
[b]=data available for 14 women
BMI=body mass index, CAKUT=congenital anomalies of kidney and urinary tract, CKD=chronic kidney disease (without pre-eclampsia), dBP=diastolic blood pressure, DM=diabetes mellitus, GN=glomerulonephritis, uPCR=protein:creatinine ratio, sBP=systolic blood pressure, ,

Diagnosis	**Superimposed pre-eclampsia**	**CKD**	**Pre-eclampsia**	**Normal pregnancy**	**Non-pregnant**
n	15	45	18	20	22
Gestation of sample Median (IQR)	33.0 (30.6-34.7)	32.0 (30.3-33.7)	33.3 (31.1-34.3)	33.1 (27.6-33.7)	-
Age (yrs.) Median (IQR)	31.0 (25.5-34.5)	34.0 (28.9-36.1)	31 (27.8-35.6)	31 (29.0-33.3)	35 (30.3-38.5)
BMI (kg/m^2) Median (IQR)	26.0 (23.8-32.8)	24.0 (22.3-29.8)	27.0 (24.2-31.1)	23.2 (21.1-28.5)	-
Ethnicity					
• White (%)	5 (33)	26 (58)	5 (28)	17 (85)	10 (45)
• Black (%)	7 (47)	10 (22)	11 (61)	2 (10)	6 (27)
• Asian (%)	0 (0)	4 (16)	2 (11)	1 (5)	5 (23)
• Other (%)	3 (20)	5 (11)	0 (0)	0 (0)	1 (5)
Nulliparous (%)	10 (67)	21 (47)	10 (56)	15 (75)	-
sBP[a] Median (IQR)	119 (110-122)	115 (110-122)	120 (111-128)	109 (101-110)	126 (120-136)
dBP[a] Median (IQR)	74 (70-83)	73 (66-80)	75 (70-85)	62 (60-70)	75 (70-82)
Chronic hypertension (%)	8 (53)	16 (36)	5 (28)	0 (0)	14 (64)
Treatment for BP <20 weeks/non-pregnant (%)	5 (33)	10 (22)	2 (11)	0 (0)	13 (59)
CKD stage					
1 (%)	8 (53)	32 (71)	0 (0)	0 (0)	0 (0)
2 (%)	3 (20)	6 (13)	0 (0)	0 (0)	1 (5)
3 (%)	2 (13)	7 (15)	0 (0)	0 (0)	14 (64)
4 (%)	0 (0)	0 (0)	0 (0)	0 (0)	5 (23)
5 (%)	0 (0)	0 (0)	0 (0)	0 (0)	2 (9)
Unknown	2 (13)	0 (0)	0 (0)	0 (0)	0 (0)
Renal diagnosis (%)					
Lupus	3 (20)	15 (33)			2 (9)
Non-lupus GN	2 (13)	10 (22)			9 (41)
Diabetic nephropathy	4 (27)	2 (4)			1 (5)

Reflux/CAKUT	2 (13)	4 (9)			5 (23)
Other	1 (7)	4 (9)			1 (5)
Unknown	3 (20)	10 (22)			4 (18)
Transplant (%)	2 (13)	3 (7)	0 (0)	0 (0)	9 (41)
≥2+ Proteinuria at booking (%)	6 (40)	15 (33)	0 (0)	0 (0)	-
Non-pregnant uPCR[b] >50mg/mmol	-	-	-	-	5 (36)
Pre-pregnancy DM (%)	4 (27)	3 (7)	0 (0)	0 (0)	1 (5)

Table 6.3 Nested case-control pregnancy outcomes.
[a]= Outcome data for 11-15 women, [b]= outcome data for 16-20 women, [c]=PCR quantified in a single normal pregnant control, Comparison between SPE and CKD (p-value): [d]=0.047,[e]=0.026, [f]=0.008, [g]=0.004, [h]=0.0004, [i]=<0.0001, Comparison between pre-eclampsia and normal pregnancy (p-value): [j]=0.017 [k]=0.014, [l]=0.007, [m]=0.005, [n]=0.003, [o]=0.002, [p]=<0.0001, Comparison between SPE and pre-eclampsia (p-value): [q]=0.0004
sBP=systolic blood pressure, dBP=diastolic blood pressure, IV=intravenous, PCR=protein:creatinine ratio, ALT=alanine aminotransferase, NNU=neonatal unit admission.

Outcome	**Superimposed pre-eclampsia (SPE) (n=15[a])**	**CKD (n=45)**	**Pre-eclampsia (n=18)**	**Normal pregnancy (n=20[b])**
Clinical features of pre-eclampsia				
Highest sBP Median (IQR)	172[i] (162-175)	130 (120-146)	170[p] (158-189)	138 (130-140)
Highest dBP Median (IQR)	97[e] (91-106)	90 (75-100)	104[p] (97-108)	83 (78-91)
Severe hypertension (sBP>160 or dBP>110 mmHg)	11 (85)[i]	7 (16)	11 (61)[p]	0 (0)
IV antihypertensives (%)	3 (33)[g]	0 (0)	3 (17)	0 (0)
IV magnesium sulphate (%)	2 (13)	0 (0)	5 (28)[j]	0 (0)
Highest urine PCR Median (IQR)	126 (113-662)	105 (33-222)	55 (45-82)	6[c]
Doubling of proteinuria >30mg/mmol (%)	10 (77)[i]	1 (2)	1 (6)[q]	0 (0)
ALT>70 iu/L (%)	0 (0)	3 (7)	3 (17)	0 (0)
Platelet count <100 x10^9/l (%)	0 (0)	1 (2)	1 (6)	0 (0)
Delivery outcomes				
Vaginal delivery (%)	1 (7)[g]	21 (47)	6 (33)[m]	16 (80)
Caesarean delivery (%)	14 (93)[g]	24 (53)	12 (67)[m]	4 (20)
Emergency Caesarean delivery (%)	9 (60)[d]	14 (31)	8 (44)	3 (15)
Neonatal outcomes				
Gestational age Median (IQR)	34.0[i] (32.4-36.6)	38.0 (37.3-39.6)	35.0[k] (32.6-35.4)	40.6 (39.9-41.0)
Preterm <37 weeks (%)	11 (73)[i]	6 (13)	15 (83)[p]	0 (0)
Preterm <34 weeks (%)	5 (33)[f]	2 (4)	6 (33)[l]	0 (0)
NNU admission (%)	7 (47)[h]	2 (4)	9 (50)[o]	1 (5)
Birthweight grams Median (IQR)	2050[i] (1284-2655)	3132 (2640-3220)	1985[p] (1588-2313)	3393 (3203-3715)
Birthweight< 10th centile (%)	7 (47)	11 (24)	10 (55)[n]	2 (10)
Birthweight<3rd centile (%)	5 (33)[f]	2 (4)	6 (33)[l]	0 (0)

The extended cohort used in the analysis of renin-angiotensin system biomarkers included 18 women with superimposed pre-eclampsia, 65 women with CKD but no superimposed pre-eclampsia, 29 women with pre-eclampsia, 23 women with chronic hypertension in the absence of both CKD and pre-eclampsia, and 65 additional normal pregnant controls. Demographic and outcome data from this extended cohort are shown in Table 6.4.

Table 6.4 Extended cohort characteristics.
[a]=BP documented in only 2 women, [b]= uPCR measured in only 4 women
ALT=alanine aminotransferase, BMI=body mass index, dBP=diastolic blood pressure, DM=diabetes mellitus, IV=intravenous, NNU=neonatal unit admission, sBP=systolic blood pressure, uPCR=protein:creatinine ratio (mg/mmol)

Diagnosis	**SPE**	**CKD**	**Pre-eclampsia**	**CHT**	**Normal pregnancy**
Number of women	18	65	29	23	65
Number of samples	27	112	32	37	112
Age at booking Median (IQR)	32.6 (27.3-36.9)	33.0 (30.3-36.8)	29.0 (26.9-35.4)	32 (29.0-39.4)	32.0 (28.2-36.3)
BMI (kg/m^2) Median (IQR)	25.9 (23.7-30.4)	24.0 (21.7-28.1)	28.0 (24.0-34.3)	30 (27.3-34.0)	22 (20-6-24.6)
Ethnicity					
• White (%)	8 (44)	32 (49)	9 (31)	11 (48)	46 (71)
• Black (%)	8 (44)	17 (26)	14 (48)	12 (52)	11 (17)
• Asian (%)	0 (0)	8 (12)	3 (10)	0 (0)	4 (6)
• Other (%)	2 (11)	8 (12)	3 (10)	0 (0)	4 (6)
Nulliparous (%)	9 (50)	34 (52)	20 (69)	10 (43)	43 (66)
First antenatal sBP Median (IQR)	119 (113-129)	120 (110-127)	123 (111-130)	130 (120-135)	100 (101-110)
First antenatal dBP Median (IQR)	77 (70-90)	78 (70-83)	76 (70-85)	81 (75-90)	62 (60-70)
Chronic hypertension (%)	13 (72)	32 (49)	10 (34)	23 (100)	0 (0)
Treatment for BP <20 weeks (%)	10 (56)	23 (35)	9 (31)	17 (74)	0 (0)
CKD Stage					
• 1 (%)	9 (50)	31 (49)	0 (0)	0 (0)	0 (0)
• 2 (%)	4 (22)	14 (22)	0 (0)	0 (0)	0 (0)
• 3 (%)	3 (17)	17 (27)	0 (0)	0 (0)	0 (0)
• 4 (%)	2 (11)	1 (2)	0 (0)	0 (0)	0 (0)
• 5 (%)	0	0 (0)	0 (0)	0 (0)	0 (0)
Renal transplant (%)	3 (17)	5 (8)	0 (0)	0 (0)	0 (0)
≥2+ Proteinuria at booking (%)	5 (28)	22 (34)	1 (3)	1 (4)	1 (2)
Pre-pregnancy DM (%)	3 (17)	4 (6)	0 (0)	0 (0)	0 (0)
Features of possible pre-eclampsia					
Highest sBP Median (IQR)	172 (166-186)	133 (123-147)	165 (159-184)	145 (134-156)	141[a]

Highest dBP Median (IQR)	103 (95-115)	90 (80-100)	103 (97-110)	92 (89-98)	81[a]
Severe hypertension (sBP>160 or dBP>110 mmHg)	18 (100)	7 (11)	20 (71)	5 (22)	0 (0)
BP treatment in pregnancy	14 (78)	25 (38)	27 (93)	13 (57)	0 (0)
Beta-blocker	8 (44)	10 (15)	7 (24)	4 (17)	0 (0)
Calcium channel blocker	4 (22)	12 (18)	10 (34)	5 (22)	0 (0)
Methyldopa	7 (39)	13 (20)	18 (62)	9 (39)	0 (0)
IV antihypertensives (%)	8 (44)	0 (0)	7 (24)	0 (0)	0 (0)
IV magnesium sulphate (%)	5 (28)	0 (0)	8 (28)	0 (0)	0 (0)
Highest uPCR Median (IQR)	305 (109-839)	109 (30-259)	60 (51-115)	17 (14-23)	13[b] (11-14)
Doubling of proteinuria >30mg/mmol (%)	15 (83)	30 (54)	3 (11)	0 (0)	0 (0)
ALT>70 iu/L (%)	2 (11)	2 (3)	2 (9)	0 (0)	0 (0)
Platelet <100 x10^9/l (%)	0 (0)	1 (2)	1 (5)	0 (0)	0 (0)
Delivery					
Vaginal delivery (%)	1 (6)	35 (54)	6 (21)	15 (65)	58 (91)
Caesarean delivery (%)	17 (94)	30 (46)	23 (79)	8 (35)	6 (9)
Emergency Caesarean (%)	13 (72)	16 (25)	15 (52)	5 (22)	4 (6)
Neonatal outcomes					
Gestational age Median (IQR)	33.3 (32.3-35.6)	38.1 (37.1-39.3)	36.6 (33.9-38.3)	39.0 (38.5-40.4)	40.0 (39.9-41.3)
Pre-term <37 (%)	15 (83)	14 (22)	16 (55)	0 (0)	3 (5)
Pre-term <34 (%)	9 (50)	7 (11)	8 (28)	0 (0)	0 (0)
NNU (%)	10 (56)	7 (11)	15 (52)	0 (0)	3 (5)
Birthweight Median (IQR)	1785 (1226-2563)	2850 (2488-3170)	2270 (1750-2825)	3300 (3020-3515)	3530 (3200-3810)
Birthweight < 10^{th} centile (%)	8 (44)	16 (25)	16 (55)	5 (22)	4 (6)
Birthweight <3^{rd} centile (%)	6 (33)	10 (15)	11 (38)	3 (13)	0 (0)

There were no significant baseline differences in women who developed superimposed pre-eclampsia compared to those with CKD who did not develop superimposed pre-eclampsia including age, BMI, black/non-black ethnicity, parity, prevalence of chronic hypertension, and booking levels of blood pressure and proteinuria. Higher systolic and diastolic blood pressures during pregnancy and a greater relative increase in proteinuria in women with superimposed pre-eclampsia were consistent with the criteria used for diagnosis. Women with superimposed pre-eclampsia delivered at an earlier gestation compared to women with CKD who did not develop superimposed pre-eclampsia. The babies of women with superimposed pre-eclampsia were more likely to be born both preterm (before 37 weeks) and very preterm (before 34 weeks), be small for gestational age, and require neonatal unit admission. These differences were also evident in women with pre-eclampsia in the absence of CKD compared to women with normal pregnancies. There were no significant differences in obstetric outcomes between women with superimposed pre-eclampsia compared to those with pre-eclampsia in the absence of CKD, with the exception of proteinuria, which was higher in women with superimposed pre-eclampsia consistent with underlying CKD. The non-pregnant controls were selected to allow biomarker quantification at higher stages of CKD; these women had an increased prevalence of chronic hypertension and more women with renal transplants compared to pregnant CKD groups. However, absolute levels of blood pressure and rates of clinically significant proteinuria were comparable.

6.4.2 Discriminatory biomarkers: plasma hyaluronan, plasma VCAM

Plasma hyaluronan and plasma VCAM concentrations were significantly higher in women with superimposed pre-eclampsia compared to women with CKD in the absence of superimposed pre-eclampsia, and in women with pre-eclampsia compared to those with normal pregnancies (Table 6.5, Figures 6.3 and 6.4). Area under the curve (AUC) estimations for the diagnosis of pre-eclampsia for hyaluronan were 0.98 (95% confidence interval 0.94-1.00) for women without CKD and 0.79 (95%CI: 0.65-

0.94) for women with CKD. Equivalent values for VCAM were 0.91 (95% CI: 0.82-1.00) for women without CKD and 0.86 (95% CI: 0.71-1.00) for women with CKD (Table 6.5, Figure 6.5 and 6.6). Sensitivity, specificity, positive and negative predictive values are given in Table 6.6. Both plasma hyaluronan and plasma VCAM correlated with PlGF, with an increase in both biomarkers when PlGF concentrations were below the 10th centile for gestation (Figure 6.7).

Table 6.5 Quantification of biomarkers in superimposed pre-eclampsia, CKD (without pre-eclampsia), pre-eclampsia (without CKD) and in normal pregnancy. Values are median (interquartile range)

[a]=comparison between CKD and SPE, #comparison between pre-eclampsia and normal pregnancy, [c]=PlGF centile not derived >37 weeks gestation.
AUROC=area under the receiver operating curve.

Biomarker	Plasma /Urine	Superimposed pre-eclampsia	CKD	p-value[a]	Geometric mean ratio[a] (95% CI)	AUROC[a] (95% CI)	Pre-eclampsia	Normal pregnancy	p-value[b]	Geometric mean ratio[b] (95% CI)	AUROC[b] (95% CI)
Discriminatory											
Hyaluronan (ng/ml)	Plasma	67.5 (39.5-160)	27.5 (15.4-42.5)	0.0017	2.47 (1.49-4.07)	0.79 (0.65-0.94)	123.7 (82.9-160)	32.2 (20.3-44.0)	<0.0001	6.12 (3.53-10.62)	0.98 (0.94-1.00)
VCAM (ng/ml)	Plasma	1132 (1060-1979)	659 (556-857)	<0.0001	1.89 (1.46-2.44)	0.86 (0.71-1.00)	1275 (966-1748)	579 (442-840)	<0.0001	2.09 (1.62-2.69)	0.91 (0.82-1.00)
PlGF centile[c]	Plasma	0 (0-4)	18 (8-40)	0.002			0 (0-1)				
Variable discrimination											
Active renin (pg/ml)	Plasma	2.87 (1.12-6.15)	11.18 (6.48-19.01)	0.02	0.27 (0.15-0.49)	0.89 (0.77-1.00)	5.56 (0.81-9.58)	17.19 (12.22-24.94)	<0.0001	0.18 (0.13-0.27)	0.92 (0.86-0.98)
Angiotensinogen: creatinine (ng/micromol)	Urine	127.5 (61.0-166.6)	9.7 (3.8-27.6)	<0.001	8.72 (3.07-24.76)	0.89 (0.78-1.00)	18.6 (6.8-85.9)	7.1 (2.7-15.6)	<0.01	3.65 (1.32-10.07)	0.76 (0.63-0.89)
CFH (mcg/ml)	Plasma	1053 (616-1228)	1060 (886-1194)	0.69	0.87 (0.72-1.06)	0.54 (0.31-0.77)	672 (567-805)	1116 (1006-1171)	<0.0001	0.62 (0.50-0.78)	0.91 (0.80-1.00)
Non-discriminatory											
Angiotensinogen (ng/ml)	Plasma	121 (87-137)	111 (86-131)	0.53	1.22 (0.60-2.48)	0.57 (0.33-0.81)	107 (70-131)	114 (89-150)	0.07	0.59 (0.40-0.87)	0.39 (0.28-0.50)
C3a (ng/ml)	Plasma	63.5 (48.0-74.5)	49.8 (41.1-64.3)	0.15	1.16 (0.91-1.49)	0.64 (0.46-0.83)	43.7 (29.6-60.2)	34.2 (30.2-50.3)	0.48	1.13 (0.85-1.50)	0.59 (0.35-0.82)
C3a:creatinine (ng/micromol)	Urine	45.2 (10.2-236.3)	46.7 (11.4-233)	0.78	0.84 (0.26-2.77)	0.47 (0.24-0.69)	14.2 (11.4-30.5)	4.2 (4.2-24.2)	0.53	2.45 (0.33-18.23)	0.64 (0.22-1.00)
C5a (ng/ml)	Plasma	1.25	1.25	0.49	0.45	0.44	1.25	1.45	0.19	0.27	0.37

		(1.25-1.28)	(1.25-1.65)		(0.07-2.81)	(0.289-0.59)	(1.25-2.17)	(1.25-3.37)		(0.05-1.61)	(0.19-0.55)
C5b-9 (ng/ml)	Plasma	367 (297-509)	339 (249-443)	0.29	1.24 (0.93-1.65)	0.61 (0.43-0.79)	294 (225-429)	238 (193-360)	0.30	1.13 (0.84-1.51)	0.61 (0.40-0.82)
C5b-9:creatinine (ng/micromol)	Urine	3.02 (0.30-4.80)	0.60 (0.33-1.69)	0.25	2.04 (0.74-5.67)	0.62 (0.40-0.84)	0.73 (0.43-0.98)	0.41 (0.41-0.73)	0.31	1.08 (0.34-3.42)	0.62 (0.35-0.89)
E-selectin (ng/ml)	Plasma	34.1 (21.0-49.4)	39.6 (27.7-43.7)	0.80	1.01 (0.76-1.35)	0.53 (0.31-0.75)	46.7 (24.2-55.8)	35.2 (26.6-43.2)	0.15	1.24 (0.93-1.64)	0.64 (0.44-0.84)
ICAM (ng/ml)	Plasma	121.5 (87.7-152.1)	147.0 (115.5-171.4)	0.13	0.67 (0.47-0.97)	0.35 (0.14-0.56)	137.7 (102.9-182.2)	131.2 (105.1-154.5)	0.64	1.11 (0.78-1.60)	0.55 (0.34-0.75)
KIM-1 (pg/ml)	Plasma	352 (313-402)	313 (273-402)	0.42	1.07 (0.85-1.35)	0.66 (0.40-0.91)	293 (253-303)	263 (253-290)	0.47	1.05 (0.81-1.35)	0.43 (0.00-0.88)
Lipocalin-2: creatinine (ng/micromol)	Urine	10.3 (3.8-25.6)	11.1 (5.8-32.9)	0.60	1.53 (1.09-2.14)	0.44 (0.23-0.65)	7.9 (4.8-12.8)	1.7 (1.0-6.2)	0.05	0.76 (0.52-1.10)	0.73 (0.51-0.95)
P-selectin (ng/ml)	Plasma	55.2 (39.3-66.4)	52.4 (40.4-62.6)	0.82	1.04 (0.84-1.28)	0.52 (0.33-0.72)	53.3 (41.0-68.8)	57.7 (44.7-71.1)	0.37	0.87 (0.71-1.07)	0.41 (0.22-0.60)

Figure 6.3 Plasma hyaluronan concentrations in superimposed pre-eclampsia (SPE), women with chronic kidney disease who do not develop pre-eclampsia (CKD), women with pre-eclampsia (in the absence of CKD), normal pregnancy (NP) and in non-pregnant controls with CKD stages 2-4 (bars at median and interquartile range).

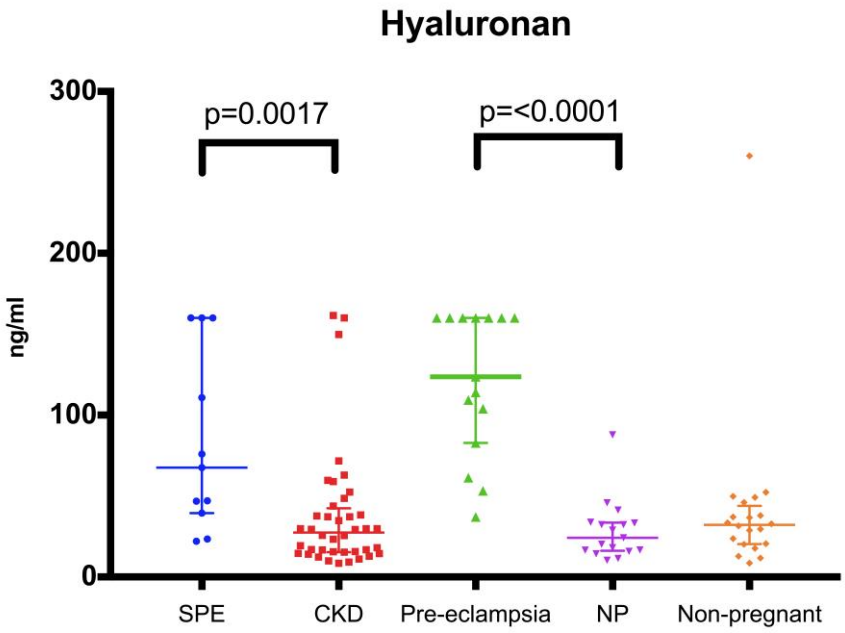


Figure 6.4 Plasma VCAM concentrations in superimposed pre-eclampsia (SPE), women with chronic kidney disease who do not develop pre-eclampsia (CKD), women with pre-eclampsia (in the absence of CKD), normal pregnancy (NP) and in non-pregnant controls with CKD stages 2-4 (bars at median and interquartile range).

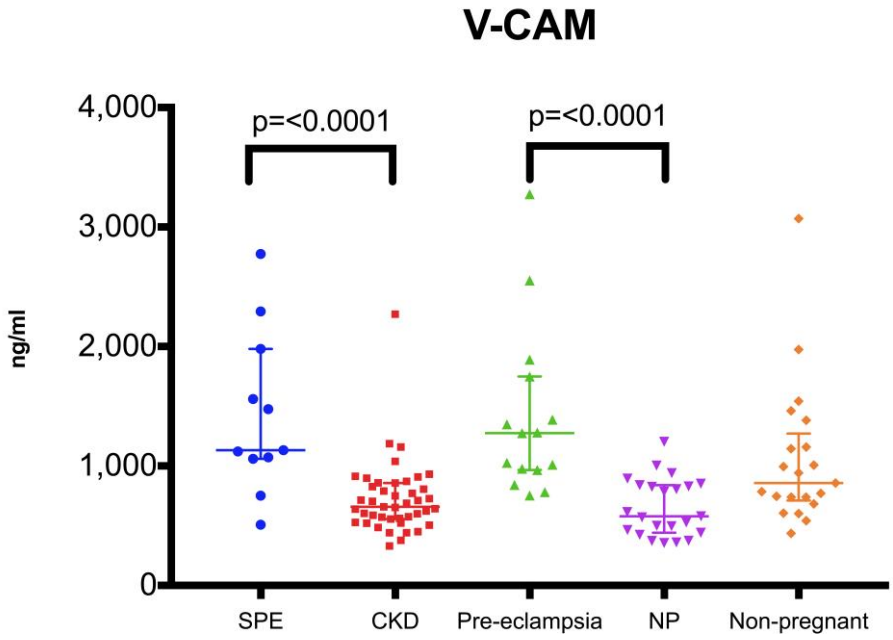


Figure 6.5 Receiver operating characteristic (ROC) curve of plasma hyaluronan in the diagnosis of pre-eclampsia in women with (red) and without (black) CKD. Values are area under the curve with 95% confidence intervals.

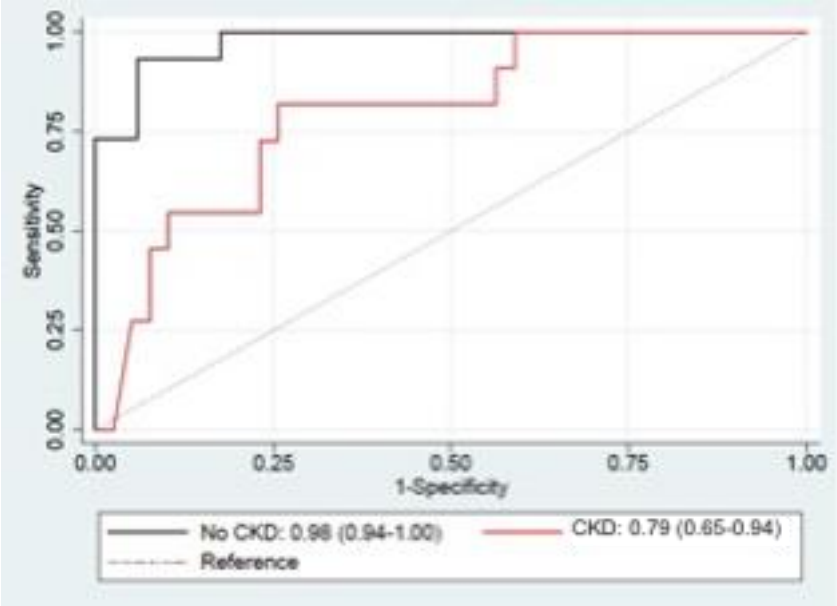


Figure 6.6 Receiver operating characteristic (ROC) curve of plasma VCAM in the diagnosis of pre-eclampsia in women with (red) and without (black) CKD. Values are area under the curve with 95% confidence intervals.

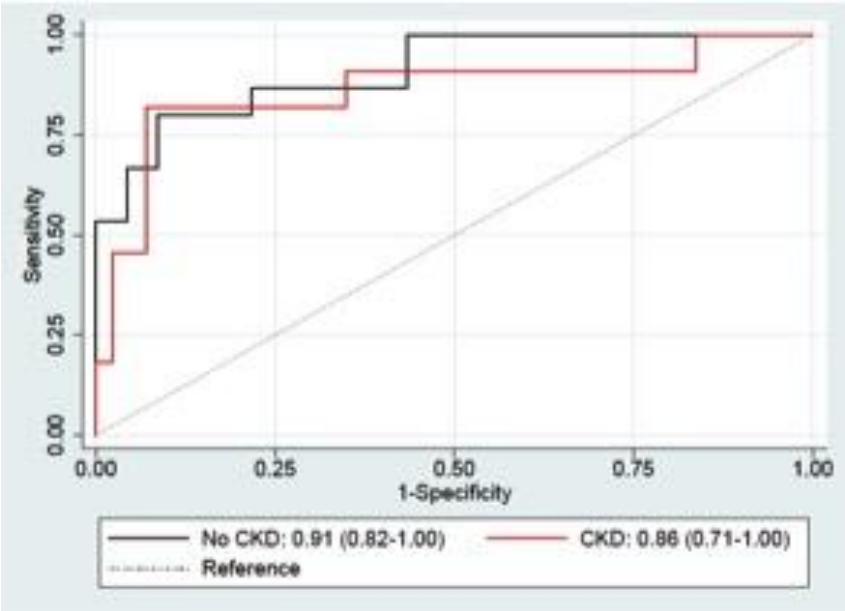
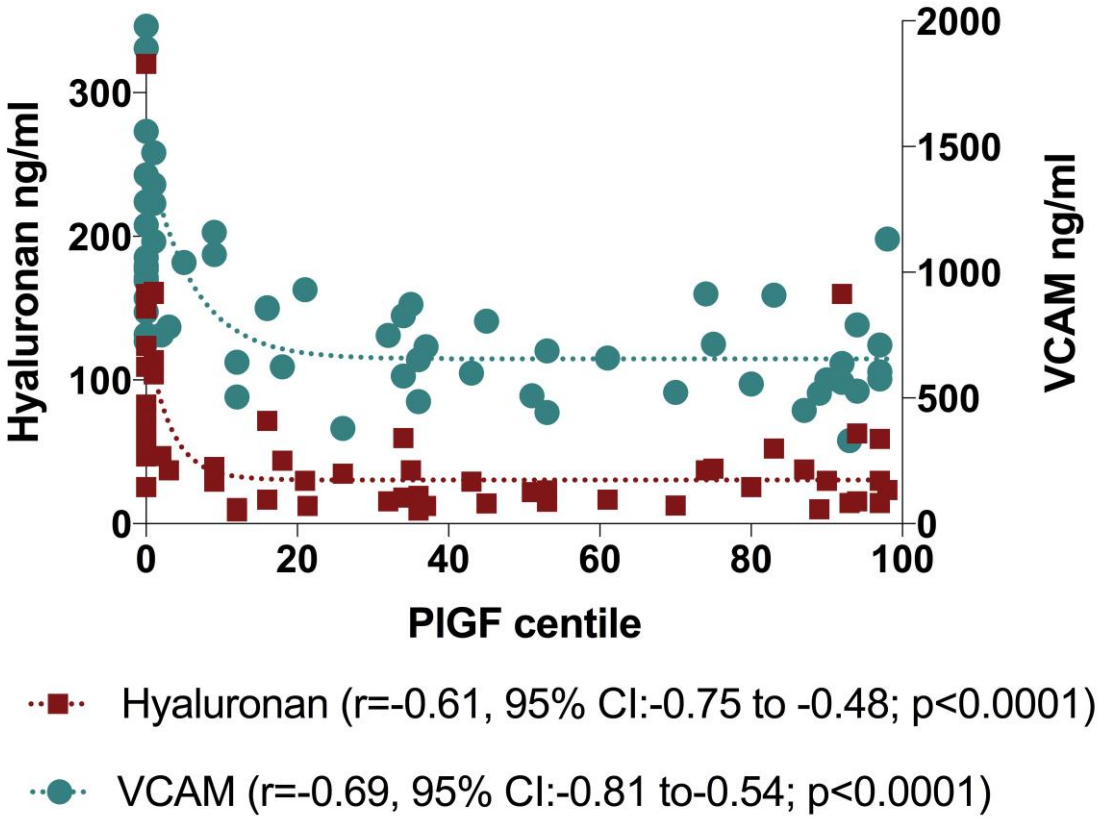


Table 6.6 Sensitivity, specificity, positive and negative predictive values (%) with 95% confidence intervals for the prediction of pre-eclampsia in women with and without CKD.

Biomarker	Sensitivity		Specificity		Negative predictive value		Positive predictive value	
	CKD	No CKD	CKD	No CKD	CKD	No CKD	CKD	No CKD
Hyaluronan >39ng/ml	82 (47-97)	93 (66-97)	74 (58-86)	82 (56-95)	94 (77-99)	93 (66-100)	47 (25-71)	84 (56-95)
VCAM >950ng/ml	82 (48-97)	80 (51-95)	91 (77-97)	91 (70-98)	95 (82-99)	88 (66-97)	69 (39-90)	86 (56-97)

Figure 6.7 Correlation of plasma hyaluronan and plasma VCAM with PlGF centile measured by Spearman's rank correlation coefficient.



Plasma hyaluronan (p=<0.0001, geometric mean ratio 4.93, 95% CI: 3.01-8.108) and plasma VCAM concentrations (p=<0.0001, geometric mean ratio 1.88, 95% CI: 1.49-2.36) were also higher in pre-eclampsia (in the absence of CKD) compared to CKD (in the absence of pre-eclampsia) facilitating diagnostic distinction between previously unknown or new CKD in pregnancy, from pre-eclampsia.

There was no detectable difference in hyaluronan concentration in non-pregnant women with CKD stage 2-4 (median 32.2ng/ml, interquartile range (IQR) 20.3-44.0ng/ml) compared to both normal pregnancy (geometric mean ratio 0.79, 95% CI: 0.50-1.26, p=0.23) and CKD in the absence of pre-eclampsia (geometric mean ratio 0.98, 95% CI: 0.66-1.46, p=0.52). However, plasma VCAM was increased in non-pregnant women with CKD stage 2-4 (median 857ng/ml, IQR 711-1270ng/ml) compared to both normal pregnancy (geometric mean ratio 1.54, 95% CI 1.22-1.94, p=0.005) and CKD in the absence of superimposed pre-eclampsia (geometric mean ratio 1.38, 95% CI 1.12-1.70, p=0.03), although this was not explained by the higher number of women with renal transplants in the non-pregnant group. No detectable differences in VCAM concentrations were detected in non-pregnant women with renal transplants (median 857ng/ml, IQR 670-1151ng/ml) compared to those without (median 883ng/ml, IQR 698-1442ng/ml), and differences in plasma VCAM concentrations in superimposed pre-eclampsia (median 1476ng/ml, IQR 911-2136ng/ml) compared to CKD (median 688ng/ml, IQR 559-858ng/ml) remained after exclusion of women with renal transplants (p=<0.0001).

Pre-pregnancy eGFR and gestation were not significant modifiers of either hyaluronan or VCAM concentrations (Table 6.7).

Table 6.7 Interval regression showing the impact of matched variables on biomarker concentrations

Biomarker	Variable	Coefficient	95% CI	p-value
Hyaluronan	eGFR	-0.0013	-0.0089 to 0.0064	0.75
	Gestation (days)	0.0088	-0.0026 to 0.0203	0.13
VCAM	eGFR	0.0005	-0.0033 to 0.0042	0.81
	Gestation (days)	0.0001	-0.0056 to 0.0058	0.97

6.4.3 Variable discrimination: plasma active renin, urinary angiotensinogen:creatinine

Plasma active renin was lower in superimposed pre-eclampsia compared to CKD (geometric mean ratio 0.27, 95% CI: 0.15-0.49) and in pre-eclampsia compared to normal pregnancy (geometric mean ratio 0.18, 95% CI:0.13-0.27) (Table 6.5). However, active renin concentrations were also lower in women with chronic hypertension compared to normotensive pregnant women (median 8.2 pg/ml (IQR 3.5-15.7) versus 17.2pg/ml, (IQR 12.2-25.0), p=<0.0001, geometric mean ratio 0.40, 95% CI: 0.30-0.53), and the weak correlation between active renin and PlGF in normotensive women (r=0.33, 95% CI: 0.17-0.48, p=<0.0001), was not evident in women with chronic hypertension (r=0.06, 95% CI: -0.14 to 0.26, p=0.55). Urinary angiotensinogen:creatinine was higher in superimposed pre-eclampsia compared to CKD (geometric mean ratio 8.72, 95% CI: 3.07-24.76), and in pre-eclampsia compared to normal pregnancy (geometric mean ratio 3.65, 95% CI: 1.32-10.07) (Table 6.5), although there was no significant correlation between urinary angiotensinogen:creatinine and PlGF centile (r=-0.14, 95% CI:-0.28 to 0.11, p=0.06). The diagnostic discrimination of both plasma active renin and urinary angiotensinogen:creatinine was reduced in women with chronic hypertension, women requiring antihypertensive treatment prior to 20 weeks' gestation and in women of black ethnicity (Table 6.8).

Table 6.8 Area under the receiver operating curve values (standard error) for the diagnosis of pre-eclampsia using plasma active renin and urinary angiotensinogen:creatinine in women with and without underlying CKD, adjusted for chronic hypertension (CHT), anti-hypertensive drug use prior to 20 weeks gestation and black/non-black ethnicity.

	Plasma active renin		Urinary angiotensinogen:creatinine	
	CKD	No CKD	CKD	No CKD
Extended cohort	0.80 (0.12)	0.88 (0.03)	0.82 (0.08)	0.80 (0.04)
Women without CHT	0.92 (0.04)	0.92 (0.04)	0.90 (0.06)	0.86 (0.04)
Women with CHT	0.61 (0.38)	0.76 (0.09)	0.68 (0.26)	0.61 (0.14)
No antihypertensive use <20 weeks	0.92 (0.04)	0.92 (0.03)	0.88 (0.07)	0.83 (0.05)
Antihypertensive use <20 weeks	0.61 (0.39)	0.73 (0.14)	0.67 (0.27)	0.65 (0.17)
Non-black ethnicity	0.90 (0.05)	0.92 (0.04)	0.89 (0.08)	0.85 (0.05)
Black ethnicity	0.71 (0.26)	0.76 (0.08)	0.69 (0.17)	0.64 (0.12)

Plasma complement factor H (CFH) was lower in pre-eclampsia compared to normal pregnancy. However, no detectable differences were seen in superimposed pre-eclampsia where diagnostic distinction was poor (Table 6.5).

6.4.4 Non-discriminatory markers

Quantification of plasma angiotensinogen, C3a, C5a, C5b-9, E-selectin, ICAM, KIM-1 and P-selectin, and urinary lipocalin-2 failed to discriminate women with superimposed pre-eclampsia from CKD in the absence of pre-eclampsia, and pre-eclampsia from normal pregnancy.

6.5 Discussion

Diagnosis of superimposed pre-eclampsia remains challenging in women with CKD, and underlying pathophysiology pre-disposing to increased risk is poorly understood.

This study demonstrates that quantification of plasma hyaluronan and plasma VCAM have the potential to distinguish superimposed pre-eclampsia in pregnant women with CKD. Correlation of both hyaluronan and VCAM concentrations with serum PlGF supports the diagnostic criteria used in this study to define superimposed pre-eclampsia. Suggested cut-offs of for the diagnosis of pre-eclampsia of >39ng/ml for plasma hyaluronan and >950ng/ml for plasma VCAM have a sensitivity of 82% and a negative predictive value of 94%-95% in women with CKD. All other markers tested showed variable discrimination or failed to discriminate pre-eclampsia in women with and without CKD.

Hyaluronan and VCAM are components of the endothelial cell glycocalyx, which is a negatively charged protective layer that sits between the endothelial cell surface and the flow of blood, with a physiological role in vascular protection, modulation and haemostasis (Reitsma et al., 2007). An increase in circulating concentrations of hyaluronan and VCAM is hypothesised to represent damage to the endothelial glycocalyx. The model of pre-eclampsia as an endothelial disorder driven by placentally derived anti-angiogenic factors is supported by both the systemic nature of disease and its resolution following delivery (Tomimatsu et al., 2017). Endothelial dysfunction in CKD is manifest by accelerated vascular disease, as well as proteinuria, which is a clinical manifestation of intra-renal endothelial disease (Padberg et al., 2014). Thus, endothelial glycocalyx dysfunction provides a mechanistic link between CKD and pre-eclampsia, whereby damage to the endothelial glycocalyx in CKD confers vulnerability to additional injury in pre-eclampsia, offering a potential explanation for the increased rates of superimposed pre-eclampsia seen in women with CKD (Piccoli et al., 2015; Zhang et al., 2015). Whilst increases in both plasma hyaluronan and VCAM have been similarly shown in small cohort studies of pregnant women without underlying CKD (Osmers et al., 1998; Matejevic et al., 1999; Berg et al., 2001; Kim et al., 2004; Chaiworapongsa et al., 2002), including women with chronic hypertension (Romão et al., 2013), this is the first report showing utility in pregnant women with CKD. This study also demonstrates the potential capacity of these markers to distinguish pre-eclampsia from a new diagnosis of CKD in pregnancy; a phenomenon that represents up to one third of CKD in pregnancy (Piccoli et al., 2012). Receiver operating curve

areas of 0.79-0.86 are higher than those for clinical variables including systolic and diastolic blood pressure and the detection of de novo proteinuria on urine dipstick testing, which may not distinguish the need for delivery due to pre-eclampsia even in the absence of complicating CKD (Chappell et al., 2013).

Biomarkers of the renin angiotensin system evaluated in this study included plasma active renin, plasma angiotensinogen and urinary angiotensinogen:creatinine. Concentrations of plasma active renin were significantly lower in both pre-eclampsia and superimposed pre-eclampsia consistent with previously published data (Brown et al., 1997), and the consensus hypothesis that hypertension in pre-eclampsia is due to an exaggerated pressor response to the renin-angiotensin system, rather than a measurable increase in renin-angiotensin components (Irani and Xia, 2008; Rodriguez et al., 2012). The finding of an increase in urinary angiotensinogen in pre-eclampsia without a measured increase in plasma levels raises the possibility of intra-renal synthesis of angiotensinogen in pre-eclampsia, with excretion into urine where it can be measured. This is substantiated by reports of angiotensinogen gene expression in renal biopsy tissue (Nishiyama et al., 2011), and the use of urinary angiotensinogen:creatinine as a marker of intra-renal renin-angiotensin system activation in both hypertension (Kobori et al., 2009; Sato et al., 2018), and CKD (Kobori et al., 2008; Nishiyama et al., 2011; Juretzko et al., 2017). However, diagnostic discrimination of both plasma active renin and urinary angiotensinogen:creatinine was reduced in the context of known modifiers of the renin-angiotensin system including chronic hypertension (Preston et al., 1998; Mulatero et al., 2007; Malha et al., 2016), hypertensive drug use (Laragh and Sealey, 2011) and ethnicity (Malha et al., 2016). Such modifiers are important, as their prevalence in CKD cohorts is high. In this study 40% (24/60) of women with CKD were hypertensive prior to pregnancy, which is comparable to other published cohorts (Piccoli et al., 2015; Bramham et al., 2016), 25% (15/60) were using antihypertensive medication before 20 weeks' gestation and 28% (17/60) of women were of black ethnicity. In addition, gestational changes in angiotensinogen are described including an altered ratio of oxidised to reduced forms in pre-eclampsia (Zhou et al., 2010), polymorphic conformational change and pregnancy-specific high molecular weight forms (Tewksbury and Dart, 1982; Lumbers

and Pringle, 2014). Such factors may contribute to the inconsistency in published data with reports both supporting (Yilmaz et al., 2015), and refuting (Pringle et al., 2018) an association between high urinary angiotensinogen:creatinine and complicated pregnancy including pre-eclampsia. In the context of multiple confounders, the use of renin-angiotensin system biomarkers in the diagnosis of superimposed pre-eclampsia is likely to be complex, with limited clinical utility.

This multi-centre study is novel in examining a well-defined cohort of pregnant women with CKD, rather than a mixed cohort of high-risk women; and in specifically examining for differences between women with CKD who do, and do not, develop superimposed pre-eclampsia in order to identify diagnostic indicators and explore mechanistic pathways. The diagnostic criteria for pre-eclampsia superimposed upon CKD are ambiguous (Brown et al., 2018); however, this study used pre-defined blood pressure and proteinuria thresholds and expert diagnostic consensus masked to biomarker concentrations for all complex cases. In addition, correlation with plasma PlGF was used as a confirmatory diagnostic adjunct. This was done on the basis of supporting data in women with a combination of chronic hypertension and/or CKD which demonstrate a capacity to predict the need for delivery, a low false positive rate (3/161), and independence from serum creatinine (Bramham et al., 2016). Although circulating s-Flt1 levels were not assessed in this study, no difference has been demonstrated between the diagnostic performance of PlGF centile when compared to s-Flt1 concentration or s-Flt-1:PlGF ratio in women with CKD and chronic hypertension (Bramham et al., 2016; McCarthy et al., 2019).

This study is limited by the sample size. Despite matching for pre-pregnancy CKD stage, the possibility that reduced renal clearance impacts biomarker quantification also warrants further assessment. Although concentrations of hyaluronan in non-pregnant women with CKD stages 2-4 were comparable to that in normal pregnancy, concentrations of VCAM were increased in both superimposed pre-eclampsia and non-pregnant CKD. Although calcineurin inhibitors have been associated with increased VCAM mRNA synthesis (Rodrigues-Diez et al., 2016), exclusion of women with renal

transplants from the study data had no impact on the results, suggesting the possibility of confounding by reduced glomerular filtration. There are limited data showing increases in both hyaluronan (Vlahu et al., 2015) and VCAM (Padberg et al., 2014) with reduced renal function and validation of the diagnostic capacity of these markers in pregnant women with advanced CKD is warranted. The urinary markers in this study utilised a ratio to urinary creatinine in order to correct for urinary flow rate and concentration. This was based on an assumption that urinary creatinine excretion is constant and that biomarker excretion has a linear relationship with creatinine excretion (Waikar et al., 2010), which does not explicitly address ethnic differences in creatinine production and excretion, or false amplification due to acute kidney injury, which may exist in the context of both pre-eclampsia and superimposed pre-eclampsia. Recruitment to this study was pragmatic, with samples taken from participants at their convenience, coordinated with other hospital attendances. In the absence of a standardised gestation over which longitudinal changes in biomarker concentration could be examined, analysis was restricted to concentrations at the time of disease (pre-eclampsia/superimposed pre-eclampsia) when biomarker changes were anticipated to be most exaggerated. Whether longitudinal changes in biomarker concentration are predictive or diagnostic of superimposed pre-eclampsia remains unknown.

The findings of this exploratory study suggest that quantification of plasma hyaluronan and VCAM have the potential to aid in the diagnosis of superimposed pre-eclampsia. Current standard diagnostic criteria can be utilised in only women who do not have pre-existing hypertension and proteinuria, excluding 75% of women with CKD in this cohort. Test performances for plasma hyaluronan and VCAM are comparable to that of sFlt:PlGF ratio>85 (Bramham et al., 2016), which is based on an anti-angiogenic, placental driven model of pre-eclampsia. However, a placental model of disease may be an inadequate representation of the pathophysiology of superimposed pre-eclampsia in women with CKD. The consistent association between CKD and pre-eclampsia, including an increment in the risk of pre-eclampsia with increasing CKD severity, suggests a significant maternal contribution to the disease process in superimposed pre-eclampsia. Yet, mechanisms by which maternal CKD influences the

pathology of pre-eclampsia remain unknown, and maternal drivers of disease are unmeasured with the isolated use of placental biomarkers. Quantification of plasma hyaluronan and VCAM therefore offers a potential measure of 'maternal disease' in the prediction, diagnosis and long-term prognosis of superimposed pre-eclampsia in women with CKD. The findings of this study warrant validation in a larger, prospective cohort including pregnant women with advanced stage CKD, and multivariable analysis to assess the value of these novel biomarkers over existing clinical parameters including PlGF and sFlt-1.

7 PLACENTAL AND ENDOTHELIAL BIOMARKERS IN THE PREDICTION OF SUPERIMPOSED PRE-ECLAMPSIA IN WOMEN WITH CHRONIC KIDNEY DISEASE.

7.1 Abstract

7.1.1 Background

Data on the utility of placental growth factor (PlGF) and the ratio of soluble fms-like tyrosine-kinase 1 (sFlt-1):PlGF in women with chronic kidney disease (CKD) are limited. Plasma hyaluronan and plasma vascular cell adhesion molecule (VCAM) are alternative markers of endothelial dysfunction in superimposed pre-eclampsia. The aim of this study was to evaluate the predictive performance of PlGF, sFlt-1, hyaluronan and VCAM for the development of superimposed pre-eclampsia in women with CKD.

7.1.2 Methods

Women with and without CKD were recruited from four specialist obstetric nephrology centres in UK. Outcomes including superimposed pre-eclampsia were based on predetermined criteria. Plasma PlGF (Quidel Triage®), serum PlGF and sFlt-1:PlGF (Roche Elecsys®), plasma hyaluronan and plasma VCAM concentrations were quantified. Test performance was evaluated as the area under the receiver-operating curve and at threshold concentrations.

7.1.3 Results

This study comprised 533 women, including 232 pregnancies in women with CKD. One third of women with CKD (76/232, 33%) developed superimposed pre-eclampsia. Women with CKD that developed superimposed pre-eclampsia had lower plasma PlGF (Quidel) concentrations than women with CKD who did not, though mean concentrations were greater than 100pg/ml. Plasma PlGF (Quidel) below 150pg/ml

had the highest sensitivity (79% 95% CI: 54-94%) and negative predictive value (97%, 95% CI: 93-99%) for the prediction of delivery with superimposed pre-eclampsia within 14 days in women with CKD. High plasma hyaluronan and VCAM concentrations were able to discriminate the need for delivery due to superimposed pre-eclampsia but predictive performance was lower than for plasma PlGF (Quidel). Predictive performance was lower for women with pre-pregnancy CKD stages 3-5 compared to women with CKD stages 1-2 for low plasma PlGF, high hyaluronan and high VCAM concentrations. Serum PlGF, sFlt-1 and the sFlt-1:PlGF ratio (Roche) did not usefully predict the need for delivery due to superimposed pre-eclampsia in women with CKD.

7.1.4 Conclusions

Increased surveillance for superimposed pre-eclampsia should take place in women with CKD and plasma PlGF (Quidel) below 150pg/ml after 20 weeks' gestation, with awareness that the predictive value for PlGF concentration for superimposed pre-eclampsia is reduced as excretory kidney function declines. The serum sFlt-1:PlGF ratio (Roche) should not be used as a diagnostic adjunct in women with CKD and suspected superimposed pre-eclampsia.

7.2 Introduction

Pre-eclampsia is estimated to affect up to 40% of pregnancies in women CKD (Zhang et al., 2015; Bramham et al., 2016). Development of pre-eclampsia is a significant determinant of maternal and neonatal outcomes in general obstetric cohorts (Mol et al., 2016) and in women with CKD (Bramham et al., 2016; Luders et al., 2018).

Renal physiological changes in pregnancy include gestational variation in serum creatinine concentrations and an increase in proteinuria, yet reference intervals that enable a distinction between gestational variation and pathology have not been established for women with CKD. The syndrome of pre-eclampsia includes maternal hypertension, proteinuria and elevated serum creatinine concentrations, thus

overlapping with the phenotype of CKD. Standard diagnostic criteria for pre-eclampsia (hypertension and proteinuria) are already present prior to pregnancy in a proportion of pregnant women with CKD (Bramham et al., 2016; Wiles et al., 2019 (see Chapter 6). In the absence of defined diagnostic criteria for women with CKD, the diagnosis of superimposed pre-eclampsia is complex; however, accurate diagnosis is required for optimum antenatal surveillance and pregnancy management, including avoidance of unnecessary iatrogenic preterm delivery.

Over recent years, angiogenic dysfunction has emerged as a common pathophysiological mechanism in pre-eclampsia. A reduction in angiogenic factors (placental growth factor [PlGF]) and an increase in anti-angiogenic factors (soluble fms-like tyrosine-kinase 1 [sFlt-1]) have been shown to be quantifiable in the maternal circulation before the clinical syndrome of pre-eclampsia manifests (Burton et al., 2019). Following evaluation, PlGF concentrations and the ratio of sFlt-1:PlGF have been implemented as diagnostic adjuncts in women with suspected pre-eclampsia in the UK (NICE, 2016). However, prospective cohort studies that have evaluated the diagnostic and prognostic utility of these factors include few women with CKD (Chappell et al., 2013; Zeisler et al., 2016), with no information available on test performance related to excretory kidney function. Data specific to superimposed pre-eclampsia in women with CKD remain limited (Masuyama et al., 2006; Masuyama et al., 2012; Bramham et al., 2016; Wiles et al., 2019 [see Chapter 6]), and the effects of reduced kidney clearance and pre-existing endothelial dysfunction on the diagnostic and predictive performance of PlGF and sFlt-1 in superimposed pre-eclampsia remain unknown.

Plasma hyaluronan and plasma vascular cell adhesion molecule (VCAM) concentrations are alternative markers of endothelial dysfunction, which have been shown to distinguish superimposed pre-eclampsia in women with CKD in a single small case-control cohort (Wiles et al., 2019 [see Chapter 6]), but require validation in a larger study.

The aims of this prospective cohort study were to evaluate the predictive performance of maternal PlGF, sFlt-1, hyaluronan and VCAM for the development of superimposed pre-eclampsia in women with CKD. The primary outcome of superimposed pre-eclampsia requiring delivery within two and four weeks of testing was used as a clinically relevant end-point (Chappell et al., 2013).

7.3 Methods

Women were recruited from four obstetric nephrology centres in London that provide regional care for women in with CKD in pregnancy (Barts Health NHS Trust, Guy's and St. Thomas' NHS Foundation Trust, King's College Hospital NHS Foundation Trust, Imperial College Healthcare NHS Trust) from 2014 to 2018. The study was approved by the Research Ethics Service and the Health Research Authority (15/WA/009) and performed in accordance with the Declaration of Helsinki.

Inclusion criteria for women with CKD were a known diagnosis based on Kidney Disease: Improving Global Outcomes (KDIGO) criteria (Levin and Stevens, 2014), or a presumed diagnosis of CKD based on either a raised creatinine (>85 μmol/l) in the absence of risk factors for acute kidney injury, or persistent proteinuria (urinary protein:creatinine ratio >30 mg/mmol), before 20 weeks' gestation (Bramham et al., 2016; Wiles et al., 2019 [see Chapter 6]). Reproductive-age women with CKD who were not pregnant; and pregnant women without CKD, including those with a clinical diagnosis of pre-eclampsia, were recruited to explore the utility of the novel biomarkers: plasma hyaluronan and VCAM.

Women were enrolled prospectively following confirmation of a viable pregnancy on ultrasound imaging. Demographic data were recorded after written informed consent. Date of conception was calculated as 280 prior to the expected date of delivery from early pregnancy scan, or by menstrual history where scan data were not available. The most recent creatinine prior to conception was converted to an estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration

(CKD-EPI) formula (Levey et al., 2009). Where no pre-pregnancy eGFR was available, women with a serum creatinine >125µmol/L prior to 20 weeks' gestation, in the absence of a precipitant for acute kidney injury, were presumed to have pre-pregnancy CKD stage 3 or greater. Estimated glomerular filtration rate before pregnancy has been approximated by increasing the first recorded antenatal creatinine concentration by 25% (Williams and Davison, 2008; Bramham et al., 2016). The cut-off of >125µmol/L used in this study was confirmed to generate an eGFR <60ml/min/1.73m^2 even in the absence of this correction, as a gestational fall in serum creatinine does not occur in all pregnant women with CKD (see Chapter 5).

Serum and plasma samples were taken at routine clinical review at up to four time points during pregnancy. Samples were stored on ice before being centrifuged at 1500xg for 10 minutes at 4^{o}C. The separated supernatant was aliquoted and stored at -80^{o}C.

Pregnancy and kidney outcomes were based on pre-determined criteria. In the absence of chronic hypertension and pre-pregnancy proteinuria (urinary protein:creatinine ratio (uPCR) <30mg/mmol prior to 20 weeks' gestation), standard criteria were used for the diagnosis of hypertensive disorders in pregnancy, including pre-eclampsia (Tranquilli et al., 2014; Brown et al., 2018). For women with CKD complicated by chronic hypertension and/or pre-pregnancy proteinuria disease definitions are outlined in Table 7.1, adapted from international consensus definitions for pre-eclampsia (Tranquilli et al., 2014).

In women with CKD without chronic hypertension, standard diagnostic criteria for gestational hypertension were used (Tranquilli et al., 2014; Brown et al., 2018), and a diagnosis of superimposed pre-eclampsia was made if gestational hypertension developed in conjunction with any one or more of the other diagnoses listed in Table 7.1. For women with chronic hypertension, a diagnosis of superimposed pre-eclampsia was made if 2 or more of the diagnoses in Table 7.1 were present. Complex cases were reviewed and a final diagnosis confirmed by two clinicians with expertise in obstetric

nephrology, assessing independently and without access to study results. Birthweight percentile was derived from INTERGROWTH-21st neonatal standards (Villar et al., 2014).

Table 7.1 Predetermined diagnostic definitions for women with CKD and chronic hypertension and/or pre-exiting proteinuria (uPCR <30mg/mmol prior to 20 weeks' gestation)

Diagnosis	Clinical features
Gestational hypertension	De novo hypertension >160/110mmHg OR An increment in antihypertensive treatment after 20 weeks' gestation to maintain BP <160/110mmHg
Gestational proteinuria	Greater than two-fold increase in uPCR after 20 weeks compared to values before 20 week' gestation. AND uPCR >30mg/mmol
Acute kidney injury	≥50% increase in serum creatinine in pregnancy not attributable to an alternate diagnosis AND Serum creatinine in pregnancy ≥27μmol/L (≥0.3 mg/dL) (Fliser et al., 2012) above pre-pregnancy concentration.
Uteroplacental dysfunction	Small for gestational age (birthweight <10th centile), or abnormal uterine artery Doppler waveform.
Severe features	Any of: • Platelet count <100 x 10^9/L • Evidence of haemolysis • Transaminitis greater than double the upper the reference limit • Epigastric or right upper quadrant pain not attributable to an alternate diagnosis • Neurological symptoms not attributable to an alternate diagnosis • Pulmonary oedema not attributable to an alternate diagnosis

7.3.1 Assays

Plasma and serum samples were tested with masking of clinical outcomes. Plasma PlGF concentrations were quantified using a point of care Triage® instrument (Quidel Cardiovascular Inc, San Diego, CA, previously Alere) according to manufacturers instructions on samples taken between 20 and 37 weeks' gestation (Chappell et al.,

2013). Serum PlGF and sFlt-1 concentrations were determined by means of a fully automated electrochemiluminescence immunoassay platform (Elecsys®, Roche diagnostics), and the ratio of sFlt-1: PlGF was calculated. Enzyme linked immunosorbent assays (ELISA) were used according to manufacturers' recommendations to determine concentrations of plasma hyaluronan (Hyaluronan Quantikine, DHYAL0, R&D Systems®) and plasma VCAM (Human sVCAM-1/CD106 Quantikine, DVC00, R&D Systems®) in duplicate at all sample gestations, with intra- and inter-assay precision of 4.8% and 10.5%, and 2.2% and 5.6% respectively.

7.3.2 Statistical methods

Demographic and outcome data were compared using Chi-square, Fisher's exact and Mann-Whitney U tests as appropriate. The outcome for predictive performance was superimposed pre-eclampsia requiring delivery within 14 and 28 days of testing. Data were censored for delivery after the 37th week of pregnancy. The effect of superimposed pre-eclampsia on biomarker concentrations was assessed using linear regression. Test performance was evaluated as the area under the receiver-operating curve (AUROC).

Sensitivity, specificity, positive and negative predictive values for PlGF and sFlt-1 were determined at concentrations with previously demonstrated utility in general obstetric cohorts: low (<100pg/ml) and very low (<12pg/ml) PlGF concentrations (Chappell et al., 2013; Duhig et al., 2019a) and sFlt-1:PlGF ratios <38 (Zeisler et al., 2016) and >85 (Rana et al., 2012; Verlohren et al., 2014). Where the AUROC suggested good test performance, alternative optimum predictive thresholds for women with CKD were assessed by examination of sensitivity and specificity at all points on the receiver operating characteristic (ROC) curve. Plamsa PlGF centiles were calculated from Quidel Triage® concentrations based on data from 1366 samples in 247 women without preeclampsia (Saffer et al., 2013) and Z scores calculated.

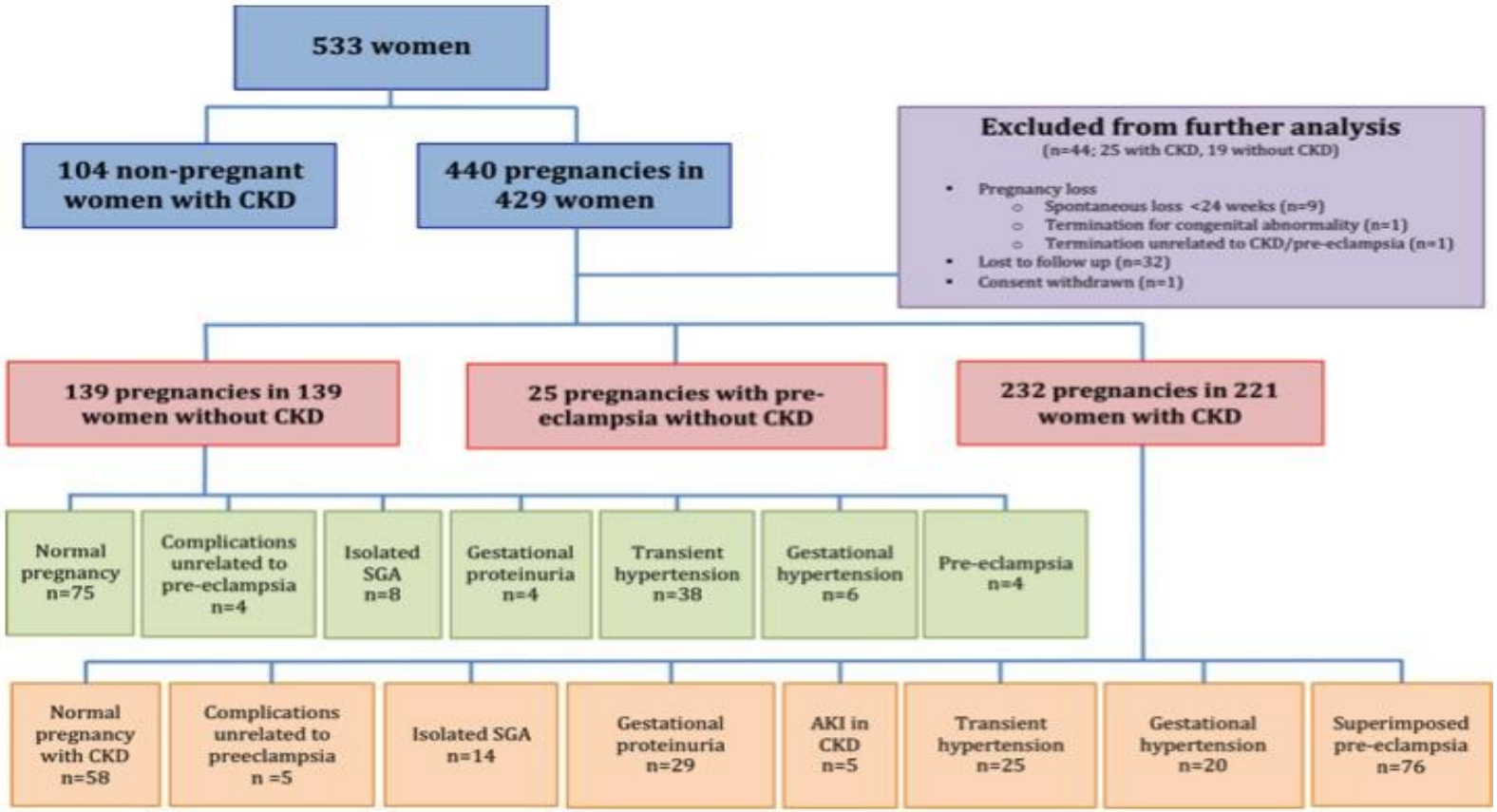
Linear regression was used to assess the impact of age, eGFR, antihypertensive medication use and calcineurin inhibitor drug use (Rodrigues-Diez et al., 2016) on hyaluronan and VCAM concentrations in non-pregnant women with CKD. The utility of hyaluronan and VCAM in predicting the need for delivery with pre-eclampsia or superimposed pre-eclampsia was assessed in pregnant women with and without CKD. Normality of distribution of plasma hyaluronan and VCAM concentrations in pregnancy were explored using a Q-Q plot with logarithmic transformation when appropriate. Reference intervals for plasma hyaluronan and plasma VCAM in pregnancy were calculated using data from women with uncomplicated pregnancies, estimated by maximum likelihood. Sensitivity, specificity, positive and negative predictive values for hyaluronan and VCAM were calculated using the derived upper reference interval (97.5^{th} centile) for pregnancy, and previously described diagnostic thresholds for superimposed pre-eclampsia in women with CKD (Wiles et al., 2019 [see Chapter 6]).

The difference between markers was assessed using a t-test. Correlation was measured using a Spearman rank correlation coefficient. Statistical analysis was performed using Stata Statistical Software Release 16.0 (College Station, TX: StataCorp LLC, 2019) and GraphPad Prism version 8.2.1 (La Jolla, CA).

7.4 Results

This study recruited 533 women, including 429 women with 440 pregnancies and 104 non-pregnant women with CKD. A final diagnosis was made in 232 pregnancies in 221 women with CKD, and 164 pregnancies in women without underlying CKD (Figure 7.1).

Figure 7.1 Flow chart showing numbers of prospectively recruited pregnancies and final pregnancy diagnoses.
AKI=acute kidney injury, CKD=chronic kidney disease, SGA=small for gestational age



Just under half of the women with CKD (106/221, 48%) were of white European ethnicity and 40 (17%) were black. The most common causes of CKD were lupus and non-lupus glomerulonephritis affecting 47% (103/221) of women. Chronic hypertension had been diagnosed in 38% (85/221) of women prior to pregnancy. The study included 37 (17%) women with a kidney transplant, five of whom had two pregnancies.

The live birth rate in women with CKD after 24 weeks' gestation was 99.6% (231/232), with one stillbirth. The most common diagnosis in women with CKD was superimposed pre-eclampsia, which affected one third (76/232) of pregnancies. Only one quarter of pregnancies in women with CKD (58/232) had a normal course.

Demographic, clinical and outcome data for the women with CKD in pregnancy are shown in Tables 7.2 and 7.3. Women with CKD who developed superimposed pre-eclampsia had a higher body mass index (BMI), a lower eGFR prior to pregnancy, and higher levels of proteinuria quantified either before pregnancy or prior to 20 weeks' gestation compared to women with CKD and a normal pregnancy course. However, there was no significant difference in the prevalence of chronic hypertension (43% versus 29%, p=0.1072) (Table 7.2). Women with superimposed pre-eclampsia had higher systolic and diastolic blood pressures, higher levels of proteinuria and higher serum creatinine concentrations in pregnancy, consistent with the diagnostic criteria used (Table 7.3). One third of pregnancies delivered before 37 weeks' gestation, with just under half of women with CKD (46%, 106/232) having a Caesarean delivery, and one in six babies weighing below the 10th centile; with all of these outcomes more prevalent in women with superimposed pre-eclampsia compared to women with CKD and a normal pregnancy course. Most women with superimposed pre-eclampsia (69%, 52/76) delivered before 37 weeks' gestation.

Table 7.2 Demographic and clinical features in women with CKD according to final diagnosis. Data are median ± interquartile range (IQR), unless stated.
[a]=Pre-eclampsia compared to women with CKD and a normal pregnancy course.
AKI=acute kidney injury (defined in Table 7.1), BMI=body mass index, CAKUT=congenital anomalies of the kidney and urinary tract, CKD=chronic kidney disease, SGA=small for gestational age, GN=glomerulonephritis.

Variable	All	Normal pregnancy	Superimposed pre-eclampsia	Gestational hypertension	Transient hypertension	Gestational proteinuria	Isolated AKI	Isolated SGA	Complications unrelated to pre-eclampsia	p-value[a]
n	232	58	76	20	25	29	5	14	5	
Age	33.7 (30.5-36.9)	33.2 (29.9-36.4)	34.1 (30.5-37.6)	35.3 (29.8-39.6)	32.8 (28.9-36.2)	34.0 (31.2-36.5)	30.5 (27.3-32.5)	33.2 (31.0-35.9)	36.8 (30.7-40.6)	0.2098
BMI (booking)	25.8 (22.8-29.7)	23.5 (21.8-27.4)	26.5 (24.0-30.5)	27.7 (22.7-43.7)	29.5 (24.3-31.4)	25.2 (21.5-29.4)	24.4 (23.7-31.0)	24.8 (22.7-26.4)	23.1 (22.6-31.6)	0.0009
Nulliparous (%)	110 (47)	25 (43)	40 (53)	12 (60)	10 (40)	8 (28)	4 (80)	8 (57)	3 (60)	0.2992
Ethnicity (%)										
• White European	114 (49)	33 (57)	32 (42)	9 (45)	13 (52)	15 (52)	3 (60)	5 (36)	4 (80)	0.0021
• Black	40 (17)	3 (5)	20 (26)	5 (25)	4 (16)	4 (14)	1 (20)	3 (21)	0 (0)	
• Asian	37 (16)	13 (22)	7 (9)	3 (15)	5 (20)	5 (17)	0 (0)	3 (21)	1 (20)	
• Other	41 (18)	9 (16)	17 (22)	3 (15)	3 (12)	5 (17)	1 (20)	3 (21)	0 (0)	
Kidney disease:										
• Lupus/vasculitis	51 (22)	18 (31)	11 (14)	5 (25)	3 (12)	9 (31)	1 (20)	4 (29)	0 (0)	0.0235
• Other GN	58 (25)	19 (33)	20 (26)	3 (15)	7 (28)	6 (21)	1 (20)	1 (7)	1 (20)	
• Reflux/CAKUT	31 (13)	4 (7)	8 (11)	6 (30)	3 (12)	4 (14)	0 (0)	3 (21)	3 (60)	
• Diabetes	11 (5)	0 (0)	11 (14)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
• Hypertension	5 (2)	2 (3)	2 (3)	1 (5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
• Genetic	22 (9)	6 (10)	6 (8)	2 (10)	6 (24)	2 (7)	0 (0)	0 (0)	0 (0)	

• Unknown • Other	33 (14) 21 (9)	5 (9) 4 (7)	14 (18) 4 (5)	1 (5) 2 (10)	3 (12) 3 (12)	6 (21) 2 (7)	0 (0) 3 (60)	4 (29) 2 (14)	0 (0) 1 (20)	
Kidney transplant	42 (18)	3 (5)	26 (52)	2 (11)	2 (9)	5 (17)	1 (20)	2 (17)	1 (25)	<0.0001
Pre-pregnancy eGFR ml/min/1.73m^2	88 (53-104)	94 (78-115)	61 (40-91)	86 (55-116)	91 (75-120)	89 (52 -105)	91 (62-117)	82 (60-91)	91 (65- 98)	<0.0001
Pre-pregnancy creatinine µmol/L	84 (66-124)	67 (60-104)	109 (78-144)	86 (60-132)	67 (51-95)	97 (66-120)	75 (64-136)	90 (75-103)	69 (67-156)	<0.0001
Pre-pregnancy CKD stage: • 1-2 • 3 • 4-5	 160 57 14	 47 11 0	 39 24 12	 13 7 0	 23 2 0	 19 10 0	 4 1 0	 11 1 2	 4 1 0	
Pre/early pregnancy (<20 weeks) proteinuria mg/mmol	42 (10-121)	17 (10-62)	95 (20-159)	19 (5-44)	19 (8-50)	63 (11-145)	212 (20-403)	20 (7-139)	60 [d]	0.0093
Chronic hypertension	91 (39)	17 (29)	33 (43)	13 (65)	8 (32)	10 (34)	2 (40)	7 (100)	1 (20)	0.1072

Table 7.3 Pregnancy outcomes in women with CKD according to final diagnosis. Data are median ± interquartile range (IQR), unless stated.
[a]=Pre-eclampsia compared to women with CKD and a normal pregnancy outcome, [b]=between highest and lowest serum creatinine values measured in pregnancy, [c]=small for gestational age (birthweight <10th centile), or abnormal uterine artery Doppler wave form.
AKI=acute kidney injury (defined in Table 7.1), ALT=alanine aminotransferase, dBP=diastolic blood pressure, SGA=small for gestational age, GN=glomerulonephritis, sBP=systolic blood pressure

Variable	All	Normal pregnancy	Superimposed pre-eclampsia	Gestational hypertension	Transient hypertension	Gestational proteinuria	Isolated AKI	Isolated SGA	Complications unrelated to pre-eclampsia	p-value[a]
n	232	58	76	20	25	29	5	14	5	
Highest sBP mmHg	147 (135-161)	130 (124-137)	169 (154-180)	158 (150-170)	146 (144-150)	141 (133-150)	137 (135-160)	137 (107-149)	123 (123-128)	<0.0001
Highest dBP mmHg	93 (84-100)	82 (75-89)	100 (93-105)	94 (90-110)	96 (92-99)	89 (80-97)	87 (82-95)	95 (87-102)	80 (78-86)	<0.0001
Highest uPCR mg/mmol	141 (46-473)	17 (10 to 62)	95 (20-159)	19 (5-44)	19 (8-50)	63 (11-145)	212 (20-403)	20 (7-139)	60 [d]	0.0093
Highest serum creatinine µg/L	97 (64-155)	64 (57-89)	160 (110-241)	84 (64-136)	67 (53-168)	94 (74-139)	180 (160-216)	96 (67-128)	81 (65-148)	<0.0001
Increase in serum creatinine in pregnancy[b] %	35 (20-59)	22 (12-34)	58 (36-87)	29 (17-47)	24 (12-42)	35 (22-51)	165 (150-199)	25 (12-44)	47 (23-77)	<0.0001
Highest ALT IU/L	19 (12-32)	14 (10-22)	21 (15-33)	20 (14-52)	19 (11-34)	19 (12-29)	12 (7-17)	14 (9-23)	23 (14-36)	0.0085
Eclampsia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	>0.9999
Uteroplacental	47 (20)	0 (0)	33 (43)	0 (0)	0 (0)	0 (0)	0 (0)	14 (100)	0 (0)	<0.0001

insufficiency[c]										
Live births	231 (100)	58 (100)	75 (99)	20 (100)	25 (100)	29 (100)	5 (100)	14 (100)	5 (100)	>0.9999
Caesarean delivery	106 (46)	22 (38)	50 (66)	6 (30)	7 (28)	12 (41)	2 (40)	5 (36)	2 (40)	0.0017
Gestational age at delivery	37.9 (35.9-39.1)	39.3 (38.6-40.5)	35.4 (33.5-37.3))	38.1 (36.4-39.1)	39.0 (37.9-40.1)	38.0 (37.1-39.0)	37.1 (33.9-40.3)	37.5 (35.5-38.8)	35.3 (28.4-40.2)	<0.0001
Delivery <37 weeks	77 (33)	2 (4)	52 (69)	5 (25)	2 (8)	5 (17)	2 (40)	6 (43)	3 (60)	<0.0001
Delivery <34 weeks	29 (13)	1 (2)	22 (29)	1 (5)	0 (0)	0 (0)	1 (20)	2 (14)	2 (40)	<0.0001
Birthweight centile	37 (15-60)	48 (28-64)	16 (8-48)	35 (23-65)	51 (40-88)	47 (29-61)	32 (20-42)	4 (3-8)	75 (22-93)	<0.0001
Birthweight <10th centile	38 (17)	0 (0)	24 (32)	0 (0)	0 (0)	0 (0)	0 (0)	14 (100)	0 (0)	<0.0001
Birthweight <3rd centile	7 (3)	0 (0)	4 (5)	0 (0)	0 (0)	0 (0)	0 (0)	3 (21)	0 (0)	0.1319
Neonatal unit admission	32 (14)	2 (4)	14 (19)	3 (16)	1 (4)	3 (11)	3 (60)	5 (36)	1 (20)	0.0074

Only 8% (3/40) of black women with CKD had a normal pregnancy course, compared to 29% (33/114) of white European women. The odds ratio for the development of superimposed pre-eclampsia in black women was 2.6 (95% confidence interval 1.2-5.3), compared to women of white European ethnicity although pre-pregnancy eGFR, proteinuria and rates of chronic hypertension were not substantially different (Table 7.4). All eleven women with diabetic nephropathy developed superimposed pre-eclampsia, including seven women with a combined kidney-pancreas transplant.

Table 7.4 Comparison of women with CKD according to ethnicity. Data are median and interquartile range unless specified.
eGFR=estimated glomerular filtration rate, uPCR=urinary protein:creatinine ratio.

	White European	Black	p-value
n	114	40	
Pre-pregnancy eGFR (ml/min/1.73m^2)	91 (62-113)	91 (53-114)	0.978
Pre-/early pregnancy (<20 weeks) uPCR (mg/mmol)	21 (10-72)	54 (9-128)	0.397
Chronic hypertension (%)	55 (48)	19 (48)	>0.999
Superimposed pre-eclampsia (%)	32 (28)	20 (50)	0.019

7.4.1 Plasma PlGF (Quidel Triage®)

The gestational profiles of plasma PlGF (Quidel) concentrations in 166 pregnant women with CKD who had samples taken between 20 and 37 weeks' gestation are shown in Figure 7.2 and Table 7.5. Women with CKD who subsequently developed superimposed pre-eclampsia had lower plasma PlGF (Quidel) concentrations compared to women with CKD in the absence of superimposed pre-eclampsia (regression coefficient -0.59, 95% confidence interval -0.95 to -0.24, p=0.001), though mean plasma concentrations did not fall below 100pg/ml. The longitudinal trends in PlGF (Quidel) concentrations in women with more than one sample taken between 20 and 37 weeks are shown according to the final diagnosis (Figure 7.3).

Figure 7.2 Plasma PlGF concentrations (Quidel) according to gestation in weeks in women with chronic kidney disease who did (dashed) and did not (line) develop superimposed pre-eclampsia. Points are geometric mean values and bars represent standard errors. Horizontal line at 100pg/ml is the threshold suggestive of placental dysfunction in general obstetric cohorts (NICE, 2016, #46720).

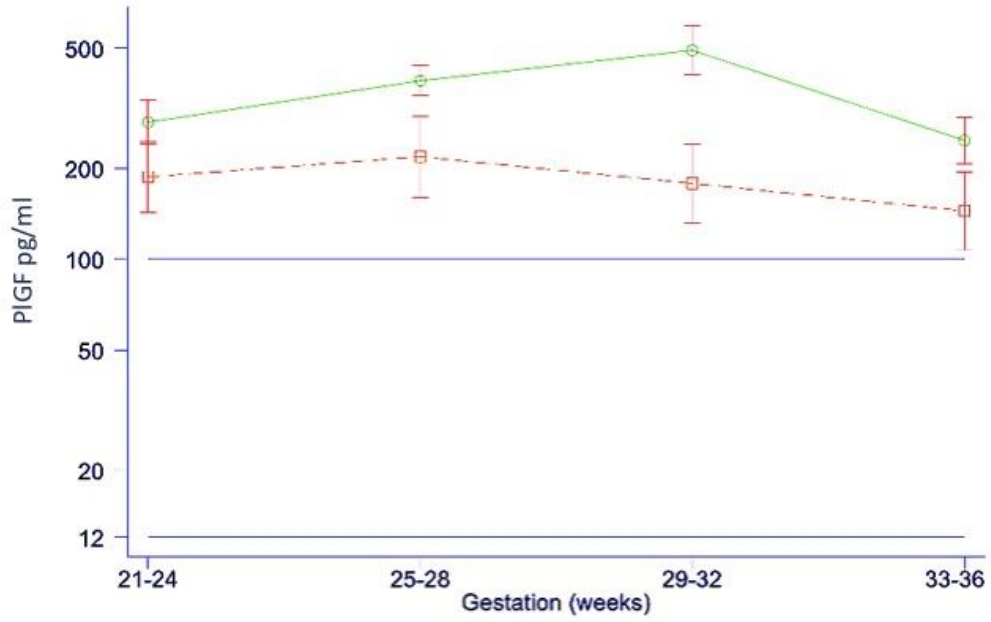
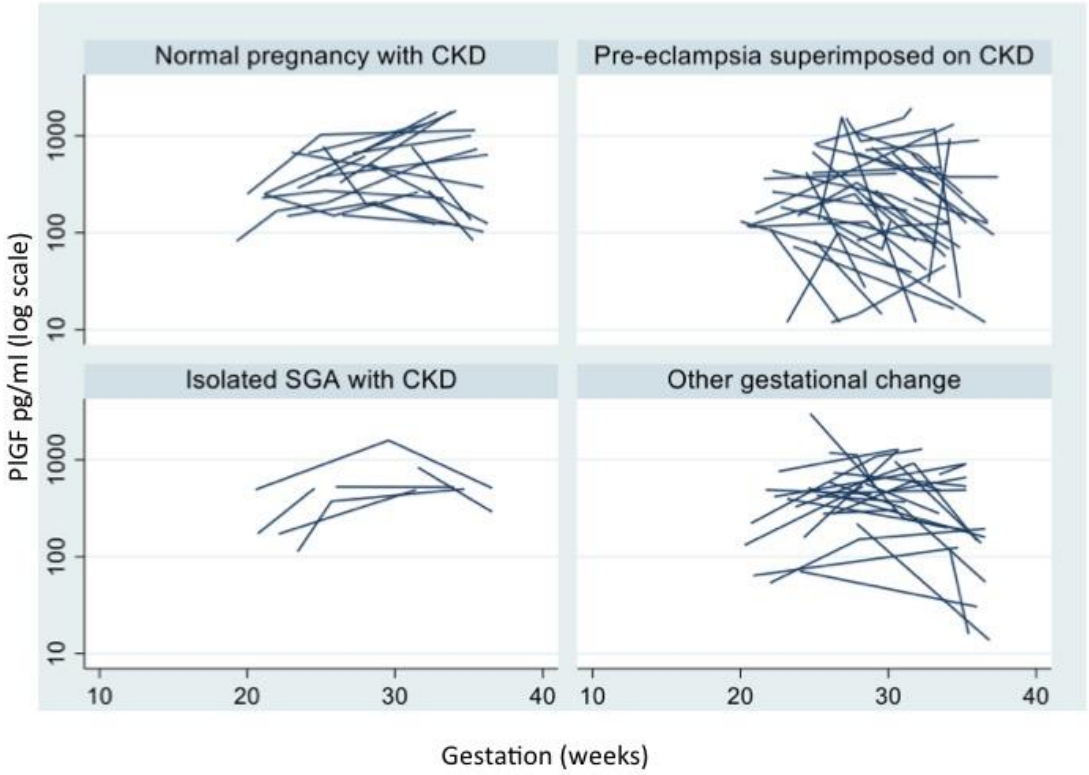


Table 7.5 Plasma PlGF concentrations (Quidel) according to gestation in women with CKD who did and did not go on to develop superimposed pre-eclampsia. Values are geometric mean (±standard error).

Gestational age (weeks)	21-24	25-28	29-32	33-36
Women with CKD who did not develop superimposed pre-eclampsia				
Number of samples	29	38	33	46
Plasma PlGF (pg/ml)	285 (240-338)	391 (348-438)	493 (409-594)	247 (208-295)
Woman with CKD who did develop superimposed pre-eclampsia				
Number of samples	14	24	26	21
Plasma PlGF (pg/ml)	188 (143-246)	219 (160-298)	178 (132-241)	145 (107-195)

Figure 7.3 Longitudinal plasma (Quidel) PlGF concentrations in women with greater than one measurement taken during pregnancy according to final diagnosis in pregnancy.
CKD=chronic kidney disease, SGA=small for gestational age, other gestational change includes gestational hypertension and gestational proteinuria in women with CKD.



Between 21 and 37 weeks' gestation, plasma PlGF (Quidel) concentrations were 45% lower (95% CI: 22 to 61%, p=0.001) in women with CKD that subsequently developed superimposed pre-eclampsia compared to women who did not. The difference in PlGF concentration was greatest in women that developed superimposed pre-eclampsia with clinical evidence of uteroplacental dysfunction (small for gestational age and/or abnormal uterine artery Doppler waveform) with concentrations 66% lower (95% CI: 44 to 80%) than women with CKD that did not develop superimposed pre-eclampsia. Gestation corrected PlGF centiles were higher in women with CKD in the absence of superimposed pre-eclampsia, compared to both women with superimposed pre-eclampsia and women with superimposed pre-eclampsia plus evidence of uteroplacental dysfunction. However, there was marked variation in centiles, including values above the 5th centile within 28 and 14 days prior to delivery with superimposed pre-eclampsia (Figure 7.4, Table 7.6).

Figure 7.4 Plasma PlGF (Quidel) centiles (median ± interquartile range) between 21 and 37 weeks' gestation in women with CKD that did not develop superimposed pre-eclampsia; women with CKD that did develop superimposed pre-eclampsia; and women with CKD that developed superimposed pre-eclampsia with evidence of uteroplacental dysfunction (small for gestational age or abnormal uterine artery Doppler wave form).

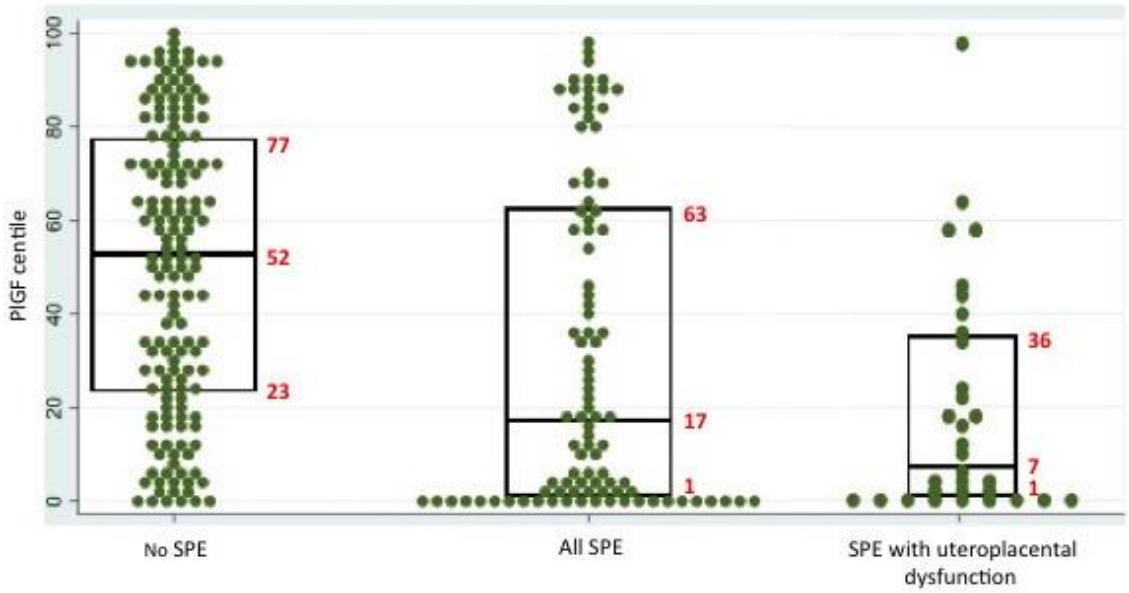


Table 7.6 Median plasma PlGF (Quidel) centiles (interquartile range) between 21 and 37 weeks' gestation and in the 14 and 28 days prior to delivery in women with CKD that did not develop superimposed pre-eclampsia and women with CKD that did develop superimposed pre-eclampsia, stratified by the presence or absence of uteroplacental dysfunction. SPE=superimposed pre-eclampsia.

	All (21-37 weeks)		28 days before delivery		14 days before delivery	
	n	PlGF centile	n	PlGF centile	n	PlGF centile
Normal pregnancy	153	52 (23-77)	36	39 (17-77)	12	35 (14-61)
All SPE	96	17 (1-63)	50	4 (0-37)	27	2 (0-36)
SPE without uteroplacental dysfunction	56	37 (5-83)	25	26 (4-84)	12	22 (2-80)
SPE with uteroplacental dysfunction	32	7 (0.6-36)	17	2 (0-15)	9	2 (0-32)

The areas under the ROC (AUROC) for low plasma PlGF (Quidel) in the prediction of delivery due to superimposed pre-eclampsia within 14 and 28 days were 0.80 (95% CI: 0.66-0.94) and 0.79 (95% CI: 0.67-0.92) respectively (Figures 7.5 and 7.6). Predictive performance was lower in women with pre-pregnancy CKD stages 3-5 compared to those with pre-pregnancy stages 1-2 (Figures 7.7 and 7.8).

Figure 7.5 Receiver operating characteristic (ROC) curve of plasma PlGF (Quidel) in predicting delivery due to superimposed preeclampsia within 14 days in women with chronic kidney disease (CKD).

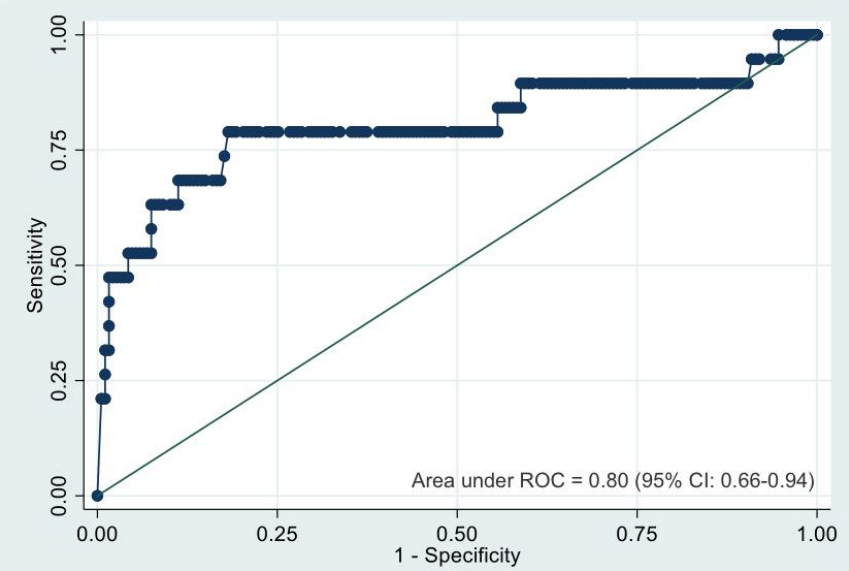


Figure 7.6 Receiver operating characteristic (ROC) curve of plasma PlGF (Quidel) in predicting delivery due to superimposed preeclampsia within 28 days in women with chronic kidney disease (CKD).

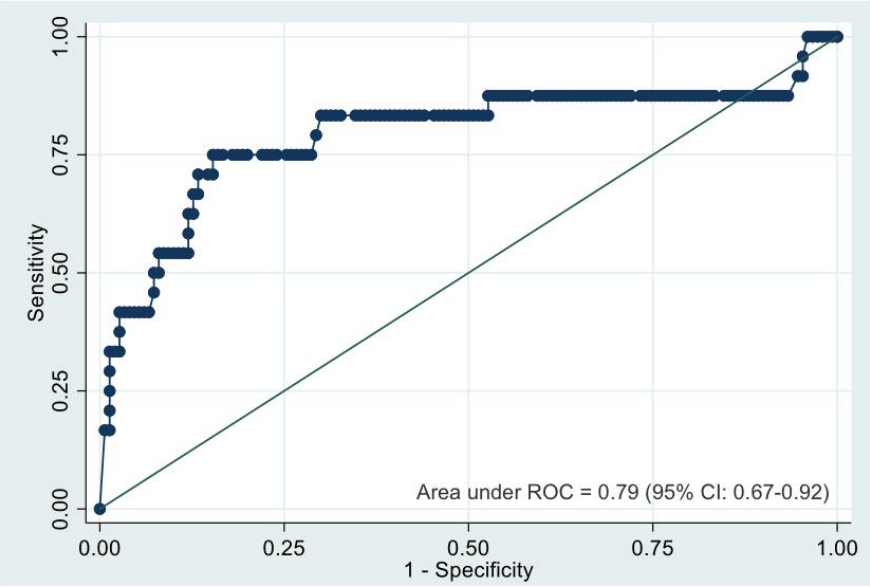


Figure 7.7 Receiver operating characteristic (ROC) curve of plasma PlGF (Quidel) in predicting delivery with superimposed preeclampsia within 14 days in women with CKD, according to pre-pregnancy CKD stage.

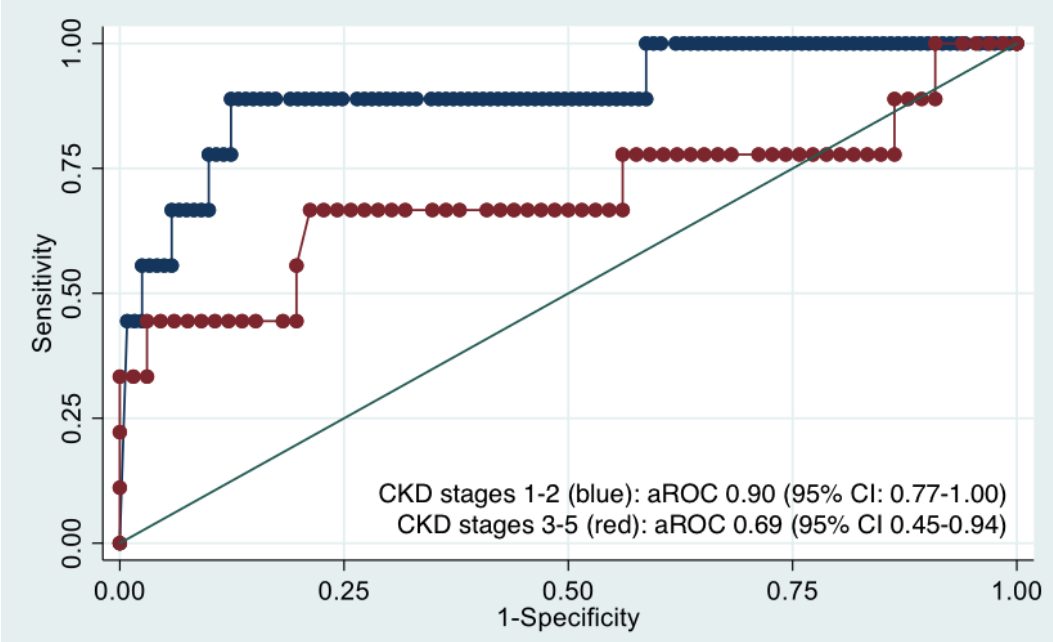
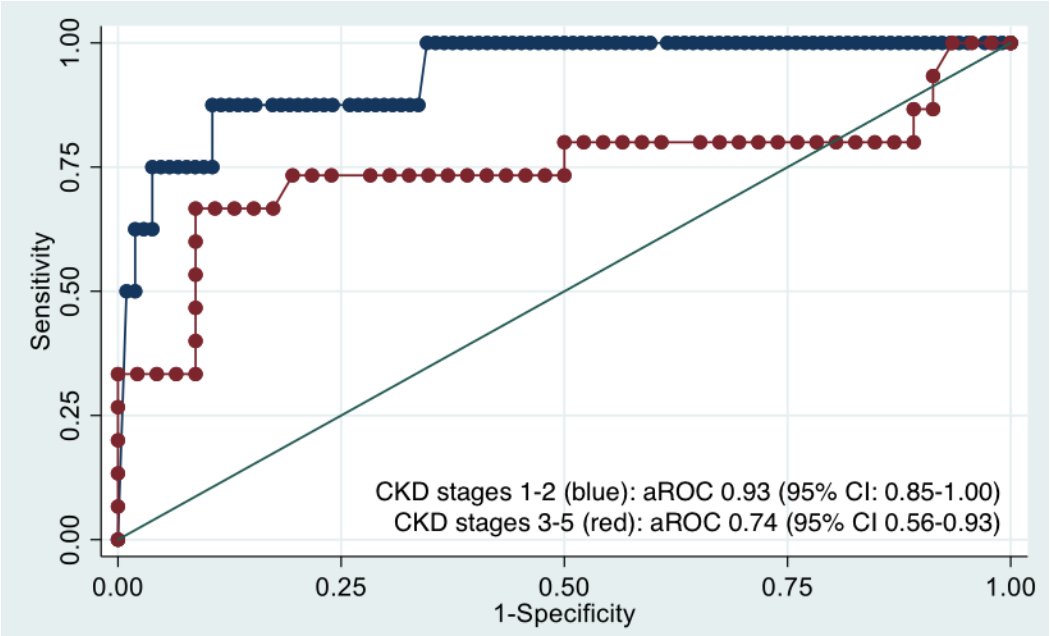


Figure 7.8 Receiver operating characteristic (ROC) curve of plasma PlGF (Quidel) in predicting delivery with superimposed preeclampsia within 28 days in women with CKD, according to pre-pregnancy CKD stage.



The optimal threshold for prediction of delivery due to superimposed pre-eclampsia within 14 and 28 days in women with CKD was 150pg/ml (Table 7.7).

Table 7.7 Predictive performance of plasma PlGF (Quidel) <12pg/ml and <100pg/ml for delivery within 14 and 28 days due to superimposed pre-eclampsia in women with CKD. The prevalence of superimposed pre-eclampsia in this cohort was 9.2% (95% confidence interval (CI): 5.6-14.0%) within 14 days and 13.8% (95% CI: 9.0-19.8%) within 28 days.

Plasma PlGF (pg/ml)	<12		<100		<150		<200	
Delivery within	14 days	28 days	14 days	28 days	14 days	28 days	14 days	28 days
Sensitivity % (95% CI)	21.1 (6.1-45.6)	16.7 (4.7-37.4)	68.4 (43.4-87.4)	54.2 (32.8-74.4)	78.9 (54.4-93.9)	75.0 (53.3-90.2)	78.9 (54.4-93.9)	75.0 (53.3-90.2)
Specificity % (95% CI)	99.5 (97.1-100)	99.3 (96.3-100)	88.2 (82.7-92.5)	91.3 (85.6-95.3)	77.5 (70.9-83.3)	83.3 (76.4-88.9)	69.5 (62.4-76.0)	74.0 (66.2-80.8)
Positive predictive value % (95% CI)	80.0 (28.4-99.5)	80.0 (28.4-99.5)	37.1 (21.5-55.1)	50.0 (29.9-70.1)	26.3 (15.5-39.7)	41.9 (27.0-57.9)	20.8 (12.2-32.0)	31.6 (19.9-45.2)
Negative predictive value % (95% CI)	92.5 (88.0-95.8)	88.2 (82.3-92.6)	96.5 (92.5-98.7)	92.6 (87.1-96.2)	97.3 (93.3-99.3)	95.4 (90.3-98.3)	97.0 (92.5-99.2)	94.9 (89.2-98.1)
Positive likelihood ratio (95% CI)	39.4 (4.6-334.6)	25.0 (2.9-214.3)	5.8 (3.5-9.6)	6.3 (3.3-11.8)	3.5 (2.5-5.0)	4.5 (2.9-6.9)	2.6 (1.9-3.6)	2.9 (2.0-4.1)
Negative likelihood ratio (95% CI)	0.8 (0.6-1.0)	0.8 (0.7-1.0)	0.4 (0.2-0.7)	0.5 (0.3-0.8)	0.3 (0.1-0.7)	0.3 (0.2-0.6)	0.3 (0.1-0.7)	0.3 (0.2-0.7)

Despite a higher median pre-pregnancy creatinine concentration; pre-pregnancy kidney function, serum creatinine concentrations in pregnancy, the incidence of uteroplacental dysfunction, gestational age at delivery and birthweight centile were not substantially different in the women who developed superimposed pre-eclampsia with a plasma PlGF (Quidel) concentration greater than 100pg/ml in the 28 days prior to delivery, compared to those with a PlGF concentration less than 100pg/ml (Table 7.8).

Table 7.8 Demographic and clinical outcome data according to plasma PlGF (Quidel) concentration in the 28 days prior to delivery in women with CKD and superimposed pre-eclampsia (SPE). Data are median ± IQR, unless stated. [a]=pre-pregnancy or before 20 weeks' gestation, [b]=percentage increase between lowest and highest serum creatinine concentration in pregnancy [c]=small for gestational age or abnormal uterine artery Doppler wave form analysis
ALT=alanine aminotransferase, BMI=body mass index, CAKUT=congenital anomalies of kidney and urinary tract, CKD=chronic kidney disease, dBP=diastolic blood pressure, eGFR=estimated glomerular filtration rate, GN=glomerulonephritis, PlGF=placental growth factor, sBP=systolic blood pressure, NNU=neonatal unit admission, sFlt-1= soluble fms-like tyrosine kinase 1, uPCR=urinary protein:creatinine ratio

Variable	PlGF >100 pg/ml	PlGF <100 pg/ml	p-value
Sample within 28 days of delivery (n)	23	20	
Sample days prior to delivery	17 (7-24)	14 (5-22)	0.3738
Age	31.3 (32.9-36.0)	35.3 (33.0-38.4)	0.0206
BMI (booking)	25.8 (23.9-29.8)	30.4 (26.0-34.6)	0.0375
Nulliparous (%)	13 (57)	6 (30)	0.1247
Ethnicity (%)			0.5911
• White European	10 (43)	6 (30)	
• Black	5 (22)	7 (35)	
• Asian	4 (17)	2 (10)	
• Other	4 (17)	5 (25)	
Kidney disease aetiology:			0.5571
• Lupus/vasculitis	3 (13)	3 (15)	
• Other GN	8 (35)	4 (20)	
• Reflux/CAKUT	2 (9)	2 (10)	
• Diabetes	5 (22)	3 (15)	
• Hypertension	0 (0)	1 (5)	
• Genetic	2 (9)	2 (10)	
• Unknown	3 (13)	2 (10)	
• Other	0 (0)	3 (15)	
Transplantation	9 (39)	5 (25)	0.3528
Pre-pregnancy eGFR ml/min/1.73m^2	49 (36-88)	69 (43-109)	0.2447
Pre-pregnancy creatinine µmol/L	127 (77-159)	93 (70-153)	0.2218
Pre-pregnancy CKD stage:			
• 1-2	9 (41)	13 (68)	
• 3-5	13 (59)	6 (32)	

Pre/early pregnancy[a] uPCR mg/mmol	104 (19-217)	60 (23-150)	0.6745
Chronic hypertension	11 (48)	15 (75)	0.1175
Highest sBP mmHg	172 (146-181)	179 (163-192)	0.0849
Highest dBP mmHg	99 (93-106)	104 (99-114)	0.1605
Highest uPCR mg/mmol	359 (134-672)	571 (146-934)	0.3746
Highest serum creatinine µg/L	176 (123-371)	153 (84-234)	0.1725
% increase in serum creatinine[b]	45 (29-71)	77 (45-118)	0.0620
Highest ALT IU/L	20 (14-33)	33 (21-47)	0.0534
Live births	23 (100)	19 (95)	0.4651
Gestational age weeks	35.4 (32.3-37.6)	34.6 (30.1-36.0)	0.2893
Preterm (< 37 weeks)	14 (61)	17 (85)	0.0785
Birth weight centile	14 (6-48)	19 (9-52)	0.4411
<10th centile	6 (26)	7 (37)	0.4530
<3rd centile	1 (4)	2 (11)	0.4390
Neonatal unit admission	11 (48)	10 (53)	>0.9999
Uteroplacental insufficiency[c]	7 (30)	9 (47)	0.502
Plasma PlGF pg/ml	227 (126-935)	40 (12-76)	<0.0001

7.4.2 Serum PlGF and sFlt-1 (Roche Elecsys®)

Serum PlGF (Roche) concentrations at 21-37 weeks' gestation (Figure 7.9 and Table 7.9) were 26% lower (95% CI: 2 to 43%, p=0.032) in women with CKD who developed superimposed pre-eclampsia compared to those who did not, especially in the context of superimposed pre-eclampsia with evidence of uteroplacental dysfunction (46% lower, 95% CI: 20-63%, p=0.002), although mean serum PlGF (Roche) concentrations did not fall below 100pg/ml. Although there was a strong correlation between serum (Roche) and plasma (Quidel) PlGF concentrations (r=0.910, p<0.0001), paired serum concentrations were twice as high as plasma concentrations (206%; 95% CI: 177-243%, mean 370pg/ml versus 180pg/ml) in the women with CKD that developed superimposed pre-eclampsia.

sFlt-1 concentrations (4% higher; 95% CI: -15 to 27%, p=0.675) and the sFlt-1:PlGF ratio (41% higher; 95% CI: -1 to 100%, p=0.057) were no different in women with CKD that developed superimposed pre-eclampsia compared to those who did not (Figures 7.10 and 7.11, Tables 7.10 and 7.11). The mean sFlt-1:PlGF ratio was not greater than 38 in women with CKD who developed superimposed pre-eclampsia.

Serum PlGF and sFlt-1 concentrations, and the sFlt-1:PlGF ratio (Roche) did not usefully predict delivery with superimposed pre-eclampsia within 14 or 28 days in women with CKD (Table 7.12). Predictive performances for sFlt-1:PlGF ratio <38 and >85 are shown in Table 7.13.

Figure 7.9 Serum PlGF (Roche) concentrations according to gestation in weeks in women with chronic kidney disease who did (dashed) and did not (line) develop superimposed pre-eclampsia. Points are geometric mean values and bars represent standard errors.

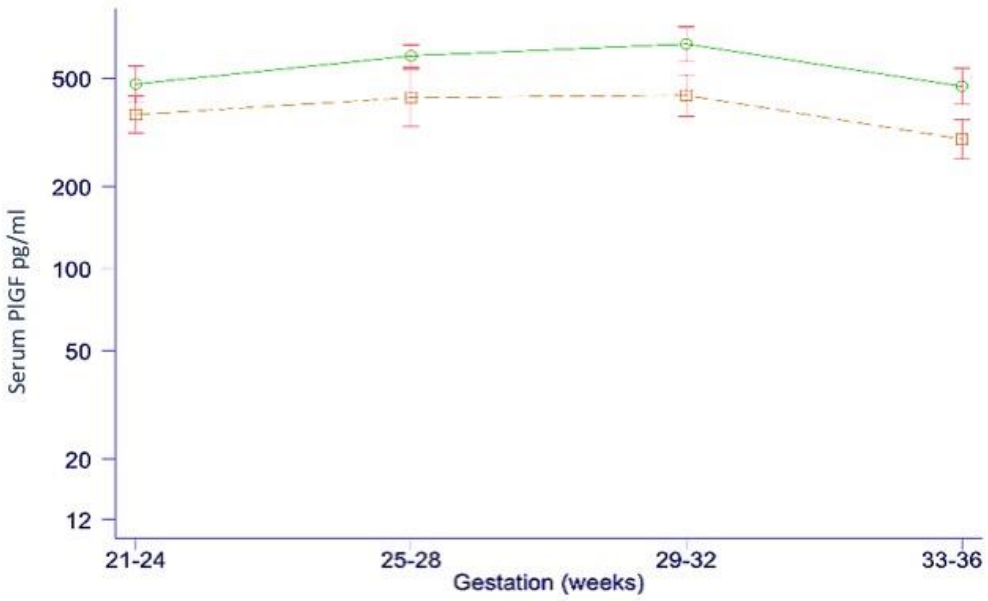


Table 7.9 Serum PlGF (Roche) concentrations according to gestation in women with CKD who did and did not go on to develop superimposed pre-eclampsia. Values are geometric mean (±standard error).

Gestational age (weeks)	21-24	25-28	29-32	33-36
Women with CKD who did not develop superimposed pre-eclampsia				
Number of samples	27	32	30	36
Serum PlGF (pg/ml)	476 (408-555)	604 (550-662)	667 (578-771)	467 (401-544)
Woman with CKD who did develop superimposed pre-eclampsia				
Number of samples	12	23	25	16
Serum PlGF (pg/ml)	368 (315-429)	424 (334-539)	432 (362-516)	299 (252-354)

Figure 7.10 Serum sFlt-1 concentrations according to gestation in weeks in women with chronic kidney disease who did (dashed) and did not (line) develop superimposed pre-eclampsia. Points are geometric mean values and bars represent standard errors.

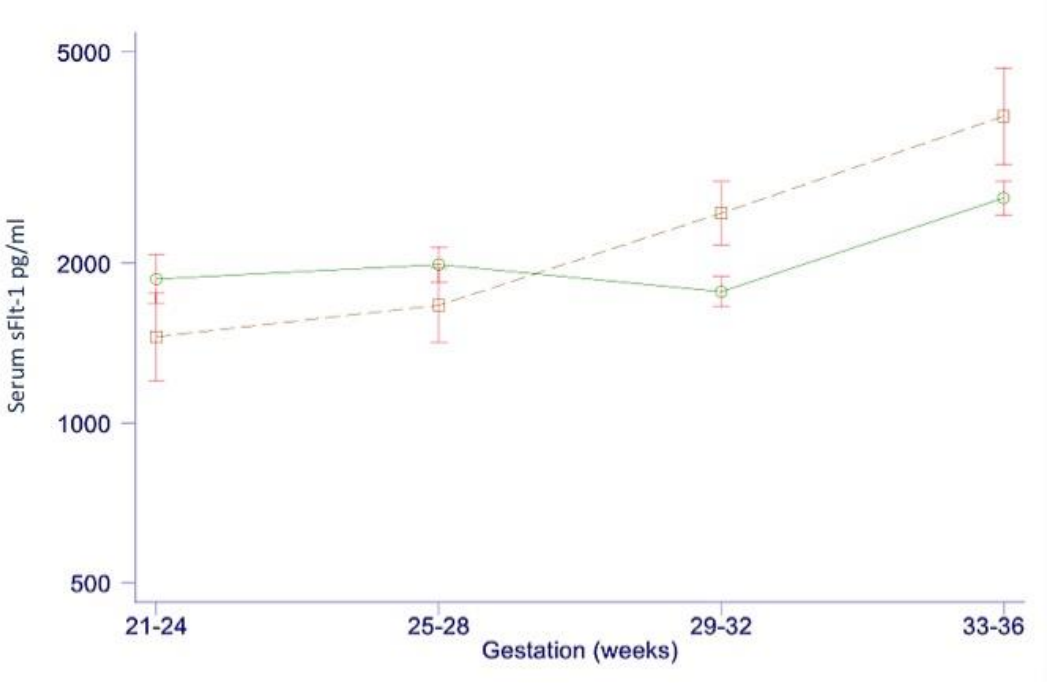


Table 7.10 Serum sFlt-1 concentrations according to gestation in women with CKD who did and did not go on to develop superimposed pre-eclampsia. Values are geometric mean (±standard error).

Gestational age (weeks)	21-24	25-28	29-32	33-36
Women with CKD who did not develop superimposed pre-eclampsia				
Number of samples	27	32	30	36
Serum sFlt-1 (pg/ml)	1867 (1679-2075)	1988 (1843-2145)	1767 (1655-1888)	2652 (2463-2857)
Woman with CKD who did develop superimposed pre-eclampsia				
Number of samples	12	23	25	16
Serum sFlt-1 (pg/ml)	1452 (1199-1760)	1666 (1420-1955)	2483 (2165-2849)	3782 (3065-4667)

Figure 7.11 Serum sFlt-1:PlGF ratio according to gestation in weeks in women with chronic kidney disease who did (dashed) and did not (line) develop superimposed pre-eclampsia. Points are geometric mean values and bars represent standard errors.

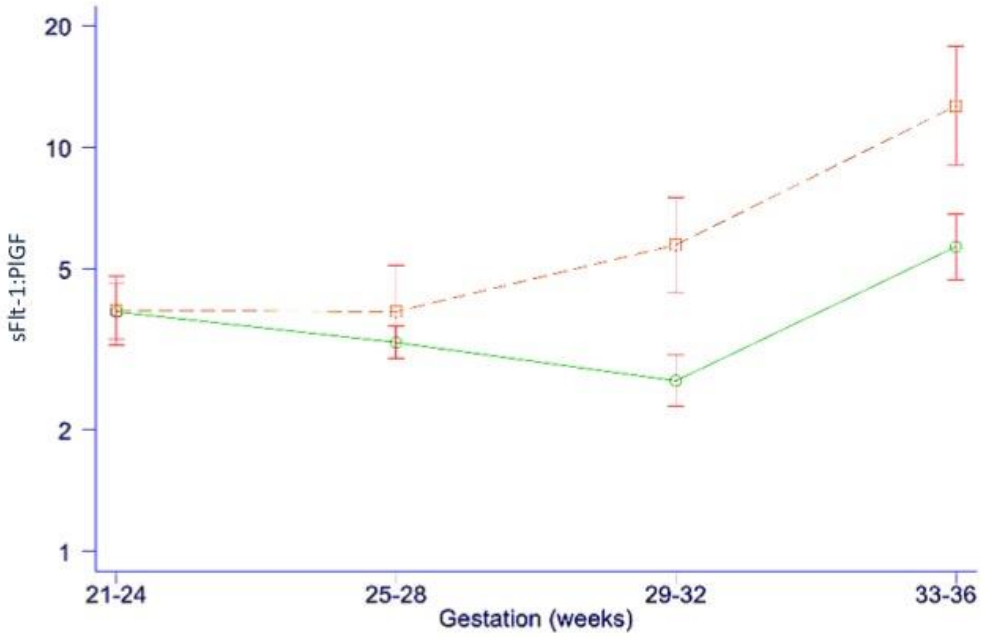


Table 7.11 Serum sFlt-1:PlGF ratio according to gestation in women with CKD who did and did not go on to develop superimposed pre-eclampsia. Values are geometric mean (±standard error).

Gestational age (weeks)	21-24	25-28	29-32	33-36
Women with CKD who did not develop superimposed pre-eclampsia				
Number of samples	27	32	30	36
sFlt-1:PlGF ratio	3.9 (3.3-4.6)	3.3 (3.0-3.6)	2.6 (2.3-3.1)	5.7 (4.7-6.8)
Woman with CKD who did develop superimposed pre-eclampsia				
Number of samples	12	23	25	16
sFlt-1:PlGF ratio	4.0 (3.2-4.8)	3.9 (3.0-5.1)	5.7 (4.4-7.5)	12.7 (9.0-17.8)

Table 7.12 Area under the receiver operating curve values (95% confidence interval) for serum PlGF, sFlt-1 and sFlt-1:PlGF (Roche) in the prediction of the need for delivery due to superimposed pre-eclampsia (SPE) within 14 and 28 days.

Delivery due to SPE within	14 days	28 days
Serum PlGF	0.53 (0.33-0.73)	0.48 (0.34-0.63)
Serum sFlt-1	0.70 (0.46-0.93)	0.70 (0.54-0.86)
Serum sFlt-1:PlGF	0.59 (0.38-0.81)	0.57 (0.43-0.72)

Table 7.13 Predictive performance of plasma sFlt-1:PlGF >38 and >85 for delivery within 14 and 28 days due to superimposed pre-eclampsia in women with CKD. The prevalence of superimposed pre-eclampsia in this cohort was 3.4% (95% confidence interval (CI): 1.7-6.2%) within 14 days and 6.4% (95% CI: 3.8-10.1%) within 28 days.

Plasma sFlt-1:PlGF	>38		>85	
Delivery within	14 days	28 days	14 days	28 days
Sensitivity % (95% CI)	20.0 (2.5-55.6)	5.9 (0.1-28.7)	20.0 (2.5-55.6)	5.9 (0.1-28.7)
Specificity % (95% CI)	92.5 (88.8-95.3)	91.9 (87.8-95.0)	97.5 (94.9-99.0)	97.2 (94.2-98.9)
Positive predictive value % (95% CI)	8.7 (1.1-28.0)	4.8 (0.1-23.8)	22.2 (2.8-60.0)	12.5 (0.3-52.7)
Negative predictive value % (95% CI)	97.0 (94.2-98.7)	93.4 (89.5-96.2)	97.2 (94.5-98.8)	93.8 (90.0-96.4)
Positive likelihood ratio (95% CI)	2.7 (0.7-9.8)	0.7 (0.1-5.1)	8.0 (1.9-33.7)	2.1 (0.3-15.9)
Negative likelihood ratio (95% CI)	0.9 (0.6-1.2)	1.0 (0.9-1.2)	0.8 (0.6-1.1)	1.0 (0.9-1.1)

7.4.3 Plasma hyaluronan and VCAM

Plasma hyaluronan and plasma VCAM were quantified in 104 non-pregnant women of reproductive age, including 69 women (66%) with CKD stages 3-5; 232 pregnancies in women with CKD; and 164 pregnant women without CKD, including 29 women with pre-eclampsia (Figure 7.1).

Non-pregnant women with higher stages of CKD had more proteinuria and a higher prevalence of non-renin-angiotensin antihypertensive drug use. There was less immunosuppressant use in non-pregnant women with CKD stage 5 (Table 7.14). There were no significant differences in plasma hyaluronan and VCAM concentrations across CKD stages outside of pregnancy (Table 7.14). Linear regression did not identify any association between age, eGFR, antihypertensive use or calcineurin inhibitor use with plasma hyaluronan and VCAM concentrations in non-pregnant women with CKD (Table 7.15).

Table 7.14 Demographics, clinical variable and plasma hyaluronan and VCAM concentrations in non-pregnant women with CKD. [a]=difference across CKD stages, [b]=includes one failed transplant in a women receiving haemodialysis.
CAKUT=congenital anomalies of the kidney and urinary tract, CKD=chronic kidney disease, eGFR=estimated glomerular filtration rate, GN=glomerulonephritis, MMF=mycophenolate mofetil, UPCR=urinary protein:creatinine ratio, VCAM=vascular cell adhesion molecule.

Variable	All	CKD Stages 1-2	CKD Stage 3a	CKD Stage 3b	CKD Stage 4	CKD Stage 5	p-value[a]
n	104	15	20	28	21	20	
Age	42.9 (34.6-46.7)	35.4 (26.1-41.5)	37.1 (31.3-42.3)	32.3 (30.0-46.2)	39.6 (35.4-43.1)	42.5 (34.3-47.3)	0.1705
Ethnicity • White European • Black • Asian • Other	 62 (60) 27 (26) 13 (13) 2 (2)	 11 (73) 4 (27) 0 0	 10 (50) 4 (20) 5 (25) 1 (5)	 19 (68) 6 (21) 3 (11) 0 (0)	 10 (48) 6 (29) 4 (19) 1 (5)	 12 (60) 7 (35) 1 (5) 0 (0)	
Kidney diagnosis • Lupus/vasculitis • Other GN • Reflux/CAKUT • Diabetes • Hypertension/vascular • Genetic • Other • Unknown	 15 (14) 26 (25) 13 (13) 12 (12) 6 (6) 8 (8) 12 (12) 12 (12)	 4 (27) 5 (33) 0 (0) 2 (13) 1 (7) 1 (7) 1 (7) 1 (7)	 1 (5) 6 (30) 5 (25) 1 (5) 2 (10) 1 (5) 0 (0) 4 (20)	 1 (4) 8 (29) 4 (14) 5 (18) 2 (7) 1 (4) 3 (11) 4 (14)	 5 (24) 3 (14) 1 (5) 2 (10) 0 (0) 4 (19) 4 (19) 2 (10)	 4 (20) 4 (20) 3 (15) 2 (10) 1 (5) 1 (5) 4 (20) 1 (50)	
Dialysis • Haemodialysis						11 (55) 7 (35)	

• Peritoneal dialysis						4 (20)	
Kidney transplant	36 (35)	5 (33)	8 (40)	13 (46)	8 (38)	2 (10)[b]	0.087
eGFR ml/min/1.73m^2	37 (19-52)	71 (66-81)	52 (48-55)	39 (33-44)	24 (18-28)	9 (6-11)	<0.0001
uPCR mg/mmol	44 (20-150)	17 (10-146)	26 (16-78)	30 (13-20)	62 (31-116)	184 (84-306)	0.0012
Antihypertensives:							
• Alpha-blocker	17 (16)	1 (7)	1 (5)	2 (7)	5 (24)	8 (40)	
• Beta-blocker	31 (30)	3 (20)	7 (35)	7 (25)	4 (19)	10 (50)	
• Calcium channel blocker	37 (36)	4 (27)	5 (25)	8 (29)	10 (48)	10 (50)	
• Diuretic	22 (21)	4 (27)	4 (20)	4 (14)	5 (24)	5 (25)	
• RAS inhibitor	41 (40)	8 (53)	5 (25)	11 (39)	9 (32)	8 (40)	
• Other	3 (3)	1 (7)	0 (0)	0 (0)	1 (5)	1 (5)	
Immunosuppression:							
• Corticosteroids	42 (40)	8 (53)	7 (35)	14 (50)	8 (38)	5 (25)	
• Calcineurin inhibitors	36 (35)	5 (33)	8 (80)	14 (50)	8 (38)	1 (5)	
• MMF/azathioprine	52 (50)	10 (67)	12 (60)	18 (64)	10 (48)	2 (10)	
• Other	7 (7)	2 (13)	1 (5)	0 (0)	2 (10)	2 (10)	
Plasma hyaluronan ng/ml	26.1 (14.3-38.1)	34.1 (14.9-84.5)	22.1 (13.6-31.1)	26.1 (12.6-35.7)	23.3 (14.8-36.5)	31.4 (26.1-52.6)	0.134
Plasma VCAM ng/ml	815 (642-1063)	834 (667-1086)	735 (602-1009)	685 (601-915)	945 (660-1087)	917 (692-1768)	0.142

Table 7.15 Linear regression of demographic and clinical variables on plasma hyaluronan and VCAM concentrations in non-pregnant women with CKD: The coefficient is a measure of the difference in biomarker concentration that can be attributed to that variable.

	Hyaluronan		VCAM	
Variable	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value
Age	1.09 (0.99-1.03)	0.278	1.00 (0.99-1.01)	0.665
eGFR	1.00 (0.99-1.01)	0.682	1.00 (0.99-1.00)	0.522
Antihypertensive use	1.12 (0.78-1.60)	0.548	0.92 (0.77-1.11)	0.040
Calcineurin inhibitor use	1.06 (0.76-1.50)	0.721	0.86 (0.73-1.02)	0.095

Women with pre-eclampsia in the absence of CKD had a higher BMI, more prevalent non-white ethnicities and increased adverse pregnancy outcomes (preterm delivery, low birthweight and neonatal unit admission) compared to those with a normal pregnancy course, mirroring findings in women with CKD and superimposed pre-eclampsia (Table 7.16).

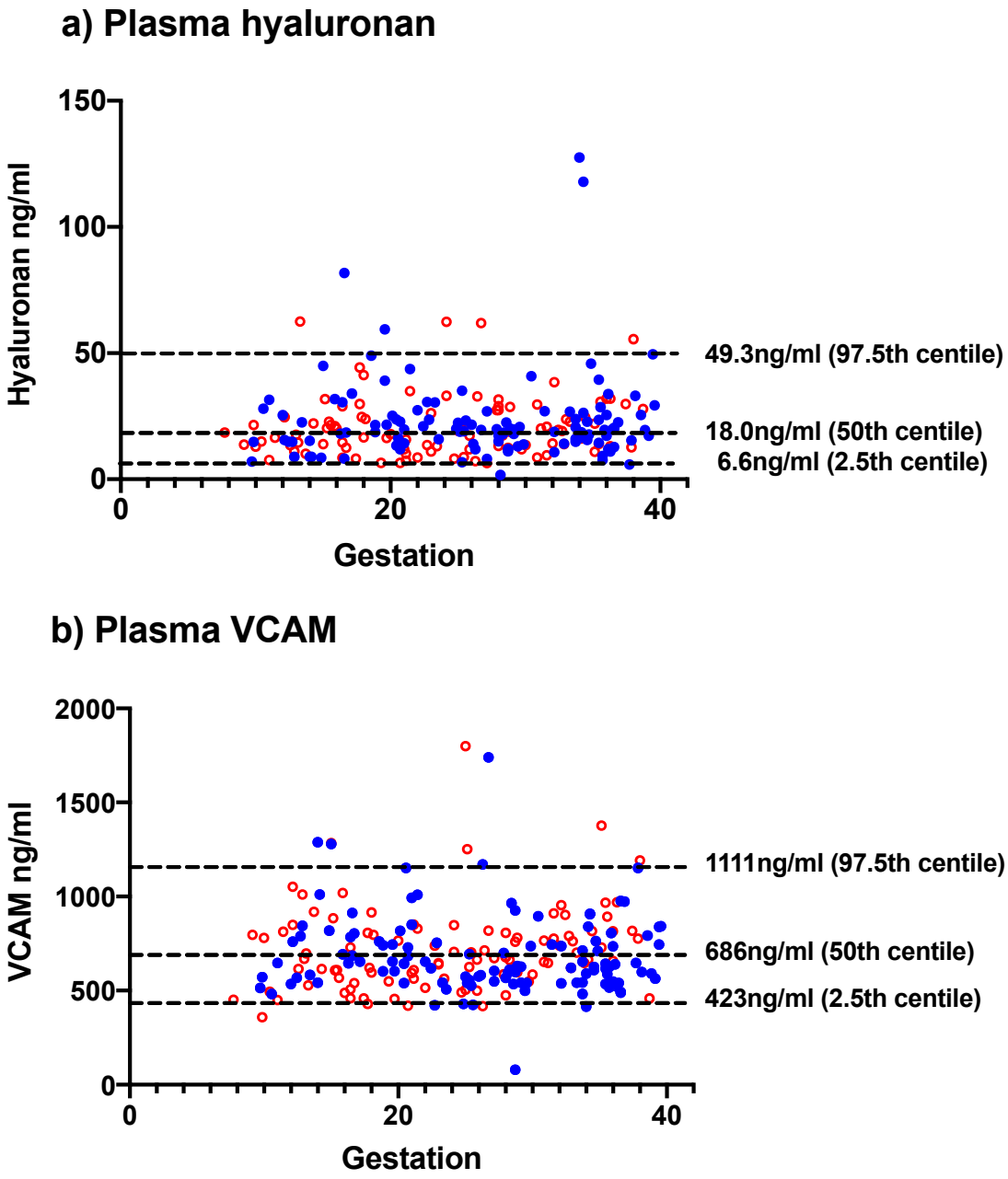
Table 7.16 Pregnancy outcomes in women without CKD according to final diagnosis. Data are median ± interquartile range (IQR), unless stated. [a]=Pre-eclampsia compared to women with a normal pregnancy outcome.
ALT=alanine aminotransferase, dBP=diastolic blood pressure, NNU=neonatal unit, SBP=systolic blood pressure, SGA=small for gestational age, uPCR=urinary protein:creatinine ratio

Variable	All	Normal pregnancy	Pre-eclampsia	Gestational hypertension	Transient hypertension	Gestational proteinuria	Isolated SGA	Complications unrelated to pre-eclampsia	p-value[a]
n	164	75	29	6	38	4	8	4	
Age	33.1 (30.7 to 35.7)	33.3 (30.9 to 36.3)	32.3 (29.0 to 36.3)	33.9 (31.7 to 36.0)	33.3 (31.1 to 35.5)	28.8 (28.1 to 30.6)	32.8 (32.1 to 35.1)	34.6 (28.2 to 38.8)	0.3489
BMI (booking)	24.5 (21.9 to 28.7)	22.7 (21.3 to 26.8)	27.9 (23.9 to 32.7)	25.2 (22.8 to 30.6)	24.8 (21.7 to 29.5)	24.9 (23.4 to 26.6)	24.9 (21.8 to 28.7)	27.6 (23.9 to 40.4)	<0.0001
Nulliparous (%)	106 (65)	41 (55)	16 (57)	5 (83)	31 (82)	3 (75)	8 (100)	2 (50)	1.000
Ethnicity (%)									
• White European	106 (64)	53 (71)	12 (41)	5 (83)	28 (74)	2 (50)	4 (50)	2 (50)	0.0021
• Black	23 (14)	10 (13)	6 (21)	0 (0)	3 (8)	0 (0)	3 (38)	1 (25)	
• Asian	18 (11)	7 (9)	5 (17)	1 (17)	2 (5)	2 (50)	1 (13)	0 (0)	
• Other	17 (10)	5 (7)	6 (21)	0 (0)	5 (13)	0 (0	0 (0)	1 (25)	
Chronic hypertension	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (25)	
Highest sBP (mmHg)	138 (130 to 150)	130 (124 to 135)	176 (165 to 184)	161 (148 to 178)	145 (140 to 150)	136[c] (131 to 144)	139[c] (130 to 144)	131 (129 to 134)	<0.0001
Highest dBP (mmHg)	86 (81 to 96)	81 (76 to 85)	108 (104 to 118)	100 (91 to 118)	92 (85 to 96)	86[c] (82 to 100)	86[c] (84 to 96)	83 (81 to 85)	<0.0001
Highest uPCR (mg/mmol)	49 (20 to 167)	11 (8 to 18)	122 (41 to 380)	17 (7 to 27)	-	74 (43 to 141)	21[d]	-	<0.0001

Highest serum creatinine (µmol/L)	62 (54 to 75)	54 (48 to 59)	75 (66 to 86)	76 (62 to 85)	60 (51 to 70)	55 (46 to 65)	60 (51 to 75)	50 (32 to 55)	<0.0001
Highest ALT (IU/L)	19 (12 to 33)	14 (10 to 28)	25 (17 to 60)	16 (10-20)	12 (10 to 18)	15 (9 to 32)	24[d]	15 (8 to 22)	0.1095
Live birth (%)	164 (100)	75 (100)	29 (100)	6 (100)	38 (100)	4 (100)	8 (100)	4 (100)	
Gestational age	39^{+6} ($37^{+6}$to 40^{+5})	40^{+1} (39^{+0} to 41^{+0})	36^{+4} (33^{+1} to 37^{+2})	39^{+0} (37^{+3} to 40^{+3})	40^{+3} (39^{+3} to 41^{+1})	39^{+3} (37^{+3} to 41^{+3})	40^{+1} (39^{+4} to 41^{+0})	33^{+1} (27^{+3} to 37^{+5})	<0.0001
Preterm (< 37 weeks) (%)	25 (15)	3 (4)	18 (62)	0 (0)	1 (3)	0 (0)	1 (13)	2 (67)	<0.0001
Birth weight centile	54 (24 to 75)	66 (48 to 81)	15 (3 to 45)	50 (21 to 87)	59 (37 to 83)	47 (42 to 66)	8 (4 to 10)	59 (20 to 74)	<0.0001
<10^{th} centile (%)	20 (12)	0 (0)	13 (45)	0 (0)	0 (0)	0 (0)	7 (88)	0 (0)	<0.0001
<3^{rd} centile (%)	10 (6)	0 (0)	9 (31)	0 (0)	0 (0)	0 (0)	1 (13)	0 (0)	<0.0001
NNU (%)	22 (14)	4 (5)	11 (41)	0 (0)	3 (8)	0 (0)	1 (13)	3 (100)	<0.0001

There was no significant gestational variation in hyaluronan or VCAM concentrations in women with a normal pregnancy course. Reference intervals (2.5th-97.5th centiles) in women with a normal pregnancy outcome were 6.6-49.3ng/ml for plasma hyaluronan and 423-1111ng/ml for plasma VCAM (Figure 7.12).

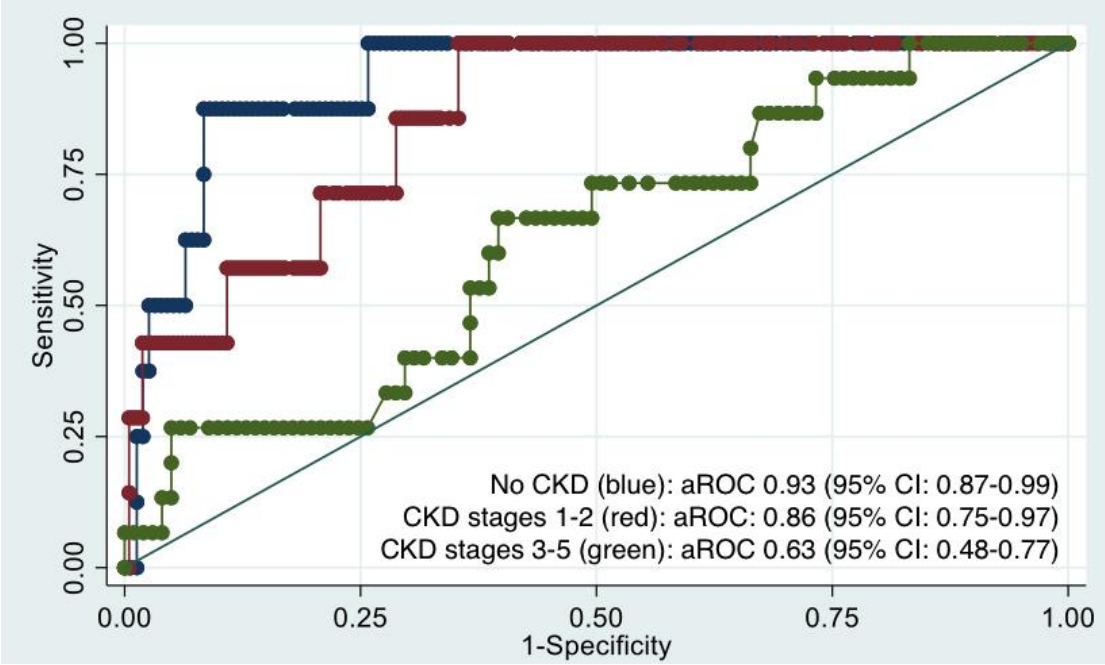
Figure 7.12 Plasma hyaluronan (a) and plasma VCAM (b) concentrations in women with a normal pregnancy course with (red) and without (blue) CKD.



Plasma hyaluronan and VCAM concentrations offered good discrimination for delivery within 14 and 28 days due to pre-eclampsia in women with and without CKD. However, discrimination was less good in women with pre-pregnancy CKD stages 3-5 compared to women with stages 1-2 (Figure 7.13 and 7.14). Predictive performance at the derived upper reference limits and at previously published diagnostic thresholds (Wiles et al., 2019 [see Chapter 6]) are shown in Table 7.17 and 7.18. For women with CKD, predictive performance was optimal at a threshold >50mg/ml for plasma hyaluronan and >1100mg/ml for plasma VCAM. Correlations between hyaluronan ($r=0.330$, $p<0.0001$) and VCAM ($r=0.221$, $p=0.0005$) with plasma PlGF (Quidel) concentrations were weak. Test performances for hyaluronan and VCAM were lower than for plasma PlGF (Quidel).

Figure 7.13 Area under the receiver operating curve for plasma hyaluronan in the prediction of delivery due to superimposed pre-eclampsia within 14 and 28 days of testing according to pre-pregnancy CKD stage (blue=no CKD, red=CKD stages 1-2, green=CKD stages 3-5).

Delivery with 14 days



Delivery within 28 days

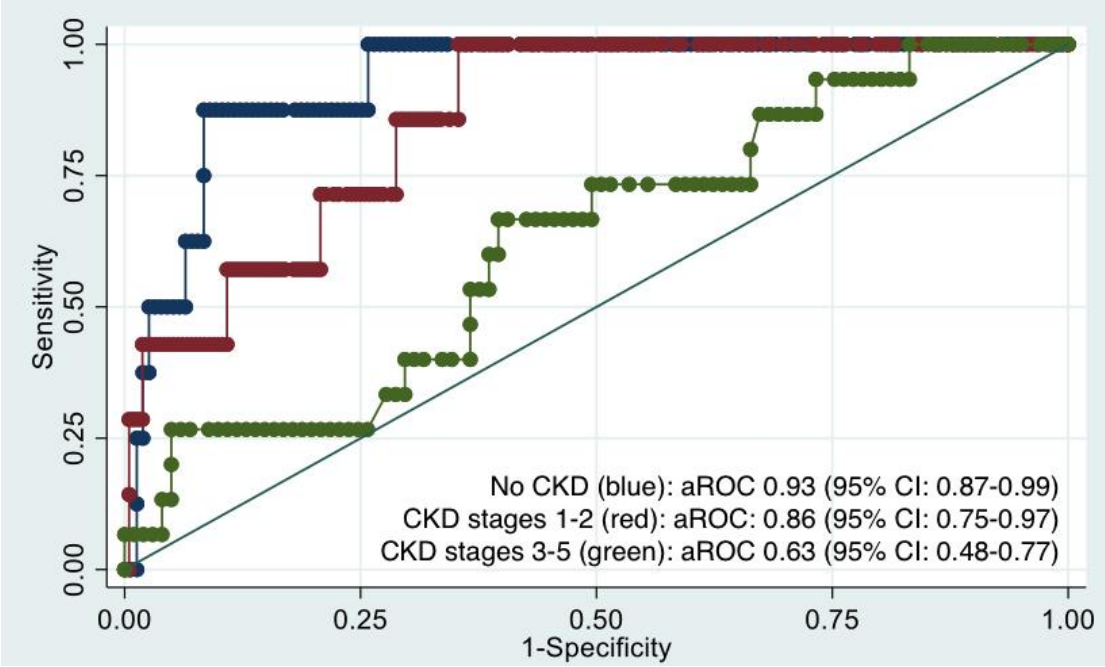
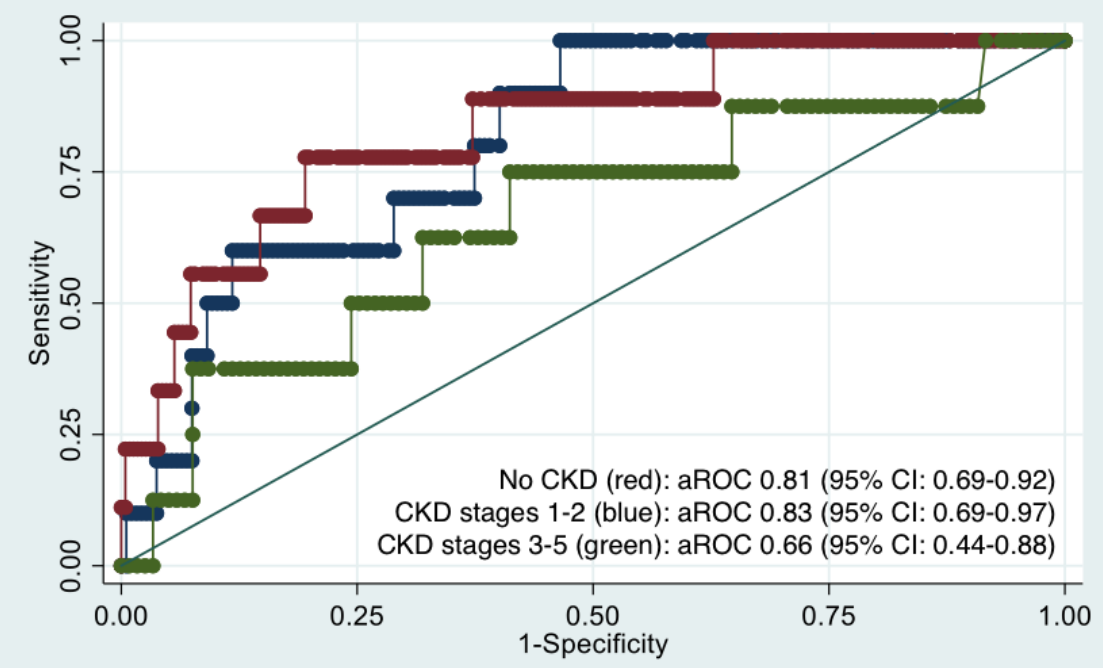


Figure 7.14 Area under the receiver operating curve for plasma VCAM in the prediction of delivery due to superimposed pre-eclampsia within 14 and 28 days of testing according to pre-pregnancy CKD stage (blue=no CKD, red=CKD stages 1-2, green=CKD stages 3-5).

Delivery within 14 days



Delivery within 28 days

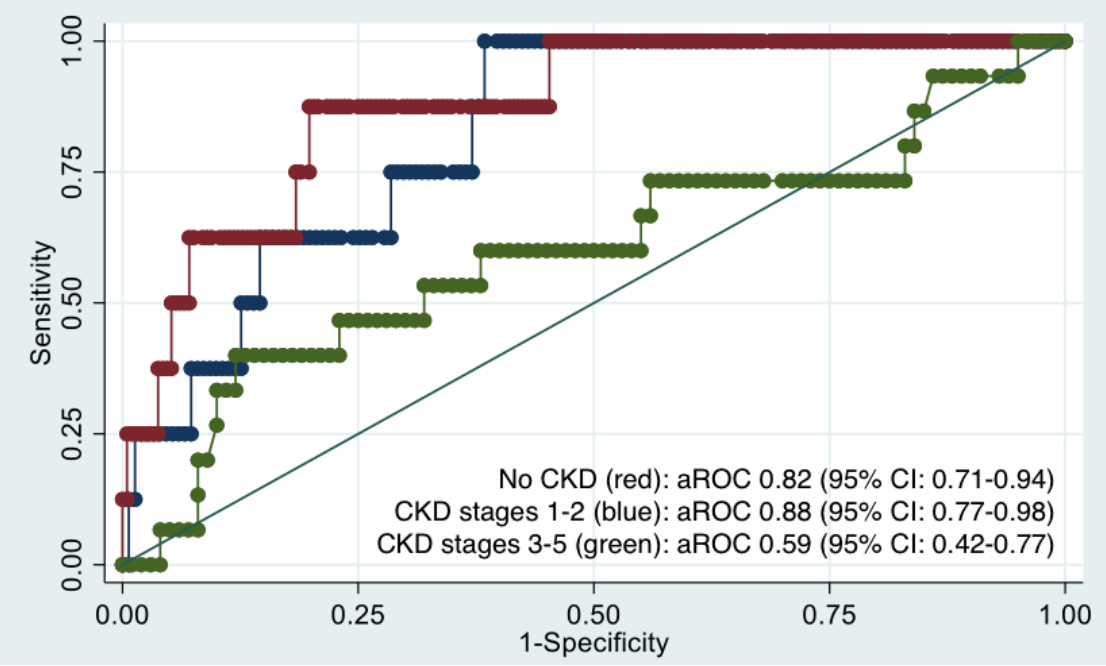


Table 7.17 Predictive performance of plasma hyaluronan for delivery due to pre-eclampsia within 14 and 28 days using the upper reference interval and previously published diagnostic thresholds [Chapter 6, (Wiles et al., 2019)], according to presence of absence of underlying CKD. The prevalence of pre-eclampsia in women without CKD was 5.0% (95% confidence interval (CI): 2.4-9.0%) at 14 days and 4.9% (95% CI: 2.1-9.4%) at 28 days. The prevalence of superimposed pre-eclampsia in women with CKD was 4.6% (95% confidence interval (CI): 2.7-7.3%) at 14 days and 6.8% (95% CI: 4.4-10.1%) at 28 days.

CKD	No				Yes			
Plasma concentration (ng/ml)	>39		>50		>39		>50	
Delivery within	14 days	28 days	14 days	28 days	14 days	28 days	14 days	28 days
Sensitivity % (95% CI)	90.0 (55.5-99.7)	87.5 (47.3-99.7)	90.0 (55.5-99.7)	87.5 (47.3-99.7)	47.1 (23.0-72.2)	39.1 (19.7-61.5)	41.2 (18.4-67.1)	39.1 (19.7-61.5)
Specificity % (95% CI)	80.1 (73.7-85.5)	84.5 (77.8-89.8)	85.9 (80.1-90.5)	90.3 (84.5-94.5)	80.1 (75.6-84.2)	81.8 (77.1-86.0)	87.5 (83.6-90.8)	89.5 (85.6-92.7)
Positive predictive value % (95% CI)	19.1 (9.1-33.3)	22.6 (9.6-41.1)	25.0 (12.1-42.2)	31.8 (13.9-54.9)	10.3 (4.5-19.2)	13.6 (6.4-24.3)	13.7 (5.7-26.3)	21.4 (10.3-36.8)
Negative predictive value % (95% CI)	99.4 (96.4-100)	99.2 (95.5-100)	99.4 (96.7-100)	99.3 (96.1-100)	96.9 (94.2-98.6)	94.8 (91.5-97.1)	96.9 (94.3-98.5)	95.3 (92.2-97.4)
Positive likelihood ratio % (95% CI)	4.5 (3.2-6.4)	5.7 (3.6-8.9)	6.4 (4.2-9.6)	9.0 (5.2-15.6)	2.4 (1.4-4.1)	2.1 (1.2-3.8)	3.3 (1.8-6.2)	3.7 (2.0-6.8)
Negative likelihood ratio % (95% CI)	0.1 (0.0-0.8)	0.2 (0.0-0.9)	0.1 (0.0-0.8)	0.1 (0.0-0.9)	0.7 (0.4-1.0)	0.7 (0.5-1.0)	0.7 (0.5-1.0)	0.7 (0.5-1.0)

Table 7.18 Predictive performance of plasma VCAM for delivery due to pre-eclampsia within 14 and 28 days using the upper reference interval and previously published diagnostic thresholds [Chapter 6, (Wiles et al., 2019)], according to presence of absence of underlying CKD. The prevalence of pre-eclampsia in women without CKD was 5.1% (95% confidence interval (CI): 2.5-9.1%) at 14 days and 5.0% (95% CI: 2.2-9.7%) at 28 days. The prevalence of superimposed pre-eclampsia in women with CKD was 4.9% (95% confidence interval (CI): 2.9-7.6%) at 14 days and 7.1% (95% CI: 4.6-10.4%) at 28 days.

CKD	No				Yes			
Plasma concentration (ng/ml)	>950		>1100		>950		>1100	
Delivery within	14 days	28 days	14 days	28 days	14 days	28 days	14 days	28 days
Sensitivity % (95% CI)	50.0 (18.7-81.3)	37.5 (8.5-75.5)	20.0 (2.5-55.6)	25.0 (3.2-65.1)	61.1 (35.7-82.7)	54.2 (32.8-74.4)	50.0 (26.0-74.0)	45.8 (25.6-67.2)
Specificity % (95% CI)	88.2 (82.7-92.5)	87.4 (81.0-92.3)	92.5 (87.8-95.8)	92.7 (87.3-96.3)	80.9 (76.3-84.8)	82.4 (77.7-86.4)	89.7 (86.0-92.7)	90.7 (86.9-93.7)
Positive predictive value % (95% CI)	18.5% (6.3-38.1)	13.6 (2.9-34.9)	12.5 (1.6-38.3)	15.4 (1.9-45.4)	14.1 (7.3-23.8)	19.1 (10.6-30.5)	20.0 (9.6-34.6)	27.5 (14.6-43.9)
Negative predictive value % (95% CI)	97.1 (93.3-99.0)	96.4 (91.7-98.8)	95.6 (91.5-98.1)	95.9 (91.3-98.5)	97.6 (95.1-99.0)	95.9 (92.8-97.9)	97.2 (94.8-98.7)	95.6 (92.6-97.6)
Positive likelihood ratio % (95% CI)	4.3 (2.0-8.9)	3.0 (1.1-8.0)	2.7 (0.7-10.2)	3.4 (0.9-13.0)	3.2 (2.1-4.9)	3.1 (2.0-4.8)	4.9 (2.8-8.5)	4.9 (2.8-8.6)
Negative likelihood ratio % (95% CI)	0.6 (0.3-1.1)	0.7 (0.4-1.2)	0.9 (0.6-1.2)	0.8 (0.5-1.2)	0.5 (0.3-0.9)	0.6 (0.4-0.9)	0.6 (0.4-0.9)	0.6 (0.4-0.9)

7.5 Discussion

Superimposed pre-eclampsia was common, affecting one third of pregnancies in women with CKD. The risk of superimposed pre-eclampsia was higher in black women with CKD despite comparable pre-pregnancy kidney function, proteinuria, and rates of chronic hypertension. Women with CKD who developed superimposed pre-eclampsia had lower plasma PlGF (Quidel) concentrations than women with CKD who did not develop superimposed pre-eclampsia, though mean concentrations did not fall below 100pg/ml. Low plasma PlGF (Quidel) (defined here as less than 150pg/ml) had the highest sensitivity and negative predictive value for the prediction of delivery due to superimposed pre-eclampsia within 14 and 28 days. In women with CKD, plasma PlGF (Quidel) concentrations greater than 150pg/ml after 20 weeks' gestation had a negative predictive value (i.e. for ruling out delivery with superimposed pre-eclampsia within the next 14 days) of 97% (95% CI: 93-99%) with a sensitivity of 79% and specificity 78%. High plasma hyaluronan and VCAM concentrations were able to discriminate the need for delivery within 14-28 days in women with and without CKD, but predictive performance was lower than for plasma PlGF (Quidel) concentrations. Predictive performance was lower for women with pre-pregnancy CKD stages 3-5 compared to women with CKD stages 1-2 for low plasma PlGF, high hyaluronan and high VCAM concentrations. Serum PlGF, sFlt-1 and the sFlt-1:PlGF ratio (Roche) did not usefully predict the need for delivery due to superimposed pre-eclampsia in women with CKD.

This is the first study to address the predictive performance of placental and novel biomarkers of superimposed pre-eclampsia in women with CKD. A strength of this study is the censoring of deliveries after the 37th week, removing the apparent 'prediction' of delivery at term. Although equivalent censoring in a general obstetric cohort would exclude the majority of pre-eclampsia (Akolekar et al., 2011; Lisonkova et al., 2014), a focus on preterm pre-eclampsia is appropriate for women with CKD as most (69%, 52/76) delivered before 37 weeks' gestation, with 29% (22/76) delivering prior to 34 weeks' gestation in this cohort. In addition, preterm pre-eclampsia is known

to be associated with the highest maternal and fetal risks (Vatten and Skjaerven, 2004; Mongraw-Chaffin et al., 2010; Lisonkova et al., 2014; Parker and Werler, 2014).

Another strength of the study is the use of delivery due to superimposed pre-eclampsia as a clinically relevant end-point. This mirrors real-world practice in which the diagnosis of superimposed pre-eclampsia in women with CKD is complex, and an adjunct that helps distinguish the women attending routine antenatal appointments in the second and third trimester that are likely to require delivery due to superimposed pre-eclampsia within the next 14-28 days can guide appropriate surveillance.

A limitation of this study is the absence of defined diagnostic criteria (in any national or international consensus definitions) for superimposed pre-eclampsia in women with CKD and chronic hypertension and/or proteinuria. This study therefore used previously reported predefined criteria (Bramham et al., 2016; Wiles et al., 2019 [see Chapter 6]) and dual diagnosis by obstetric nephrologists. Though relative increases in blood pressure and proteinuria are considered insufficient in isolation for the diagnosis of pre-eclampsia (Brown et al., 2018), the use of 'clinically relevant' increments in these parameters including severe hypertension (>160/110mmHg) and a greater than 100% increase in proteinuria after 20 weeks are valid, particularly in the context of early pre-term pre-eclampsia (Piccoli, 2019). The diagnosis of pre-eclampsia in women with CKD encompasses a spectrum of features that may include transient and gestational hypertension and gestational proteinuria, all of which may or may not progress to the clinical syndrome of pre-eclampsia. It is therefore possible that the decision to deliver may occur before pre-eclampsia manifests, affecting the final diagnosis made. However, this study was carried out in centres with experience and expertise in obstetric nephrology hoping to minimise this treatment paradox, whilst maintaining the real-world heterogeneity of CKD in pregnancy.

This study suggests that plasma PlGF (Quidel) at a concentration greater than 150pg/ml has utility as a clinical adjunct in women with CKD, excluding delivery due to superimposed pre-eclampsia within the next 14 days in the majority (97%), with a sensitivity of 79% and specificity 78%. In pre-eclampsia in the absence of CKD, high

sensitivity is considered to be a more useful attribute than specificity because consideration of benefits, harms and costs indicates a preference for minimizing false negatives rather than false positives (Cnossen et al., 2009). However, women with CKD are considered high risk in pregnancy and the default is close antenatal surveillance (Wiles et al., 2019 [see Chapter 6]). A balance between sensitivity and specificity is therefore warranted in women with CKD, in order to optimise frequency of antenatal care but minimise adverse outcomes. Of note, blood pressure measurement and assessment of proteinuria have a reported positive predictive value of only 20% for adverse outcomes in pre-eclampsia, even in the absence of confounding by CKD (Zhang et al., 2001). The only other available published data on the predictive performance of plasma PlGF in women with CKD are from a combined cohort of women with CKD and/or chronic hypertension in which PlGF <5th centile (<100pg/ml) was demonstrated to have a negative predictive value of 80%, sensitivity of 63% and specificity of 75% in 24 women with CKD (Bramham et al., 2016), with no assessment of test performance at alternative threshold concentrations.

Case-control (Verlohren et al., 2014) and prospective cohort studies (Rana et al., 2012; Chappell et al., 2013; Zeisler et al., 2016), and a recent randomised controlled trial (Duhig et al., 2019a) support the implementation of PlGF and sFlt-1:PlGF based testing as diagnostic adjuncts in women with suspected pre-eclampsia (NICE, 2016). Recommendations for general obstetric populations include increased surveillance of women for the development of pre-eclampsia if plasma PlGF (Quidel) is less than 100pg/ml (Chappell et al., 2013, Duhig et al., 2019a), which means a lower threshold of angiogenic dysfunction in women with CKD is demonstrated here. Reduced angiogenic dysregulation has been described in pre-eclampsia, particularly when occurring at later gestations and in the absence of fetal growth restriction (Soto et al., 2012, Zeisler et al., 2016; McLaughlin et al., 2018). However, this phenomenon is not apparent here with no difference in clinical evidence of placental dysfunction, gestational age or birthweight centile in women with a PlGF concentration above 100pg/ml in the 28 days before delivery due to superimposed pre-eclampsia, compared to PlGF values below 100pg/ml. Data from general obstetric cohorts contain a minority of women with CKD, with no detail of CKD stage or co-existing comorbidities such as chronic

hypertension and proteinuria (Chappell et al., 2013; Verlohren et al., 2014; Zeisler et al., 2016; Duhig et al., 2019a), and generalizability of angiogenic marker thresholds established predominantly in women without CKD fails to consider the effects of impaired kidney clearance and pre-existing endothelial dysfunction.

PlGF is excreted by the kidney and is detectable in the urine of women with pre-eclampsia (Levine et al., 2005). It is therefore feasible that impaired kidney clearance limits the reduction in plasma PlGF concentrations seen in women with CKD and superimposed pre-eclampsia. Although this theory is supported by the lower predictive performance of plasma PlGF concentrations in women pre-pregnancy CKD stages 3-5 compared to stages 1-2, there was no substantial difference in pre-pregnancy kidney function in women with superimposed pre-eclampsia and plasma PlGF (Quidel) concentrations above 100pg/ml in the 28 days prior to delivery, compared to those with concentrations below 100pg/ml. In addition, reduced performance for plasma hyaluronan and VCAM concentrations in women with CKD stage 3-5 is evident even though these factors rise in superimposed pre-eclampsia rather than fall, and are therefore unaffected by renal clearance. The impact of acute kidney injury on the utility of PlGF concentrations in pre-eclampsia in general obstetric cohorts has not specifically been explored, but no signal related to reduced excretory kidney function has become apparent to date. Such evidence suggests factors in addition to kidney clearance may also be contributory.

Endothelial dysfunction is a common pathophysiological mechanism underlying both pre-eclampsia (Powe et al., 2011) and CKD (Vila Cuenca et al., 2019). It is possible that pre-existing endothelial dysfunction in CKD allows clinical features of superimposed pre-eclampsia to manifest at lower concentrations of placental angiogenic dysfunction compared to women without CKD. Thus, placental angiogenic dysfunction is less predictive of superimposed pre-eclampsia in women with higher stages of CKD due to an increased burden of endothelial disease.

The reason for the limited performance of serum PlGF, sFlt-1, and sFlt-1:PlGF ratio (Roche) in distinguishing the need for delivery in women with CKD and superimposed pre-eclampsia is unclear. Although comparable test performances of the Triage® assay (plasma) and Elecsys® platform (serum) have been demonstrated in general obstetric cohorts, these data include small numbers of women with CKD (72/396, 18%) with no detail of disease severity, and analysis according to the presence or absence of kidney disease has not been performed (McCarthy et al., 2019). The finding here that concentrations of PlGF are higher in serum compared to matched plasma samples is consistent with both previous studies of PlGF (Oggè et al., 2010) and structurally related vascular endothelial growth factors (VEGF) (Webb et al., 1998; Nielsen et al., 1999; Jelkmann, 2001). This difference has been attributed to the release of growth factors by platelets and alternative cellular sources during the clotting process in serum preparation, leading to a recommendation that plasma be preferentially used for quantification (Webb et al., 1998; Jelkmann, 2001). We therefore hypothesise that CKD is associated with an increase in interfering sources of PlGF, which reduce clinical utility when quantification is undertaken in serum, masking the usual fall in PlGF in superimposed pre-eclampsia. The possibility of a specific effect in women with CKD in relation to the different target epitopes also warrants exclusion.

On the basis of this study, increased surveillance for superimposed pre-eclampsia should take place in women with CKD and plasma PlGF (Quidel) concentrations below 150pg/ml, with awareness that the predictive value for PlGF concentrations for delivery due to superimposed pre-eclampsia is reduced as excretory kidney function declines. In the absence of better evidence, the serum sFlt-1:PlGF ratio should not be used as a diagnostic adjunct in women with CKD. Plasma hyaluronan and VCAM concentration are alternative measures of endothelial dysfunction in pre-eclampsia though additional utility over plasma PlGF (Quidel), which is currently recommended for clinical practice (NICE, 2016), is not suggested. Future intervention studies are warranted to evaluate whether incorporation of PlGF-based testing into current management algorithms improves maternal and perinatal outcomes in women with CKD both within, and outside of expert centres. The disparity by ethnicity in this study of superimposed pre-eclampsia mirrors that in women with pre-eclampsia in the

absence of CKD (Shahul et al., 2015; Singh et al., 2018; Gyamfi-Bannerman et al., 2019) and further research into the aetiology of this health inequality is warranted to enable these differences to be addressed.

8 CONCLUSIONS

8.1 Summary of new knowledge

The upper limits of the reference interval for serum creatinine in pregnancy are 85%, 80% and 86% of the upper limit outside of pregnancy in sequential trimesters. This means that for an upper reference limit of 90µmol/L for serum creatinine in non-pregnant females, values greater than 76µmol/L in the first trimester, 72µmol/L in the second trimester, and 77µmol/L in the third trimester should be considered to be outside the upper limit of normal for pregnancy.

Serum AMH concentrations in women with CKD aged less than 35 years are lower than in women without CKD. Lower serum AMH concentrations are evident across all CKD stages with no evidence that glomerular filtration rate is an independent modifier of serum AMH concentrations. Women with CKD aged 20-24 years have comparable serum AMH concentrations to women aged 35 years and over without CKD.

Preterm delivery, low birthweight and loss of maternal renal function complicate pregnancies in women with pre-pregnancy CKD stages 3-5. Chronic hypertension is the strongest predictor of delivery before 34 weeks' gestation, with additional risk conferred if the gestational fall in serum creatinine is less than 10% of pre-pregnancy values. Pre- or early pregnancy proteinuria is the strongest predictor of birthweight below the 10th centile. There is a step-decline in renal function in relation to pregnancy in most women with pre-pregnancy CKD stages 3-5, equivalent to between 1.7 and 4.9 years of background renal disease depending on pre-pregnancy CKD stage and rate of decline in kidney function prior to pregnancy. Chronic hypertension, pre-pregnancy proteinuria and the absence of a gestational fall in serum creatinine are stronger predictors of adverse pregnancy outcomes than CKD stages 3-5. There is no evidence that renal transplantation confers additional risk in women with pre-pregnancy CKD stages 3-5.

Superimposed pre-eclampsia affects one third of women with CKD. Although plasma PlGF concentrations are lower in women with CKD who develop superimposed pre-eclampsia compared to those who do not, mean concentrations do not fall below 100pg/ml. Plasma PlGF (Quidel) concentrations below 150pg/ml have the highest sensitivity and negative predictive value for the prediction of delivery with superimposed pre-eclampsia within 14 and 28 days. Although high plasma hyaluronan and VCAM concentrations discriminate superimposed pre-eclampsia and pre-eclampsia in the absence of CKD, predictive performance is lower than for plasma PlGF concentrations. Quantification of PlGF, sFlt-1 and the sFlt-1:PlGF ratio in serum do not usefully predict the need for delivery due to superimposed pre-eclampsia in women with CKD. Diagnostic discrimination of superimposed pre-eclampsia using biomarkers from the renin-angiotensin system is reduced in the context of known modifiers including chronic hypertension, hypertensive drug use and black ethnicity, all of which are prevalent in CKD. Despite mechanistic plausibility, biomarkers of complement and kidney injury do not discriminate superimposed pre-eclampsia in CKD.

8.2 Strengths and limitations

A strength of this thesis is the focus on reproductive health and pregnancy exclusively in women with CKD, rather than as a combined cohort including women with chronic hypertension and/or cardiovascular disease in the absence of CKD. The prevalence of CKD in pregnancy is comparable to that of pre-eclampsia, yet research into pathophysiology, risk assessment, diagnosis, and prognosis of women with CKD in pregnancy remains relatively scarce.

The numbers of women with CKD included in the experimental sections of this thesis exceed those in published literature to date. This thesis includes the largest study to date examining serum AMH concentrations in women with CKD and is the first to assess serum AMH levels across the spectrum of CKD severity. To my knowledge, this thesis also encompasses the largest study of obstetric and renal outcomes in women with pre-pregnancy CKD stages 3-5, surpassing recent contemporary cohorts, and including twice as many pregnancies as the largest study to date, which examined

outcomes in women delivering up to 47 years ago. Research into diagnostic and predictive markers of superimposed pre-eclampsia in women with CKD is limited to small and mixed cohorts. In contrast, this thesis describes a multicentre, prospective cohort of 232 pregnancies in women with CKD, including 76 women with superimposed pre-eclampsia.

The thesis examines the spectrum of reproductive health in women with CKD including pre-pregnancy assessment and post-partum disease progression. A focus on pregnancy in isolation does not reflect the reality of reproductive health for women with CKD who may or may not proceed with pregnancy having consulted for pre-pregnancy advice, and fails to consider the specific implications of pregnancy for long-term renal outcomes and future health.

This thesis focuses on specific research questions that have not been addressed for women with CKD to date. In the absence of data specific to women with CKD, the interpretation of investigations and the management of reproductive health and pregnancy in women with CKD are generalised from data derived from cohorts of women predominantly without CKD. This fails to acknowledge the potential impact of both impaired renal clearance and coexisting morbidity. National guidance on the interpretation of anti-Müllerian hormone concentrations, plasma PlGF concentrations and serum sFlt-1:PlGF values fails to consider the possibility that interpretation differs in women with CKD. This thesis addresses these knowledge gaps and offers practical interpretation of data, which has not been available to date.

The main limitation of this thesis is the unavoidable heterogeneity that exists in CKD, particularly in relation to reproductive health. CKD is an umbrella term that includes a spectrum of kidney disease aetiologies, with an emphasis on glomerular filtration rate at a specific time-point, rather than disease activity, progression or co-morbidity. Such facets of CKD may be neglected in research stratified by CKD stage. Although attempts have been made in the statistical models contained with this thesis to examine for the impact of disease aetiology and activity where mechanistic impact was possible (e.g. cyclophosphamide exposure on ovarian reserve; glomerulonephritis and

transplantation as modifiers of long-term renal outcome) this assessment was limited by the clinical data available, and exclusion of aetiologies (or even possible aetiologies) where data were insufficient led to a reduced amount of data available for analysis.

The 'heterogeneity' of superimposed pre-eclampsia must also be considered. In the absence of diagnostic criteria for superimposed pre-eclampsia in any national or international consensus definitions, this thesis uses used pre-defined blood pressure and proteinuria thresholds, in conjunction with expert diagnostic consensus masked to biomarker concentrations for all complex cases. However, the possibility of a treatment paradox exists in which the decision to deliver occurs prior to the development of superimposed pre-eclampsia by defined criteria, thereby affecting the final diagnosis made. The work completed in this thesis was undertaken in centres with experience and expertise in obstetric nephrology, aiming to minimise treatment paradox, whilst maintaining the real-world heterogeneity of CKD in pregnancy. However, any research into superimposed pre-eclampsia in women with CKD remains limited by diagnostic ambiguity, where the need to distinguish gestational variation in blood pressure and proteinuria from pathological change is complex. The prospective study of superimposed pre-eclampsia in this thesis was pragmatic i.e. with biological samples taken from participants at their convenience, coordinated with other hospital attendances. Overlap in the clinical phenotypes of CKD and superimposed pre-eclampsia means that time-of-disease could not be assessed with precision and so prediction of the need for delivery, censored to exclude term delivery, was used as a clinically relevant end-point. The decision to proceed to iatrogenic preterm delivery is informed by the well being of the fetus in conjunction with the presence of organ and/or life-threatening complications in the mother. Therefore, regardless of specific clinical and biochemical parameters, the capacity of biomarkers to predict this need for delivery is clinically useful. However, the capacity of an isolated biomarker to predict a heterogeneous outcome in a heterogeneous group of women may always be limited.

8.3 Impact

This thesis provides a reference range for serum creatinine in pregnancy that allows a diagnosis of CKD (or acute kidney injury) to be made in women of different ethnicities, using a local creatinine assay. Based on a non-pregnant female reference range for serum creatinine, a trimester-specific serum creatinine concentration that raises the possibility of previously undiagnosed CKD predating pregnancy (or acute kidney injury) is now available, offering the opportunity for timely diagnosis, appropriate counselling and surveillance.

Women aged 36 years or older are eligible for early referral for fertility assessment and treatment in the UK. Serum AMH concentrations suggest that ovarian reserve in women with CKD at younger ages is comparable to that of women aged over 35 years without CKD. Women with CKD should therefore be considered for similar early referral. AMH concentrations are currently used to predict the response to ovarian stimulation in women undergoing assisted reproduction. Although women with CKD have lower concentrations of serum AMH compared to women without CKD, age remains the best predictor of reproductive success. A younger age, in conjunction an increased risk of harm from hyperstimulation and intravascular fluid depletion, mean gonadotrophin dosing should not be based on AMH concentrations in isolation in women with CKD.

Women with CKD stages 3-5 considering pregnancy can now be informed of contemporary risks of adverse pregnancy outcomes including preterm delivery, low birthweight and loss of maternal renal function. Chronic hypertension and pre-pregnancy proteinuria should inform risk assessment and counselling. A gestational fall in serum creatinine concentrations of less than 10% of pre-pregnancy values is associated with delivery before 34 weeks (in women with chronic hypertension) and loss of maternal renal function. The effect of pregnancy can be estimated to bring forward to need for renal replacement by 1.7, 2.1 and 4.9 years in women with pre-pregnancy stage 3a, 3b and 4-5 respectively. This is a novel and tangible measure of the effect of pregnancy on renal function, which can be used by clinicians for

appropriate surveillance, planning of renal replacement therapy, and aid in the counselling of women with CKD.

Increased surveillance for superimposed pre-eclampsia should take place in women with CKD and plasma PlGF (Quidel) concentrations less than 150pg/ml after 20 weeks' gestation. This plasma PlGF concentration is higher than the threshold recommended in national guidance for general obstetric cohorts. Clinicians should also be aware that the value of PlGF concentrations in predicting the need for delivery due to superimposed pre-eclampsia is reduced for women with lower excretory kidney function (CKD stage 3-5). Plasma hyaluronan and VCAM concentration are alternative measures of endothelial dysfunction in pre-eclampsia, though predictive utility over plasma PlGF is not suggested. The serum sFlt-1:PlGF ratio should not be used as a diagnostic adjunct in women with CKD and suspected superimposed pre-eclampsia.

The first evidence based national guideline is now available in the UK for women with CKD who are considering pregnancy, pregnant or post-partum. The aim of this guideline is to improve the reproductive health care of women with CKD, and reduce regional variations in care.

8.4 Future work

Assessment of renal function in pregnancy remains limited to serum creatinine despite known insensitivity and inter-assay variability. Future research is required into gestational patterns of serum creatinine change in women with CKD who do and do not develop adverse pregnancy outcomes.

Prospective studies on reproductive success in women with CKD are needed. Given the particular risks of hyperstimulation, optimum gonadotrophin dosages according to clinical parameters including age and kidney function are required for women with CKD.

The generation of a prediction model for women with CKD in pregnancy will aid in the provision of appropriate counselling and surveillance. Clinical indicators for the commencement of dialysis in pregnancy for the optimisation of maternal and neonatal outcomes are warranted. Research into the association between superimposed pre-eclampsia and adverse renal outcomes in women with CKD is needed.

Future intervention studies are warranted to evaluate whether incorporation of PlGF-based testing into current management algorithms improves maternal and perinatal outcomes in women with CKD.

Ethnic disparities in pregnancy outcomes are evident in women with and without CKD. Further research into the aetiology of this health inequality is warranted to enable these differences to be addressed.

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APPENDIX: UK CLINICAL PRACTICE GUIDELINE: PREGNANCY AND RENAL DISEASE

Clinical Practice Guideline

Pregnancy and Renal Disease

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The National Institute for Health and Care Excellence (NICE) has accredited the process used by the Renal Association to produce its Clinical Practice Guidelines. Accreditation is valid for 5 years from January 2017. More information on accreditation can be viewed at www.nice.org.uk/accreditation.

Conflicts of Interest Statement

All authors made declarations of interest in line with the policy in the Renal Association Clinical Practice Guidelines Development Manual. Further details can be obtained on request from the Renal Association.

Method used to arrive at a recommendation

The recommendations for the first draft of this guideline resulted from a collective decision reached by discussion between the authors and, whenever necessary, with input from the Chair of the Clinical Practice Guidelines Committee. If no agreement had been reached on the appropriate grading of a recommendation, a vote would have been held and the majority opinion was carried. However, this was not necessary for this guideline.

The level of agreement with the first draft of recommendations was examined via a modified Delphi process. An electronic survey of the authors' recommendation was circulated nationally to members of the UK Renal Association and to obstetric medicine groups. In addition, invitations to complete the survey were sent to clinicians known to be working in obstetric nephrology multidisciplinary teams in the UK, consultant midwives' group of the Royal College of Midwives and the UK Renal Pharmacy Group. Participants were asked for their level of agreement with the authors' recommendations on a 4-point scale (agree, mostly agree, mostly disagree, disagree) with the additional option of 'not relevant to my practice'.

There were 156 respondents to the survey, including 76 (49%) nephrologists, 36 (23%) obstetricians, 16 (10%) pharmacists, 12 (8%) midwives, 7 (4%) obstetric physicians, 5 (3%) physicians, 2 (1%) patients, 1 dietician and 1 person with role in guideline development. Of those completing the survey, 57 (37%) were part of a specialist multidisciplinary team managing women with CKD in pregnancy and 72 (46%) were routinely involved in either the renal or obstetric care of pregnant women with CKD. The strength of the recommendation was assigned as 'strong' ('we recommend...') or conditional ('we suggest...') based on a threshold of 75% of respondents agreeing with the recommendation, and where benefits outweigh risks for most, if not all patients.

I. INTRODUCTION

1. Background

Chronic kidney disease (CKD) is estimated to affect 3% of pregnant women in high-income countries, (Piccoli et al., 2018, #13860) which equates to between 15,000-20,000 pregnancies per year in England. The prevalence of CKD in pregnancy is predicted to rise in the future due to increasing maternal age and obesity.

Although CKD is not a barrier to reproduction in most women, the risk of adverse pregnancy outcomes is increased in women with CKD including pre-eclampsia, fetal growth restriction, preterm delivery and accelerated loss of maternal renal function. CKD impacts on communication, decision-making, and the surveillance and management of women before, during, and after pregnancy.

Existing guidance on the management of CKD in pregnancy includes the UK Consensus Group on Pregnancy in Renal Disease (ISBN 978-1107124073) and expert review. Neither Kidney Disease Outcomes Quality Initiative (KDOQI) or National Institute of Health and Care Excellence (NICE) have produced specific guidance on the management of renal disease in pregnancy. Published guidance containing information relevant to the care of women with CKD in pregnancy includes:

- KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD). UK Renal Association Commentary available at: BMC Nephrology 2018; 19: 240.
- KDOQI Clinical Practice Guideline for Haemodialysis, 2015.
- KDIGO Clinical Practice Guideline for the Evaluation and Management of CKD, 2012
- KDIGO Clinical Practice Guideline for Glomerulonephritis, 2012
- KDIGO Guideline for the Care of Kidney Transplant Recipients, 2009.
- KDIGO Clinical Practice Guidelines for Nutrition in Chronic Renal Failure, 2008.
- NICE: Intrapartum Care for Women with Existing Medical Conditions or Obstetric Complications and their Babies [NG121], 2019.
- NICE: Urinary Tract Infection (Lower) Antimicrobial Prescribing [NG109], 2018
- NICE: Urinary Tract Infection (Recurrent) Antimicrobial Prescribing [NG112], 2018.
- NICE: Antenatal Care for Uncomplicated Pregnancies [CG62], 2008, updated 2017.
- NICE: Vitamin D supplement use in specific population groups [PH56], 2017
- NICE: Diabetes in Pregnancy: Management from Pre-conception to the Post-partum Period [NG3], 2015.
- NICE: Antenatal and postnatal mental health: clinical management and service guidance [CG192], 2014, updated 2018.

- NICE: Fertility: Assessment and Treatment for People with Fertility Problems, 2013.
- NICE: Weight management before, during and after pregnancy [PH27], 2010 [additional data from 2017 surveillance available at: https://www.nice.org.uk/guidance/ph11/evidence/appendix-a-summary-of-evidence-from-surveillance-pdf-4671107966
- NICE: Hypertension in Pregnancy: Diagnosis and Management [CG107], 2011 (update awaited 2019).
- UK Renal Association Clinical Practice Guidelines: Undernutrition in Chronic Kidney Disease, June 2019.
- RCOG: Thrombosis and Embolism During Pregnancy and the Puerperium, Reducing the Risk [Green-Top Guideline 37a], 2015.
- MBBRACE Confidential Enquiry into Maternal Deaths and Morbidity: lessons learned to inform maternity care (triennial reports)
- www.european-renal-best-practice.org/content/erbp-documents

1. Aims

The aim of this guideline is to improve the standard of, and to reduce regional variation in, the care of women with CKD in the UK who are pregnant, planning a pregnancy or post-partum.

2. Scope

This guidance covers the care of women with CKD (including renal transplant recipients) who are planning a pregnancy, pregnant, or in the post-partum period. It also covers contraception and fertility for women with CKD.

This guideline can be used in the following settings:

- General practice
- Community and hospital antenatal clinics
- Antenatal, labour and postnatal wards
- Renal out-patients
- Renal wards
- Dialysis units

The target audience and intended users of this guideline are nephrologists, obstetricians, obstetric physicians, midwives, renal nurses, pharmacists, specialist trainees in both nephrology and obstetrics, and women with CKD who are pregnant or considering pregnancy. Qualitative data on the experience of pregnancy and renal disease is provided in Appendix 1. A summary of clinical responsibility for elements of the guideline is provided in Appendix 2.

The clinical issues covered in this guideline are:

1. **Structure of care**
2. **Medication**
3. **Pre-pregnancy care**
   - 3.1 Contraception
   - 3.2 Fertility
   - 3.3 Pre-pregnancy counselling and optimisation for pregnancy
4. **Pregnancy care**
   - 4.1 Assessment of renal function in pregnancy
   - 4.2 Antenatal care
   - 4.3 Pre-eclampsia prophylaxis
   - 4.4 Blood pressure management
   - 4.5 Thromboembolism prophylaxis
   - 4.6 Anaemia
   - 4.7 Bone health
   - 4.8 Renal biopsy
   - 4.9 Peripartum care
   - 4.10 Postnatal care
5. **Specific conditions**
   - 5.1 Renal transplantation
   - 5.2 Dialysis
   - 5.3 Lupus
   - 5.4 Diabetic nephropathy
   - 5.5 Urinary tract infection (UTI)
   - 5.6 Congenital Abnormalities of the Kidney and Urinary Tract (CAKUT)

Clinical issues that will not be covered are acute kidney injury and renal stone disease. In addition, fertility, contraception, teratogenicity and genetic implications in men with CKD will not be addressed.

3. Search strategy

Literature searches were undertaken using Ovid Medline (1946 to 2018) using specific search terms related to each of the clinical issues covered in the guideline. Search terms are detailed in Appendix 3.

II. SUMMARY OF CLINICAL PRACTICE GUIDELINES

1. Structure of care

Guideline 1.1

We recommend multidisciplinary teams (including a consultant obstetrician, consultant nephrologist/expert physician, and expert midwife or midwifery team) are established to offer advice and care for women with CKD who are pregnant or planning a pregnancy. All healthcare professionals caring for women with CKD should be able to access this MDT (1D).

2. Medication in pregnancy and lactation

Guideline 2.1

We recommend that low dose aspirin, low molecular weight heparin, labetalol, nifedipine, methyldopa, prednisolone, azathioprine, ciclosporin, tacrolimus and hydroxychloroquine are safe for use in pregnancy (1B).

Guideline 2.2

We recommend concentrations of calcineurin inhibitors (tacrolimus, ciclosporin) are checked throughout pregnancy and immediately postpartum, as blood concentrations may change (1C).

Guideline 2.3

We recommend that medications which interfere with calcineurin inhibitor metabolism (e.g. erythromycin, clarithromycin) are avoided in pregnant and post-partum women taking tacrolimus or ciclosporin whenever possible (1D).

Guideline 2.4

We recommend mycophenolate mofetil, methotrexate and cyclophosphamide are not taken in pregnancy as they are teratogenic (1B).

Guideline 2.5

We recommend mycophenolate mofetil is stopped before pregnancy, as use in pregnancy is associated with an increased risk of spontaneous miscarriage and fetal abnormality. A 3-month interval is advised before conception to allow conversion to a pregnancy-safe alternative and ensure stable disease/kidney function (1C).

Guideline 2.6

We recommend that, when other treatment options exist, rituximab is avoided in pregnancy due to the risk of neonatal B cell depletion and unknown long-term outcomes (1D).

Guideline 2.7

We recommend sirolimus and everolimus are avoided in pregnancy due to insufficient safety data (1D).

Guideline 2.8

We suggest the benefits of eculizumab in pregnancy for organ threatening disease are likely to outweigh risk (2D).

Guideline 2.9

We recommend metformin can be used in pregnancy for women with a pre-pregnancy eGFR>30mls/min/1.73m^2 and stable renal function during pregnancy (1D).

Guideline 2.10

We recommend immunosuppressive treatment is not increased routinely in the peripartum period and that dose changes are based on clinical indications and blood concentrations (1D).

Guideline 2.11

We recommend women can breastfeed whilst taking prednisolone, hydroxychloroquine, azathioprine, ciclosporin, tacrolimus, enalapril, captopril, amlodipine, nifedipine, labetalol, atenolol and low molecular weight heparin (1C).

3. Pre-pregnancy care

3.1 Contraception

Guideline 3.1.1

We recommend advice on safe and effective contraception is offered to all women of reproductive age with CKD (1D).

Guideline 3.1.2

We recommend safe and effective contraception is offered to women of reproductive age who are taking teratogenic medication, have active glomerulonephritis, are within one year of renal transplantation or acute graft rejection, and for any woman who does not wish to conceive (1D).

Guideline 3.1.3

We recommend that the progesterone only-pill, a progesterone subdermal implant, and the progesterone intra-uterine system are safe and effective for women with CKD (1C).

Guideline 3.1.4

We recommend that progesterone-only emergency contraception is safe for women with CKD (1C).

3.2 Fertility

Guideline 3.2.1

We suggest fertility preservation is considered for women of reproductive age who require treatment with cyclophosphamide (2C).

Guideline 3.2.2

We recommend women who have had previous treatment with cyclophosphamide have early investigation of infertility (1D).

Guideline 3.2.3

We suggest women with CKD are referred for pre-pregnancy counselling before receiving assisted reproduction (2D).

Guideline 3.2.4

We recommend single-embryo transfer is performed to reduce risk of complications associated with multifetal pregnancies in women with CKD (1C).

3.3 Pre-pregnancy counseling and optimization for pregnancy

Guideline 3.3.1

We suggest women with CKD considering pregnancy are offered pre-pregnancy counselling by a multidisciplinary team including a consultant obstetrician and nephrologist or expert physician (2D).

Guideline 3.3.2

We recommend women with CKD are advised there is an increased risk of complications in pregnancy including pre-eclampsia, preterm birth, fetal growth restriction, and neonatal unit (NNU) admission, and that they are more likely to require caesarean delivery (1C).

Guideline 3.3.3

We recommend women with known or suspected inheritable renal diseases are offered genetic counselling including inheritance risk, prognosis, and intervention options including pre-implantation genetic diagnosis (1C).

Guideline 3.3.4

We recommend pre-pregnancy counselling for the optimisation of maternal and neonatal outcomes in women with CKD, which may include:

- stabilising disease activity in advance of pregnancy on minimised doses of pregnancy-appropriate medications (1B).

- optimising blood pressure control (<140/90mmHg) on pregnancy-appropriate medications (1B).
- optimising glycaemic control in women with diabetes mellitus (1A) (see section 5.4).
- minimising risk of exposure to teratogenic medications (1C) (see section 2).
- making a treatment plan in the event of hyperemesis or disease exacerbation/relapse during pregnancy (1D).

Guideline 3.3.5

We recommend women with CKD who are taking angiotensin converting enzyme inhibitors have a plan for discontinuation/conversion guided by the strength of indication for renin-angiotensin blockade and the likelihood of pregnancy confirmation in the first trimester (1B).

Guideline 3.3.6

We recommend angiotensin receptor antagonists are discontinued in advance of pregnancy (1D).

Guideline 3.3.7

We suggest women with CKD stages 4 and 5 contemplating pregnancy are offered pre-dialysis education (2D).

4. Pregnancy Care

4.1 Assessment of renal function in pregnancy

Guideline 4.1.1

We recommend renal function in pregnancy is assessed using serum creatinine concentrations as estimated GFR (eGFR) is not valid for use in pregnancy (1C).

Guideline 4.1.2

We recommend women with CKD have formal quantification of proteinuria in pregnancy (1D).

Guideline 4.1.3

We recommend quantification of proteinuria is undertaken by protein:creatinine ratio (uPCR) or albumin:creatinine ratio (uACR). Twenty-four hour urine collection for quantification of protein is not required (1B).

4.2 Antenatal care

Guideline 4.2.1

We suggest pregnant women with CKD who have not had pre-pregnancy counselling by the MDT are referred to the MDT and receive the same counselling and optimisation as for women attending pre-pregnancy (2D).

Guideline 4.2.2

We recommend pregnant women with CKD receive routine antenatal care, in addition to specialist input (1D).

Guideline 4.2.3

We recommend pregnant women with CKD be referred for assessment by a consultant obstetrician (1D).

Guideline 4.2.4

We recommend pregnant women with CKD have access to usual trisomy screening with specialist interpretation of high-risk results (1C).

Guideline 4.2.5

We recommend women with CKD exposed to teratogenic drugs in the first trimester are referred to a specialist fetal medicine unit (1D).

Guideline 4.1.6

We recommend pregnant women with CKD have scans to assess fetal growth and wellbeing in the third trimester (1C).

Guideline 4.2.7

We recommend pregnant women taking prednisolone and/or calcineurin inhibitors are screened for gestational diabetes (1C).

4.3 Pre-eclampsia prophylaxis

Guideline 4.3.1

We recommend women with CKD are offered low-dose aspirin (75-150mg) in pregnancy to reduce the risk of pre-eclampsia (1B).

Guideline 4.3.2

We suggest kidney donors are offered low dose aspirin (75mg-150mg) to reduce the risk of pre-eclampsia (2D).

4.4 Blood pressure management

Guideline 4.4.1

We recommend that the target blood pressure during pregnancy for women with CKD is 135/85mmHg or less, which should be documented in the woman's healthcare record (1D).

Guideline 4.4.2

We suggest antihypertensive treatment in women with CKD is continued in pregnancy unless systolic blood pressure is consistently <110mmHg systolic, or diastolic blood is pressure consistently <70mmHg diastolic BP, or there is symptomatic hypotension (2D).

Guideline 4.4.3

We recommend labetalol, nifedipine and methyldopa can be used to treat hypertension in pregnancy (1B).

Guideline 4.4.4

We recommend angiotensin converting enzyme inhibitors, angiotensin receptor antagonists and diuretics are not used to treat hypertension in pregnancy (1B).

Guideline 4.4.5

We recommend a diagnosis of superimposed pre-eclampsia is considered:

- in a woman with non-proteinuric CKD, if she develops new hypertension (systolic BP >140mmHg and/or diastolic BP >90mmHg) and proteinuria (uPCR >30mg/mmol or uACR >8mg/mmol) or maternal organ dysfunction after 20 weeks' gestation (1B).
- in a women with proteinuric CKD if she develops new hypertension (systolic BP >140mmHg and/or diastolic BP >90mmHg) or maternal organ dysfunction after 20 weeks' gestation (1B)
- in a women with chronic hypertension and proteinuria, if she develops maternal organ dysfunction after 20 weeks' gestation (1B).

Guideline 4.4.6

We suggest in women with chronic hypertension and proteinuria that the development of sustained severe hypertension (systolic BP >160mmHg and/or diastolic BP >110mmHg or doubling of antihypertensive agents) and/or a substantial rise in proteinuria (doubling of uPCR or uACR compared to early pregnancy) should prompt clinical assessment for superimposed pre-eclampsia (2D).

Guideline 4.4.7

We suggest a role for angiogenic markers (PlGF±sFlt-1) is considered as an adjunct to diagnose superimposed pre-eclampsia, dependent upon on-going research in women with CKD (2C).

4.5 Venous thromboembolism

Guideline 4.5.1

We recommend that women with nephrotic-range proteinuria (uPCR>300mg/mmol or ACR >250mg/mmol) be offered thromboprophylaxis with low molecular weight heparin in pregnancy and the post-partum period unless there is a specific contraindication including risk of labour or active bleeding (1D).

Guideline 4.5.2

We suggest that non-nephrotic range proteinuria in pregnancy is a risk factor for thrombosis and thromboprophylaxis with low molecular weight heparin should be considered in the presence of additional risk factors (2D).

4.6 Anaemia

Guideline 4.6.1

We recommend pregnant women with CKD are given parenteral iron if indicated (1C).

Guideline 4.6.2

We recommend erythropoietin stimulating agents are given if indicated in pregnancy (1C).

4.7 Bone health

Guideline 4.7.1

We recommend women with CKD who are vitamin D deficient be given vitamin D supplementation in pregnancy (1B).

Guideline 4.7.2

We recommend calcimimetics are discontinued in pregnancy (1D).

Guideline 4.7.3

We recommend non-calcium based phosphate binders are discontinued in pregnancy (1D).

4.8 Renal biopsy

Guideline 4.8.1

We recommend if a histological diagnosis will change management in pregnancy then renal biopsy can be performed in the first and early second trimester of pregnancy (1C).

4.9 Peripartum care

Guideline 4.9.1

We recommend women with CKD receive routine peripartum care, with additional specialist input (1D).

Guideline 4.9.2

We recommend women with CKD have observations taken and documented during any hospital admission. This includes temperature, heart rate, blood pressure, respiratory rate, and oxygen saturation. An early warning score should be calculated and actioned appropriately (1D).

Guideline 4.9.3

We recommend additional assessment for women with an elevated early warning score, for women considered to be high-risk, and for any women in whom there is any clinical concern. This includes examination of jugular venous pressure, lung auscultation and urine output monitoring (in-dwelling catheter not usually required) in addition to routine parameters (1D).

Guideline 4.9.4

We recommend women with CKD at risk of volume depletion or volume overload are highlighted by the MDT in advance of delivery (1D).

Guideline 4.9.5

We recommend that fluid balance is managed with the aim of maintaining normal fluid volume, avoiding dehydration and pulmonary oedema, with input from clinicians with expertise in fluid balance and renal disease (1D).

Guideline 4.9.6

We recommend all clinicians are aware of the increased risk of pulmonary oedema in women with CKD and pre-eclampsia (1D).

Guideline 4.9.7

We recommend the timing of birth for women with CKD is determined by obstetric indications, with consideration of renal factors including deteriorating renal function, symptomatic hypoalbuminaemia, pulmonary oedema, and refractory hypertension (1D).

4.10 Postnatal care

Guideline 4.10.1

We recommend that non-steroidal anti-inflammatories should not be given (1C).

Guideline 4.10.2

We recommend women with CKD have a planned early postpartum renal review (1D).

Guideline 4.10.3

We recommend that women with CKD are prescribed medications that are compatible with breastfeeding whenever possible (1D).

Guideline 4.10.4

We recommend that women with CKD are offered safe and effective contraception post-partum and receive updated pre-pregnancy counselling before future pregnancies (1D).

5. Specific conditions

5.1 Renal transplantation

Guideline 5.1.1

We recommend women with renal transplants wait until their kidney function is stable on medications that are safe in pregnancy before conceiving, which is usually more than one year after transplantation (1D).

Guideline 5.1.2

We recommend that plans for delivery in a woman with a renal transplant are discussed with the local surgical transplant team (1D).

Guideline 5.1.3

We recommend that mode of delivery in women with renal transplants is based on obstetric indications and maternal preference (1D).

Guideline 5.1.4

We recommend that caesarean delivery in a woman with a renal transplant patient is performed by the most senior obstetrician available, ideally a consultant (1D).

Guideline 5.1.5

We recommend that women with kidney-pancreas transplants, kidney-liver transplants, and dual kidney transplants are managed during pregnancy and delivery by a multidisciplinary team including transplant physicians and surgeons, at a transplant centre (1D).

5.2 Dialysis

Women receiving maintenance dialysis before pregnancy

Guideline 5.2.1

We recommend women established on dialysis prior to pregnancy receive pre-pregnancy counselling including the options of postponing pregnancy until transplantation (when feasible) and the need for long frequent dialysis prior to and during pregnancy (1C).

Guideline 5.2.2

We recommend women established on haemodialysis prior to pregnancy receive long, frequent haemodialysis either in-centre or at home to improve pregnancy outcomes (1C).

Guideline 5.2.3

We suggest women receiving haemodialysis during pregnancy have dialysis dose prescribed accounting for residual renal function, aiming for a pre-dialysis urea <12.5mmol/l (2C).

Guideline 5.2.4

We recommend women established on peritoneal dialysis prior to pregnancy should convert to haemodialysis during pregnancy (1D).

Initiating dialysis during pregnancy

Guideline 5.2.5

We suggest haemodialysis should be initiated in pregnancy when the maternal urea concentration is 17-20mmol/L and the risks of preterm delivery outweigh those of dialysis initiation. Gestation, renal function trajectory, fluid balance, biochemical parameters, blood pressure and uraemic symptoms should be considered in addition to maternal urea concentration (2D).

5.3 Lupus nephritis and vasculitis

Guideline 5.3.1

We recommend that women with lupus or vasculitis should be advised to wait until their disease is quiescent for at least 6 months before conceiving (1B).

Guideline 5.3.2

We recommend that all women with lupus should be advised to take hydroxychloroquine in pregnancy unless it is contraindicated (1C).

Guideline 5.3.3

We recommend that women with lupus be monitored for disease activity during pregnancy (1D).

Guideline 5.3.4

We recommend that women who are positive for anti-Ro (SSA) or anti-La (SSB) antibodies be referred for fetal echocardiography in the second trimester (1C).

Guideline 5.3.5

We recommend women with antiphospholipid syndrome and a history of a confirmed thromboembolic event or previous adverse obstetric outcome (excluding recurrent early fetal loss) receive low molecular weight heparin in pregnancy and for six weeks postpartum (1B).

Guideline 5.3.6

We recommend that steroids, azathioprine, calcineurin inhibitors, intravenous immunoglobulin and plasma exchange can be used to treat lupus in pregnancy (1C).

5.4 Diabetic nephropathy

Guideline 5.4.1

We recommend that women with diabetic nephropathy have optimisation of blood glucose, blood pressure and proteinuria prior to conception (1C).

Guideline 5.4.2

We recommend that women with diabetic nephropathy continue angiotensin converting enzyme inhibitors until conception, with regular pregnancy testing during attempts to conceive (1C).

Guideline 5.4.3

We recommend that the schedule of care, surveillance and management of women with diabetic nephropathy should be untaken according to national guidelines for diabetes in pregnancy, in addition to specialist monitoring of renal disease in pregnancy (1D).

5.5 Urinary Tract Infection (UTI)

Guideline 5.5.1

We suggest women with reflux nephropathy, congenital anomalies of the kidneys and urinary tract (CAKUT), women with CKD taking immunosuppression, and women with a history of recurrent UTI should be offered antibiotic prophylaxis during pregnancy after a single UTI in pregnancy, including asymptomatic bacteriuria (2D).

Guideline 5.5.2

We recommend pre-pregnancy UTI prophylaxis be continued in pregnancy using agents known to be safe (1D).

5.6 Reflux nephropathy and Congenital Abnormalities of the Kidney and Urinary Tract (CAKUT)

Guideline 5.6.1

We recommend women with previous bladder surgery (re-implantation of ureter, bladder reconstruction, all complex paediatric urology) should be discussed during pregnancy with a urologist with expertise in bladder reconstruction to evaluate options for delivery (1D).

Guideline 5.6.2

We recommend that antenatally detected abnormalities in the fetal kidneys and/or urinary tract should be discussed with fetal medicine and paediatric nephrology specialists to determine appropriate neonatal management (1D).

Guideline 5.6.3

We recommend that children with antenatally detected abnormalities in the fetal kidneys and/or urinary tract should have specialist follow up if features of urinary tract infection are identified (1C).

III. SUMMARY OF AUDIT MEASURES

- **Audit Measure 1:** Proportion of UK renal units and obstetric centres with access to a multidisciplinary team (including a consultant obstetrician, consultant nephrologist/expert physician, and expert midwife or midwifery team) to advise and/or manage renal disease in pregnancy.
- **Audit Measure 2:** Incidence of pregnancies (including spontaneous miscarriage and elective terminations of pregnancy) exposed to mycophenolate mofetil and cyclophosphamide within 6 weeks prior to date of conception.
- **Audit Measure 3:** Proportion of women of reproductive age with CKD within the first year of transplantation offered safe and effective contraception.
- **Audit Measure 4:** Proportion of women of reproductive age with CKD within 6 months of a lupus flare offered safe and effective contraception.
- **Audit Measure 5:** Proportion of women of reproductive age with CKD taking teratogenic medication (mycophenolate mofetil, cyclophosphamide, methotrexate) offered safe and effective contraception.
- **Audit Measure 6:** Proportion of pregnant women with CKD with quantification of proteinuria before 20 weeks' gestation.
- **Audit Measure 7:** Proportion of women with CKD taking prednisolone or calcineurin inhibitors who are screened for gestational diabetes.
- **Audit Measure 8:** Proportion of pregnant women with CKD offered low dose aspirin (75-150mg) before 16 weeks' gestation.
- **Audit Measure 9:** Proportion of pregnant women with CKD that have a target blood pressure for pregnancy documented in their antenatal record.
- **Audit Measure 10:** Proportion of women with CKD given non-steroidal anti-inflammatory drugs in the post-partum period.
- **Audit Measure 11:** Proportion on women with CKD who are breastfeeding their infants (exclusively or mixed feeding) at 6 weeks post-partum.

IV. SUMMARY OF RESEARCH RECOMMENDATIONS

The UK Kidney Research Consortium has highlighted the need for better evidence in order to define care pathways, assess acceptability to patients and ensure optimum outcomes. These recommendations for research are very relevant to pregnancy in women with CKD. The guideline committee therefore suggest the following research recommendations:

Research recommendation 1: Qualitative evaluation of methods used to communicate risk in pregnancy in order to achieve understanding of risk and facilitate shared decision-making regarding reproductive health.

Research recommendation 2: Establishment of multicentre registries with standardisation of data collection from pregnant women with CKD to allow prospective, large cohort studies to evaluate:

- renal disease aetiology and mechanisms of disease progression
- factors influencing outcomes in women with dialysis, transplantation
- optimal schedule of care in pregnancy
- optimal management of hypertension, proteinuria, medications, anaemia, vitamin D concentrations
- impact of kidney donation on pregnancy and renal outcomes

Research recommendation 3: Assessment of the impact of CKD on aneuploidy screening methods including cell-free fetal DNA.

Research recommendation 4: Validation of angiogenic (PlGF) and antiangiogenic (sFlt-1) biomarkers in the diagnosis of superimposed pre-eclampsia and prediction of adverse pregnancy outcomes in women with CKD.

Research recommendation 5: Evaluation of short- and long-term outcomes in the children of women with CKD, including the excretion into breast milk of medications used in women with CKD.

V. RATIONALE FOR CLINICAL PRACTICE GUIDELINES

1. Structure of care

Guideline 1.1

We recommend multidisciplinary teams (including a consultant obstetrician, consultant nephrologist/expert physician, and expert midwife or midwifery team) are established to offer advice and care for women with CKD who are pregnant or planning a pregnancy. All healthcare professionals caring for women with CKD should be able to access this MDT (1D).

Rationale

Women with CKD have an increased risk of adverse pregnancy outcomes including pre-eclampsia, fetal growth restriction, preterm delivery and deterioration in maternal renal function. A recommendation for expert multidisciplinary care in pregnancy exists for women with other medical comorbidities associated with increased risk in pregnancy including cardiac disease[1], diabetes[2], epilepsy[3], and cancer.[4] It is unlikely that there will ever be randomised trial evidence supporting multidisciplinary care in pregnancy for women with CKD given the lack of perceived equipoise, but it was the consensus opinion of the guideline committee that multidisciplinary team working is critical for optimum care and timely clinical decision-making for women with CKD in pregnancy. The deficiencies in management identified in the care of women with pre-existing medical conditions that die during or shortly after pregnancy have been linked consistently to an absence of coordinated, expert, multidisciplinary care.[5,6] A MDT is therefore recommended to facilitate informed decision-making regarding pregnancy, and to prevent and/or manage obstetric, renal and neonatal complications that may develop. The MDT should be available prior to, during, and following pregnancy. Options for accessing the MDT include remote advice, face-to-face counselling, and the direct delivery of maternity care.

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2. Medication in pregnancy and lactation

Guideline 2.1

We recommend that low dose aspirin, low molecular weight heparin, labetalol, nifedipine, methyldopa, prednisolone, azathioprine, ciclosporin, tacrolimus and hydroxychloroquine are safe for use in pregnancy (1B).

Guideline 2.2

We recommend concentrations of calcineurin inhibitors (tacrolimus, ciclosporin) are checked throughout pregnancy and immediately postpartum, as blood concentrations may change (1C).

Guideline 2.3

We recommend that medications which interfere with calcineurin inhibitor metabolism (e.g. erythromycin, clarithromycin) are avoided in pregnant and post-partum women taking tacrolimus or ciclosporin whenever possible (1D).

Guideline 2.4

We recommend mycophenolate mofetil, methotrexate and cyclophosphamide are not taken in pregnancy as they are teratogenic (1B).

Guideline 2.5

We recommend mycophenolate mofetil is stopped before pregnancy, as use in pregnancy is associated with an increased risk of spontaneous miscarriage and fetal abnormality. A 3-month interval is advised before conception to allow conversion to a pregnancy-safe alternative and ensure stable disease/kidney function (1C).

Guideline 2.6

We recommend that, when other treatment options exist, rituximab is avoided in pregnancy due to the risk of neonatal B cell depletion and unknown long-term outcomes (1D).

Guideline 2.7

We recommend sirolimus and everolimus are avoided in pregnancy due to insufficient safety data (1D).

Guideline 2.8

We suggest the benefits of eculizumab in pregnancy for organ threatening disease are likely to outweigh risk (2D).

Guideline 2.9

We recommend metformin can be used in pregnancy for women with a pre-pregnancy eGFR>30mls/min/1.73m^2 and stable renal function during pregnancy (1D).

Guideline 2.10

We recommend immunosuppressive treatment is not increased routinely in the peripartum period and that dose changes are based on clinical indications and blood concentrations (1D).

Guideline 2.11

We recommend women can breastfeed whilst taking prednisolone, hydroxychloroquine, azathioprine, ciclosporin, tacrolimus, enalapril, captopril, amlodipine, nifedipine, labetalol, atenolol and low molecular weight heparin (1C).

Rationale

Prescribing any medication in pregnancy should involve balancing the risks to the women of uncontrolled disease, with any real or theoretical perceived harm to the fetus. Inappropriate cessation or failure to initiate therapy when clearly indicated can be more harmful than judicious use to maintain maternal health. Medication should be prescribed in pregnancy if the benefit to the woman (and therefore the fetus) outweighs the potential or theoretical risk to the fetus. The woman should be involved in discussions about medication in pregnancy, which should ideally take place before the pregnancy as part of pre–pregnancy counseling.[1]

Very few drugs are licensed for use in pregnancy. Surveillance of pregnancy outcomes in women exposed to drugs is therefore used to assess safety in pregnancy. Such outcomes may be confounded by the underlying medical conditions for which treatment is required, and clinical interpretation of data must be balanced and pragmatic. There are no randomised controlled trials of medication in pregnancy in women with CKD. Where randomised controlled trial data are available, they are generalised from unselected or control obstetric cohorts.[2,3]

Table 1 provides a summary of the relevant safety data for medications commonly used in women with CKD in relation to conception, pregnancy and lactation.

Table 1: Medication in women with CKD in relation to conception, pregnancy and lactation. Adapted from Wiles et al.[53]

Drug	Conception (see Section 3.3)	Pregnancy			Lactation	References
		Overall	Maternal considerations	Fetal considerations		
Antihypertensive drugs (see section 4.4)						
Labetalol	Safe.	Safe.	License for pregnancy. Avoid if asthmatic.	No association with congenital abnormalities. Reduced birth weight in unadjusted observational data. Neonatal bradycardia (2%) and hypoglycaemia (5%).	Safe	4-9
Nifedipine	Safe.	Safe.	None.	No association with congenital abnormalities.	Safe.	7,8
Amlodipine	Safe	Limited data.	None.	Limited data. No adverse effects reported.	Safe.	10,11
Methyldopa	Safe.	Safe.	Avoid in depression or if risk of depression.	No association with congenital abnormalities.	Avoid in all due to risk of postnatal depression.	7,8
Doxazosin	Safe	Limited data	None	No evidence of harm in animal studies	<1% maternal dose detected.	8
Hydralazine	Safe	Safe	Risk of hypotension, tachycardia	No association with congenital abnormalities	Safe	8
Beta-blockers	Safe	Limited data on individual drugs	Avoid if asthmatic. Use in pregnancy determined by maternal indication.	No association with congenital abnormalities. Reduced birth weight, clinical significance unclear. Neonatal bradycardia (1%) and hypoglycaemia (3%).	No adverse effects reported	8, 9, 12-15

Drug	Conception (see Section 3.3)	Pregnancy			Lactation	References
		Overall	Maternal considerations	Fetal considerations		
Angiotensin converting enzyme inhibitors	No apparent increase in risk with first trimester use when data are corrected for underlying hypertension. Continue until conception if required for nephroprotection.	Unsafe.	None.	Fetotoxic in second and third trimesters leading to fetal and neonatal renal failure, bone and aortic arch malformations, oligohydramnios, and pulmonary hypoplasia.	Safety data available for captopril and enalapril.	7,8, 16-18
Angiotensin receptor antagonists	Insufficient data on exposure in early pregnancy. Discontinue in advance of pregnancy.	Unsafe.	None.	Fetotoxicity in second and third trimesters comparable to angiotensin converting enzyme inhibitors.	No data.	7,8
Thiazide diuretics	Insufficient data on exposure in early pregnancy. No evidence of harm.	Unsafe.	Reduced plasma volume expansion in pregnancy (n=10)	No evidence of thrombocytopenia, jaundice, hypokalaemia or hyponatraemia in meta-analysis (n=5292) but advised to avoid.	Potential suppression of lactation. Avoid.	8,19,20
Immunosuppressant drugs (see Section 5.1 and 5.3)						
Corticosteroids	Safe.	Safe.	Potential risks: diabetes, hypertension, pre-eclampsia, infection, preterm rupture of membranes. Aim for minimum maintenance dose.	Fetus exposed to <10% maternal dose due to placental deactivation. No evidence of increase in congenital abnormalities.	Safe. Small amounts in breast milk. Consider timing feeds to 4 hours post administration if high dose given (e.g. methylprednisolone induction) and monitor neonate.	8, 21-24

Drug	Conception (see Section 3.3)	Pregnancy			Lactation	References
		Overall	Maternal considerations	Fetal considerations		
Hydroxychloroquine	Safe.	Safe.	Withdrawal may precipitate lupus flare. Indicated throughout pregnancy if patient has a history of lupus nephritis.	Placental transfer. No increase in miscarriage or congenital abnormality. May reduce risk of congenital heart block if maternal anti-SSA and or anti-SSB antibodies.	Safe.	8, 25-30
Azathioprine	Safe.	Safe.	Recommend check TPMT status before dosing.	Placental transfer. No association with congenital abnormalities.	Safe. Low concentration in breast milk	1,8,31-33
Ciclosporin	Safe.	Safe.	Monitor pre-dose levels more frequently in pregnancy and immediately post partum. May need higher dose in pregnancy. Avoid medications which interfere with calcineurin inhibitor metabolism (e.g. erythromycin, clarithromycin). Increased risk of gestational diabetes	Placental transfer. No association with congenital abnormalities.	Safe.	8,34,35

Drug	Conception (see Section 3.3)	Pregnancy			Lactation	References
		Overall	Maternal considerations	Fetal considerations		
Tacrolimus	Safe.	Safe.	Monitor pre-dose levels more frequently in pregnancy and immediately post-partum. May need a higher dose in pregnancy. Avoid medications which interfere with calcineurin inhibitor metabolism (e.g. erythromycin, clarithromycin). Increased risk of gestational diabetes	Placental transfer. No association with congenital abnormalities.	Safe.	8,36-38
Mycophenolate mofetil	Unsafe. Effective contraception during treatment and for 6 weeks after treatment. Ensure disease/transplant stability prior to conception.	Unsafe.	None.	Placental transfer. Teratogenic causing ear, heart, eye, lip/palate, kidney, and bone abnormalities, tracheoesophageal fistula, congenital diaphragmatic hernia. Increased miscarriage.	Avoid use during lactation due to insufficient data.	1,8,32,39
Cyclophosphamide	Unsafe. Effective contraception during and for 3 months after treatment. Dose- and age-related risk of infertility.	Unsafe.	None.	Placental transfer. Teratogenic. Congenital abnormalities of the skull, ear, face, limb and visceral organs. Increased risk of miscarriage.	Excreted in breast milk. Discontinue breast-feeding during and for 36 hours after treatment.	1,8,27,40, 41

Drug	Conception (see Section 3.3)	Pregnancy			Lactation	References
		Overall	Maternal considerations	Fetal considerations		
Rituximab	Unclear (limited data available). Treatment decision depends on indication and alternative options.	Unclear (limited data available).	If indicated for severe disease, aim to give dose before, or in early, pregnancy to minimise the risk of neonatal B-cell depletion.	Active placental transfer in 2nd and 3rd trimester. Potential risk of neonatal B-cell depletion. Avoid unless potential benefit to woman outweighs risk. Long term effects unknown.	Unclear (limited data available). Possible excretion of trace amounts but neonatal absorption unlikely.	1,8,32,42, 43
Sirolimus / Everolimus	Unsafe – fetal toxicity in rats. Effective contraception during and for 3 months after treatment.	Unsafe	Impaired wound healing. Proteinuria.	Likely placental transfer. Toxicity in animal studies	Limited data available. Avoid	8,44,45
Eculizumab	Unclear (limited data available). Treatment decision depends on indication and alternative options.	Unclear (limited data available)	Morbidity of underlying condition may mean treatment in pregnancy is required. Monitor for increased dosage requirements.	Active placental transfer in 2nd and 3rd trimester. No congenital abnormality reported in 20 infants. Long-term effects unknown.	Limited data available. Possible excretion of trace amounts but neonatal absorption unlikely.	8,46,47
Other drugs						
Aspirin (75–150mg) (see Section 4.3)	Safe.	Safe.	Decreases risk of pre-eclampsia in general obstetric population. No evidence of maternal haemorrhagic complications. Insufficient data on optimum dose (i.e. 75mg versus 150mg).	No association with congenital abnormalities.	Safe.	(2,3,7,8)

Drug	Conception (see Section 3.3)	Pregnancy			Lactation	References
		Overall	Maternal considerations	Fetal considerations		
Iron (see Section 4.6)	Safe.	Safe.	Intravenous preparations may offer better bioavailability in CKD	Safety data available in 2nd and 3rd trimesters but limited data on exposure on the first trimester. Expert consensus is not to withhold IV iron if indicated in the first trimester.	Safe.	8,48-52
Low-molecular- weight heparin	Safe	Safe	Level of proteinuria which confers a significant risk of VTE in pregnancy is unclear. All pregnant women should be risk assessed for VTE.	No placental transfer.	Safe.	8,53
Erythropoietin (see section 4.6)	Safe.	Safe.	Monitor blood pressure.	No placental transfer.	Safe.	8,54-56
Metformin (see Section 5.4)	Safe	Safe	Use contraindicated outside of pregnancy if eGFR <30ml/min/1.73m^2 (approximates to serum creatinine >150µmol/L in pregnancy).	None	Levels in milk are low, infants receive <0.5% of maternal weight-adjusted dosage. No reported adverse effects.	8,57

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3. Pre-pregnancy care

3.1 Contraception

Guideline 3.1.1

We recommend advice on safe and effective contraception is offered to all women of reproductive age with CKD (1D).

Rationale

Although CKD impacts on mechanistic and psychological aspects of fertility, reducing the likelihood of spontaneous conceptions (see section 3.2), unintended pregnancies occur. Although there are no recent data, a historical questionnaire study of 76 women with CKD revealed that despite 50% being sexually active, only 36% used contraception, and only 13% had discussed reproductive health issues with their nephrologist[(1)]. A survey of 212 women with lupus revealed that 46% were at risk of unintended pregnancy, with 23% having unprotected sex 'most of the time'.[(2)] Based on the use of folic acid supplementation at the time of conception, a nationwide survey in the UK estimates that one third of pregnancies in renal transplant recipients are unplanned.[(3)] Contraceptive counselling of women on dialysis is largely neglected in published literature despite increasing pregnancy rates in contemporary dialysis cohorts, and an association between intensive dialysis and an increased rate of conception.[(4)] A systematic review of observational studies shows that unintended pregnancy is associated with an increased risk of obstetric complications, even in the absence of co-morbidity[(5)], with important additional considerations in women with CKD including optimisation of disease management prior to pregnancy, avoidance of teratogenic medication, and providing an awareness of an increased risk of adverse pregnancies outcomes (see Section 3.3).

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Guideline 3.1.2

We recommend safe and effective contraception is offered to women of reproductive age who are taking teratogenic medication, have active glomerulonephritis, are within one year of renal transplantation or acute graft rejection, and for any woman who does not wish to conceive (1D).

Rationale

Exposure to teratogenic medications such as mycophenolate mofetil and cyclophosphamide in the first trimester of pregnancy can lead to abnormalities in the developing fetus (see Section 2). Meta-analyses of observational studies show that active lupus nephritis is a significant risk factor for the development of maternal hypertension and preterm delivery (see Section 5.3).[1,2] The first year after transplantation carries the highest risk of rejection, is most likely to require management with teratogenic medication and is associated with adverse pregnancy outcomes (see Section 5.1).[3–5] All such women should therefore be offered safe and effective contraception.

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Guideline 3.1.3

We recommend that the progesterone only-pill, a progesterone subdermal implant, and the progesterone intra-uterine system are safe and effective for women with CKD (1C).

Guideline 3.1.4

We recommend that progesterone-only emergency contraception is safe for women with CKD (1C).

Rationale

The risks and acceptability of different contraceptive methods should be balanced against the risks of an unplanned pregnancy. All oestrogen-containing contraceptives confer risk of hypertension, venous thromboembolism (VTE), arterial thrombosis and cervical cancer.[1] These risks are particularly relevant for women with CKD with co-existing chronic hypertension and those known to be at increased risk of vascular disease, venous thromboembolism (due to anti-phospholipid antibodies or nephrotic syndrome), or cervical neoplasia in the context of immunosuppression. Oestrogen-containing methods are therefore likely to be contraindicated for many women with CKD, particularly given the availability of safer, effective methods.

Progesterone-only methods including the progesterone-only pill (‘mini-pill), the progesterone-containing intrauterine system (Mirena®) and the progesterone subdermal implant (Nexplanon®), do not confer these risks and are therefore considered safe.[2] The ability of the progesterone-only pill to inhibit ovulation varies but one study showed that desogestrel provides consistent inhibition of ovulation in 102 out of 103 women and that this inhibition is maintained even after 12-hour delays before re-dosing.[3] This therapy can therefore be hypothesised to confer improved ‘typical-use’ efficacy over other oral progesterone preparations that require re-dosing within a 3-hour window each day.

There is theoretical concern that the efficacy of intrauterine devices is reduced in women taking immunosuppression due to inhibition of uterine inflammation, which is believed to contribute to the underlying contraceptive mechanism. However, the uterine milieu is predominantly populated by macrophages, and immunosuppression used in the management of immune-mediated renal disease and transplantation acts predominantly via lymphocyte inhibition. There is no evidence of an excess of

intrauterine device failures following transplantation.[4,5] Concern regarding pelvic infection in the context of immunosuppression also seems to be unfounded. Data from women with HIV-mediated immunosuppression show no correlation between infective complications and the level of immune suppression measured by $CD4^+$ T cell count.[6] A retrospective study of 11 women with renal transplants and a total of 484 months of progesterone-intrauterine device use reported no cases of pelvic infection or unplanned pregnancy.[7]

Data on the risk of breast cancer with progesterone methods of contraception are conflicting with a large population study suggesting[8] and a large case-control study refuting[9] a link. Non-hormonal methods (i.e. copper intrauterine device) should be used in women with either a diagnosis or history of breast cancer, and the potential risk of progesterone should be considered in women who are known to have a genetic mutation that confers an increased future risk of breast-cancer.[2] The excess number of cases of breast cases linked to hormone-containing contraceptives is age-related and hormone use should therefore be carefully weighed in women over 40 years.[10]

Assessment of contraceptive efficacy should be based on 'typical use' rather than presuming 'perfect use', as discrepancies exist in the failure rate of some contraceptive methods.[11] Typical use failure rates for the contraceptive pill, implant and progesterone-containing intra-uterine device (Mirena®) are 9%, 0.2% and 0.05% respectively within the first year of use. Although barrier methods are effective in preventing transmission of HIV and sexually transmitted disease, 18-21% of couples will conceive within the first year of typical use meaning that condoms cannot be considered to be a reliable, long-term form of contraception for most couples.

In the UK, emergency contraceptive pills (levonorgestrel, ulipristal) do not contain oestrogen and can be safely prescribed in women with CKD within 72 hours of unprotected sexual intercourse to prevent pregnancy.

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3.2 Fertility

Guideline 3.2.1

We suggest fertility preservation is considered for women of reproductive age who require treatment with cyclophosphamide (2C).

Guideline 3.2.2

We recommend women who have had previous treatment with cyclophosphamide have early investigation of infertility (1D).

Rationale

Cohort studies show that cyclophosphamide causes age and dose-dependent gonadotoxicity in women with systemic lupus erythematosus[1,2] and a diminished ovarian reserve (quantified by longitudinal serum AMH concentrations) in women with granulomatosis with polyangiitis.[3] Systematic review data show that, in addition to fertility effects, chemotherapy-induced premature ovarian insufficiency in young women treated for breast cancer has a negative effect on quality of life and is associated with vasomotor symptoms and sexual dysfunction.[4] Fertility preservation should therefore be considered for women of childbearing age receiving cyclophosphamide.

Fertility preservation techniques will depend upon the urgency of treatment of the underlying condition and availability. Cryopreservation of oocytes and gametes can be undertaken, but this usually requires ovarian stimulation, which will typically delay cyclophosphamide administration and, given the immunomodulatory role of oestrogen believed to underlie the female predominance of lupus, carries a theoretical risk of lupus flare. Published data on the risks of ovarian stimulation are limited, conflicting,

and there is an absence of prospective trials.[5,6] Natural cycle in-vitro fertilization (IVF) negates the need for ovarian stimulation and has been described in six patients with nephritis.[7] However, pregnancy rates with natural cycle IVF are lower compared to stimulated cycles and natural cycle retrieval is not recommended for women without CKD.[8]

Luteinising hormone releasing hormone analogues (LHRHa)/gonadotrophin releasing hormone agonists (GnRHa) can be used to inhibit the hypothalamic-pituitary-ovarian axis, leading to a protective reduction in ovarian blood flow for the duration of cyclophosphamide treatment. Data on the use of LHRH/GnRHa in women with CKD are limited. A retrospective cohort of 20 women receiving cyclophosphamide (cumulative mean dose 12.5g) for lupus nephritis showed a reduction in the incidence of premature ovarian failure (amenorrhoea >12 months and follicle-stimulating hormone level >40mIU/ml) with use of an LHRH analogue compared to that of age and dose-matched controls (5% versus 30%, respectively).[9] Most data come from populations treated with chemotherapy for breast cancer with randomised controlled trials[10,11] and a large meta-analysis of >1,200 patients[12] suggesting that LHRH analogues are safe and effective in reducing premature ovarian failure associated with chemotherapy. In contrast, a recent randomized-controlled trial in young women with lymphoma (mean age 26 years) showed no significant difference in the incidence of pregnancy rate after 5 years of follow-up between women treated with GnRHa at the time of chemotherapy (cyclophosphamide in 67% of women) compared to controls, with age and cumulative dose of cyclophosphamide (>5g/m^2) being better predictors of premature ovarian failure than GnRHa use.[13] Use of surrogate markers of fertility (with pregnancies occurring in patients with protocol-defined premature ovarian failure[13]), and inadequate follow-up of both pregnancy intent and outcome are possible contributors to inconsistency in published data. In the context of conflicting evidence, the American Society of Clinical Oncology recommends that LHRHa/GnRHa may be offered to patients in the hope of reducing the likelihood of chemotherapy-induced ovarian insufficiency when proven fertility preservation methods such as oocyte or embryo cryopreservation are not feasible.[14]

Age, anticipated cyclophosphamide dose and patient preference should inform fertility preservation in women with CKD. Whether the assessment of ovarian reserve by serum anti-Müllerian hormone concentrations has clinical utility in predicting benefit from fertility preservation remains unknown.

As cyclophosphamide exposure is a recognized predisposing factor for infertility, a referral for fertility assessment can be made before one year of regular unprotected intercourse, particularly in women with CKD who are aged 36 and over, according to national guidance.[8].

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Guideline 3.2.3

We suggest women with CKD are referred for pre-pregnancy counselling before receiving assisted reproduction (2D).

Rationale

Women with CKD considering pregnancy should be offered pre-pregnancy counselling by an expert multidisciplinary team (see Section 3.3). Healthcare providers should recognise that discussions of fertility and referrals for fertility assessment provide an opportunity for expert pre-pregnancy counselling in women with CKD.

Guideline 3.2.4

We recommend single-embryo transfer is performed to reduce risk of complications associated with multifetal pregnancies in women with CKD (1C).

Rationale

A small case-control study of 15 twin pregnancies in women with CKD shows a higher risk of preterm delivery, growth restriction, neonatal unit admission, weight discordance, perinatal mortality and neonatal mortality compared to both low-risk twin pregnancies and twin pregnancies complicated by either chronic hypertension or collagen disease.[(1)] This generates a difficult ethical balance between an increased risk of adverse pregnancy outcome due to multifetal pregnancy and the likely success of implantation. There was unanimous consensus amongst the guideline committee that avoidance of iatrogenic twinning with single embryo transfer in CKD patients is safer with regard to maternal-fetal outcomes and should be recommended. It is also worthy of note that in available case series[(1)], three of the six patients who underwent assisted fertilization were diagnosed with CKD during pregnancy, suggesting that urinalysis and eGFR quantification should be performed as part of the evaluation for assisted fertilization.

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3.3 Pre-pregnancy counseling and optimization for pregnancy

Guideline 3.3.1

We suggest women with CKD considering pregnancy are offered pre-pregnancy counselling by a multidisciplinary team including a consultant obstetrician and nephrologist or expert physician (2D).

Guideline 3.3.2

We recommend women with CKD are advised there is an increased risk of complications in pregnancy including pre-eclampsia, preterm birth, fetal growth restriction, and neonatal unit (NNU) admission, and that they are more likely to require caesarean delivery (1C).

Rationale

Cohort studies[1-3] and meta-analysis[4,5] show that women with CKD have an increased risk of antenatal complications including pre-eclampsia, preterm delivery, fetal growth restriction compared to women without CKD, although a successful pregnancy is feasible for most women. A meta-analysis that compared 2682 pregnancies in women with CKD with 26,149 pregnancies in healthy controls showed that weighted averages of adverse maternal events in women with CKD and healthy controls were 11.5% and 2% respectively, with a two-fold increase in adverse neonatal outcomes (premature births, fetal growth restriction, small for gestational age, neonatal mortality, stillbirths, and low birth weight) in women with CKD.[4] The likelihood of adverse outcomes are predominantly dependent on baseline excretory renal function, hypertension, proteinuria and, to a lesser extent, aetiology of renal disease.[1,2,6,7] However, as adverse outcomes are more common even in women with preserved excretory renal function (pre-pregnancy CKD stages 1 and 2) than the general obstetric population, counselling should be offered to all women with CKD.[1] A questionnaire study in the UK found that over 90% of women with CKD attending pre-pregnancy counselling found consultations informative and helpful in making a decision on pursuing pregnancy.[8]

The provision of pre-pregnancy counselling is likely to depend upon local availability of expertise. However the guideline committee recommend expert, multidisciplinary pre-pregnancy counselling for women with an eGFR <60ml/min/1.73m^2, women with CKD progression, women with uncontrolled hypertension (>140/90mmHg), women with nephrotic-range proteinuria, women with active renal disease, women with lupus nephritis, women with renal transplants and all women with previous adverse obstetric outcomes.

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Guideline 3.3.3

We recommend women with known or suspected inheritable renal diseases are offered genetic counselling including inheritance risk, prognosis, and intervention options including pre-implantation genetic diagnosis (1C).

Rationale

Genetic counselling is indicated for families with a history of known or suspected inheritable renal disease to assist in decision-making regarding pursuing a pregnancy. Referral for specialist counselling with clinical genetics teams may be indicated to facilitate genetic diagnosis, the testing of family members or for discuss regarding the possibility of pre-implantation genetic diagnosis (PGD). PGD is approved by the Human Fertilisation and Embryology Authority for autosomal dominant and recessive forms of polycystic kidney disease, Alport syndromes, Fabry disease and cystinosis[(1)] and this option might be a consideration for some families.

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Guideline 3.3.4

We recommend pre-pregnancy counselling for the optimisation of maternal and neonatal outcomes in women with CKD, which may include:

- stabilising disease activity in advance of pregnancy on minimised doses of pregnancy-appropriate medications (1B).
- optimising blood pressure control (<140/90mmHg) on pregnancy-appropriate medications (1B).
- optimising glycaemic control in women with diabetes mellitus (1A) (see section 5.4).
- minimising risk of exposure to teratogenic medications (1C) (see section 2).
- making a treatment plan in the event of hyperemesis or disease exacerbation/relapse during pregnancy (1D).

Rationale

In addition to specialist renal care, pre-pregnancy advice for women with CKD should follow advice available from the National Institute for Health and Care Excellence to promote optimal long and short-term health outcomes of all women and their children during and after pregnancy.(1)

There are observational data that associate active lupus nephritis, nephrotic syndrome and small vessel vasculitis are associated with increased risks of adverse pregnancy outcomes including fetal demise.(2-4) These data and others report more favourable outcomes in women with quiescent disease at the time of conception.(5) Although longitudinal patient data are not available to confirm that disease stabilisation improves pregnancy outcomes, the aim of disease quiescence prior to conception is recommended.

Hypertension is a recognised risk factor for progression of CKD. Non-pregnant women with CKD should therefore be treated according to up to date blood pressure targets. In addition, prospective cohort studies of preconception hypertension show an association with pregnancy loss.(6,7)

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Guideline 3.3.5

We recommend women with CKD who are taking angiotensin converting enzyme inhibitors have a plan for discontinuation/conversion guided by the strength of indication for renin-angiotensin blockade and the likelihood of pregnancy confirmation in the first trimester (1B).

Guideline 3.3.6

We recommend angiotensin receptor antagonists are discontinued in advance of pregnancy (1D).

Rationale

Angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor antagonists are fetotoxic in the second and third trimesters. Exposure to ACEi in the second and third trimester may lead to major birth defects including renal agenesis, and should be avoided. Although retrospective cohort studies show an apparent increased rate of congenital malformation associated with first trimester exposure to ACEi[(1)], such association is lost after adjustment for confounding factors including hypertension, diabetes, age, obesity and parity.[(2,3)] In the largest published cohort, which included 2626 exposed pregnancies, adjusted relative risks associated with first-trimester ACEi exposure compared to unexposed pregnancies were 0.89 (95% CI 0.75-1.06) for overall malformations, 0.95 (95% CI 0.75-1.21) for cardiac malformations, and 0.54 (95% CI 0.26-1.11) for central nervous system malformations.[(3)]

To avoid the risk of inadvertent second trimester exposure to ACEi, these agents can be stopped prior to pregnancy, or as soon as pregnancy is confirmed in women with a strong indication for continued renin-angiotensin blockade during the unknown period of time taken to conceive, such as proteinuric renal disease. Women who continue to take ACEi during attempts to conceive need to be counselled to perform regular pregnancy tests, at least monthly.

There are limited data addressing the risks of exposure to angiotensinogen receptor antagonists in the first trimester. Limited reports of harm[4] and inadequate evidence of safety mean that first trimester exposure to angiotensin receptor antagonists should be avoided. Hence angiotensin receptor blockers should be stopped or substituted before contraception is discontinued.

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Guideline 3.3.7

We suggest women with CKD stages 4 and 5 contemplating pregnancy are offered pre-dialysis education (2D).

Rationale

Observational data from the 1970s identified that women commencing pregnancy with advanced CKD had a 1 in 3 risk of requiring dialysis within a year of the pregnancy. Cohort studies from the 1980s, 1990s and 2000s continue to describe a 1 in 3 risk of dialysis for patients whose serum creatinine approximates to pre-pregnancy CKD stage 4 and 5.[1–4] Education about kidney failure and the possibility of antenatal or post-partum dialysis initiation, including treatment options, modality choice (see section 5.2) and access, is therefore recommended prior to conception in line with recommendations for non-pregnant patients approaching dialysis.[5]

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4. Pregnancy Care

4.1 Assessment of renal function in pregnancy

Guideline 4.1.1

We recommend renal function in pregnancy is assessed using serum creatinine concentrations as estimated GFR (eGFR) is not valid for use in pregnancy (1C).

Rationale

Due to increased plasma flow and dynamic changes in filtration fraction during pregnancy[1], glomerular filtration increases up to 50% with a consequent fall in serum creatinine concentrations.[2] Analysis of cross sectional serum creatinine concentrations from 243,534 pregnant women in Ontario, Canada defined mean serum creatinine as 60µmol pre-pregnancy, falling to a nadir of 47µmol between 16-32 weeks' gestation, peaking at 64µmol within the first post-partum weeks, before returning to pre-pregnancy concentrations by 18 weeks post-partum. The 95th centile values for serum creatinine were 78µmol prior to pregnancy, 59µmol during the second trimester, and 84µmol in the post-partum period.[3]. Meta-analysis of serum creatinine values in pregnancy suggests that the upper reference limits for serum creatinine in pregnancy are 85%, 80% and 86% of non-pregnant reference values in the first, second and third trimesters respectively.[4]

Estimated glomerular filtration rate (eGFR) derived by both Modified Diet in Renal Disease (MDRD)[5,6] and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)[7] equations have been compared with formal assessment of glomerular filtration rate (GFR) quantified with inulin and found underestimate formal GFR by up to 20% in pregnancy, thus cannot be used. In addition, the dynamic nature of gestational and immediate post-partum change in renal function means that steady state cannot be presumed, prohibiting the use of eGFR. Quantification of GFR by creatinine clearance in pregnancy is unreliable and impractical.[6] Alternative markers of glomerular filtration have not been extensively studied; however cystatin-C has been

demonstrated to rise in the second trimester despite a fall in GFR suggesting that additional gestational factors modify renal handling of cystatin-C in pregnancy, preventing utility in the assessment of renal function.[8,9]

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Guideline 4.1.2

We recommend women with CKD have formal quantification of proteinuria in pregnancy (1D).

Rationale

The amount of protein excreted into urine increases in normal pregnancy as a consequence of physiological changes in the kidney with gestation. These changes include an increase in renal blood flow with a corresponding increase in glomerular filtration, a more porous glomerular basement membrane, and altered tubular reabsorption. The amount of protein excreted by the kidney in pregnancy is greater than that in the non-pregnant population. The 95% confidence interval for 24 hour

urinary protein excretion in 270 healthy pregnant women was found to be 259.4mg[1], hence abnormal proteinuria is defined as proteinuria levels of >300mg/24 hours, twice the normal limit in non-pregnant women. For women with CKD, renal adaptation to pregnancy and relative change in proteinuria are not predictable. Formal quantification of proteinuria is therefore required in order to be able to assess relative change in pregnancy, particularly after 20 weeks' gestation when pre-eclampsia may develop (see sections 4.4.5 and 4.4.6), and in conditions where an increase in proteinuria may represent disease flare or progression.

Proteinuria in early pregnancy also predicts adverse fetal and maternal outcomes in women with CKD. The Torino-Cagliari Observational Study compared obstetric and renal outcomes in 504 women with CKD with 836 women without CKD. Proteinuria (>1g/24h) was an independent risk factor for preterm birth before 37 weeks' gestation (odds Ratio (OR) 3.65; 95% confidence interval (CI): 1.61-8.24) and 34 weeks' gestation (OR 4.81; 95% CI 1.48-15.66).[2] Adverse outcomes associated with proteinuria were corroborated in a systematic review and meta-analysis of 23 studies including 621 pregnancies in women with CKD.[3] This study showed that women with macroproteinuria (albuminuria ≥300 mg/24h or proteinuria ≥500 mg/24h) had an increased risk of pre-eclampsia (OR 13.76; 95% CI 8.02-23.63) and preterm birth (OR 5.19; 95% CI 3.21-8.40).

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Guideline 4.1.3

We recommend quantification of proteinuria is undertaken by protein:creatinine ratio (uPCR) or albumin:creatinine ratio (uACR). Twenty-four hour urine collection for quantification of protein is not required (1B).

Rationale

Dipstick testing of urine with reagent strips to detect proteinuria preferentially detects albumin. False positives occur with dehydration, exercise, infection and alkaline urine. False negatives occur with dilute urine, and non-albumin proteinuria. A systematic review of seven prospective studies showed that the sensitivity and specificity of a dipstick result of ≥1+ protein for predicting abnormal proteinuria in pregnancy

(>300mg/24h) ranges from 47-86% and 39-95% respectively, leading to the conclusion that the accuracy of dipstick urinalysis with a 1+ threshold in the prediction of significant proteinuria is poor.[1] However, automated dipstick urinalysis provides a more accurate screening test for the detection of proteinuria than visual testing in hypertensive pregnancies.[2]

24-hour urine collection is time-consuming and subject to inadequacies in collection.[3] Outside of pregnancy, uPCR and uACR are highly correlated with 24-hour urine collection and are more convenient in clinical practice.[4] Pregnant cohorts show a similar correlation between 24-hour urine protein excretion and both uPCR[5] and uACR[6]. A prospective multi-centre cohort study of 959 pregnant women after 20 weeks' gestation with hypertension and trace protein or more on urine dipstick found that both uPCR and uACR could be both used as rule out tests for preeclampsia with no additional benefit from 24-hour urine collection.[7]

There is on-going debate as to whether uPCR or uACR should be preferentially used for the quantification of proteinuria in pregnancy. In non-pregnant patients with CKD, uACR is the investigation of choice as it provides greater sensitivity at lower levels of proteinuria, although uPCR can be used as an alternative, particularly where uACR is 70mg/mmol or greater.[8] In contrast, uPCR is currently the most common test used to quantify proteinuria in pregnancy.[9] A single centre experience of 181 pregnant women without CKD showed that uACR and uPCR were highly correlated to each other, with equivalent performance in the prediction of adverse pregnancy outcomes.[10] More recent, larger, prospective cohort data from normal pregnancies show that although uACR and uPCR are comparable in performance, uACR had a significantly higher area under the receiver-operating curve (ROC) for the diagnosis of severe pre-eclampsia compared to local laboratory uPCR (ROC 0.89 versus 0.87, p=0.004). However it remains unclear whether this small absolute difference translates into significant clinical benefit. Cost effectiveness for uACR over uPCR was also suggested, although 95% confidence intervals for the incremental cost-effectiveness ratio crossed zero due to significant uncertainty and the small difference in incremental cost and quality added life years[7]. There are no published data on the predictive and/or diagnostic benefits of uACR compered to uPCR in pregnant women with CKD. It is therefore the consensus of the guideline group that the decision to use uACR or uPCR should be based on local obstetric experience ensuring a baseline measurement in early pregnancy in order to be able to recognise relative change in proteinuria in pregnancy. In women without pre-existing proteinuria, diagnostic performance equivalent to 30 mg/mmol of uPCR is achieved with a uACR cut-off of 8 mg/mmol.[7]

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4.2 Antenatal care

Guideline 4.2.1

We suggest pregnant women with CKD who have not had pre-pregnancy counselling by the MDT are referred to the MDT and receive the same counselling and optimisation as for women attending pre-pregnancy (2D).

Guideline 4.2.2

We recommend pregnant women with CKD receive routine antenatal care, in addition to specialist input (1D).

Guideline 4.2.3

We recommend pregnant women with CKD be referred for assessment by a consultant obstetrician (1D).

Guideline 4.2.4

We recommend pregnant women with CKD have access to usual trisomy screening with specialist interpretation of high-risk results (1C).

Guideline 4.2.5

We recommend women with CKD exposed to teratogenic drugs in the first trimester are referred to a specialist fetal medicine unit (1D).

Guideline 4.1.6

We recommend pregnant women with CKD have scans to assess fetal growth and wellbeing in the third trimester (1C).

Guideline 4.2.7

We recommend pregnant women taking prednisolone and/or calcineurin inhibitors are screened for gestational diabetes (1C).

Rationale

Women with CKD who present for the first time in pregnancy should have an opportunity for individualised risk counselling and optimisation of health for pregnancy. These women should therefore be referred to the MDT as early as possible in pregnancy to ensure that the same topics are covered as for women receiving pre-pregnancy counselling (see section 3.3). This reflects lessons learned from MBRRACE-UK (Mothers and Babies: Reducing Risk through Audit and Confidential Enquiries across the UK), which has identified maternal medical comorbidities to be significantly associated with maternal morbidity and mortality.[1,2]

There is no specific literature on the schedule of care for women with CKD. Women with CKD should be supported to access routine antenatal care, with increased surveillance in line with national guidance for antenatal care[3], and guidance on the management of hypertension in pregnancy.[4] A personalised care plan including a named midwife should be made[5], ensuring access to the specialist MDT. It is good practice that a consultant obstetrician reviews all women with CKD to help ensure that the most appropriate care pathway is identified.

Pathways for care for women with CKD in pregnancy should map to those agreed for the regional Maternal Medicine Network and Maternal Medicine Centre. If the Maternal Medicine Centre and the regional renal unit are not co-located (which was the case for 31% of responders to the consensus survey undertaken for this guideline) then the consultant obstetrician and consultant nephrologist should communicate regularly during the pregnancies of women with CKD, ensuring access to all notes and

results.

Women with CKD should be offered usual trisomy screening. If they have abnormal renal function, the pre-test counselling for combined screening using blood markers should include discussion of a potentially increased false positive rate as the multiple of the median may be increased for beta human chorionic gonadotrophin, though not for pregnancy associated plasma protein-A.[6] Other screening options such as the non-invasive prenatal testing of cell-free fetal DNA, either as a first line or subsequent to combined screening, currently depend upon local availability. Women with CKD and abnormal renal function should be referred to a specialist Fetal Medicine Unit for interpretation of positive results.

The care pathway should include determination of frequency of third trimester ultrasound for evaluation of fetal growth based on a woman's individualised risk assessment for fetal growth problems. In light of the known association between steroids and calcineurin inhibitors with impaired glucose metabolism[7], screening for gestational diabetes should be arranged for women taking these medications.

Options for maternity care, determined by the MDT, include:

- Advice regarding pregnancy care and delivery, with referral back to the local maternity unit
- Shared maternity care between the Maternal Medicine Centre and the local unit
- Maternal Medicine Centre to lead and deliver maternity care

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4.3 Pre-eclampsia prophylaxis

Guideline 4.3.1

We recommend women with CKD are offered low-dose aspirin (75-150mg) in pregnancy to reduce the risk of pre-eclampsia (1B).

Guideline 4.3.2

We suggest kidney donors are offered low dose aspirin (75mg-150mg) to reduce the risk of pre-eclampsia (2D).

Rationale

Women with CKD have an increased risk of pre-eclampsia compared to women without CKD[1] and should be offered pre-eclampsia prophylaxis with aspirin. This recommendation is generalised from high-quality evidence that low dose aspirin is associated with a reduced incidence of pre-eclampsia in other high-risk cohorts[2,3], although there is limited definitive evidence as to the optimal gestation and dose for women with CKD. A recent subgroup analysis of women with chronic hypertension from a randomised-controlled trial of 150mg aspirin (150mg) failed to show a reduction in the risk of subsequent pre-eclampsia, although these data are difficult to interpret in the absence of standardised diagnostic criteria for superimposed pre-eclampsia. Current national guidance recommends prescribing 75-150mg of aspirin from 12 weeks' gestation onwards[3,4], but future research may elucidate optimisation of prophylaxis in women with CKD.

Women who have donated a kidney are at increased risk of pre-eclampsia (odds ratio 2.4; 95% confidence intervals 1.0–5.6).[5] Pre-eclampsia prophylaxis with aspirin should be discussed with these women, particularly in the presence of other known risk factors as outlined in national guidelines.[4]

The benefit of calcium supplementation in reducing the prevalence of pre-eclampsia remains unclear. A Cochrane systematic review of randomised controlled trials showed that supplementation of a least 1g calcium per day was associated with a 55% reduction in pre-eclampsia, although the effect was mostly shown in smaller trials, with possible confounding by low dietary calcium intake.[6] In contrast, large randomised controlled trials of calcium supplementation starting both before[7] and after 20 weeks' gestation[8] have failed to show a benefit in reducing the incidence of pre-eclampsia. In the absence of evidence specific to women with CKD, and given the potential cardiovascular sequelae of a positive calcium balance in women with CKD[9,10], it was the consensus opinion of the guideline committee that calcium

supplementation to reduce the risk of pre-eclampsia cannot be recommended for women with CKD, based on current evidence.

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4.4 Blood pressure management

Guideline 4.4.1

We recommend that the target blood pressure during pregnancy for women with CKD is 135/85mmHg or less, which should be documented in the woman's healthcare record (1D).

Guideline 4.4.2

We suggest antihypertensive treatment in women with CKD is continued in pregnancy unless systolic blood pressure is consistently <110mmHg systolic, or diastolic blood is pressure consistently <70mmHg diastolic BP, or there is symptomatic hypotension (2D).

Guideline 4.4.3

We recommend labetalol, nifedipine and methyldopa can be used to treat hypertension in pregnancy (1B).

Guideline 4.4.4

We recommend angiotensin converting enzyme inhibitors, angiotensin receptor anatgonists and diuretics are not used to treat hypertension in pregnancy (1B).

Guideline 4.4.5

We recommend a diagnosis of superimposed pre-eclampsia is considered:

- in a woman with non-proteinuric CKD, if she develops new hypertension (systolic BP >140mmHg and/or diastolic BP >90mmHg) and proteinuria (uPCR >30mg/mmol or uACR >8mg/mmol) or maternal organ dysfunction after 20 weeks' gestation (1B).
- in a women with proteinuric CKD if she develops new hypertension (systolic BP >140mmHg and/or diastolic BP >90mmHg) or maternal organ dysfunction after 20 weeks' gestation (1B)
- in a women with chronic hypertension and proteinuria, if she develops maternal organ dysfunction after 20 weeks' gestation (1B).

Guideline 4.4.6

We suggest in women with chronic hypertension and proteinuria that the development of sustained severe hypertension (systolic BP >160mmHg and/or diastolic BP >110mmHg or doubling of antihypertensive agents) and/or a substantial rise in proteinuria (doubling of uPCR or uACR compared to early pregnancy) should prompt clinical assessment for superimposed pre-eclampsia (2D).

Guideline 4.4.7

We suggest a role for angiogenic markers (PlGF±sFlt-1) is considered as an adjunct to diagnose superimposed pre-eclampsia, dependent upon on-going research in women with CKD (2C).

Rationale

There is no evidence on treatment initiation thresholds or blood pressure targets in pregnancy for women with CKD. Randomised controlled trial data from women with non-proteinuric hypertension demonstrate that tight blood pressure control (aiming for a diastolic BP of 85mmHg) reduces severe maternal complications, with no evidence of perinatal harm.[1] Evidence from systematic reviews has shown that beta blockers (such as labetalol) and calcium channel blockers (such as nifedipine) appear to be more effective than methyldopa in avoiding an episode of severe hypertension (RR 0.70; 95% CI 0.56 to 0.88; 11 trials, n=638).[2] Antihypertensive agents such as ACE inhibitors, angiotensin receptor blockers and diuretics should be avoided in pregnancy due to potential for fetal harm (see section 2). In women who have been maintained on these antihypertensive agents whilst waiting to conceive, they should be switched to labetalol or nifedipine (or a suitable alternative) within two days of notification of pregnancy.[3]

Making the diagnosis of superimposed pre-eclampsia is complex in women with chronic kidney disease, particularly in the presence of pre-existing proteinuria and/or hypertension as these two signs are part of the diagnostic criteria for pre-eclampsia. Appearance of a new feature and/or the development of maternal organ dysfunction (Box 1) should lead to a diagnosis of preeclampsia being considered. Proteinuria is usually a feature of pre-eclampsia; however it is not required for diagnosis where there is other maternal organ dysfunction.[4] Although it is recognized that gestational rises in blood pressure or protein excretion may occur, sudden and substantial change in these parameters in a woman with CKD should prompt her clinicians to evaluate her for a diagnosis of superimposed pre-eclampsia.

Box 1: Maternal organ dysfunction in pre-eclampsia. Adapted from[4]

- New proteinuria (uPCR>30mg/mmol or ACR >8mg/mmol)
- AKI (serum creatinine ≥90µmol/L in a woman with previously normal creatinine concentrations)
- Liver involvement (alanine aminotransferase or aspartate aminotransferase >40 IU/L) with or without right upper quadrant or epigastric pain
- Neurological complications (eclampsia, altered mental status, blindness, stroke, clonus, severe headache, persistent visual scotomata)
- Hematological complications (platelet count <150,000/µL, disseminated intravascular coagulation, hemolysis)
- Uteroplacental dysfunction (fetal growth restriction, abnormal umbilical artery Doppler wave form analysis, stillbirth

National guidelines recommend the use of placental growth factor-based testing (e.g. Triage placental growth factor (PlGF) test or the Elecsys immunoassay soluble fms-like tyrosine kinase 1 (sFlt-1)/PlGF ratio), alongside standard clinical assessment and subsequent clinical follow-up, to help rule-out pre-eclampsia in women presenting with suspected pre-eclampsia between 20 weeks and 34 weeks plus 6 days of gestation.[5] These tests have high sensitivity and negative predictive value for the diagnosis of pre-eclampsia and the need for delivery within 14 days in general obstetric cohorts[6,7]; use of revealed PlGF testing halves the time to diagnosis of pre-eclampsia and reduces severe maternal adverse outcomes.[8] PlGF-based testing has been reported to have similar diagnostic utility in small cohorts of women with CKD.[9,10]

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4.5 Venous thromboembolism

Guideline 4.5.1

We recommend that women with nephrotic-range proteinuria (uPCR>300mg/mmol or ACR >250mg/mmol) be offered thromboboprophylaxis with low molecular weight heparin in pregnancy and the post-partum period unless there is a specific contraindication including risk of labour or active bleeding (1D).

Guideline 4.5.2

We suggest that non-nephrotic range proteinuria in pregnancy is a risk factor for thrombosis and thromboprophylaxis with low molecular weight heparin should be considered in the presence of additional risk factors (2D).

Rationale

The guideline committee endorses the assessment and management of VTE risk in women with CKD according to guidance from the Royal College of Obstetricians and Gynaecologists (RCOG) which states that all pregnant women undergo a documented assessment of risk factors for venous thromboembolism.[1] Nephrotic syndrome is included as a significant risk factor in RCOG guidance with thromboprophylaxis offered to women with nephrotic syndrome in the third trimester and post-partum in the absence of other risk factors. However, there is inherent difficulty in making the diagnosis of nephrotic syndrome in pregnancy as physiological adaptation to pregnancy includes increased proteinuria, a fall in serum albumin concentrations, and peripheral oedema. Gestation specific thresholds for proteinuria and serum albumin for the diagnosis of nephrotic syndrome in pregnancy have not been established. This guideline therefore opts to use the Renal Association threshold for nephrotic range proteinuria (uPCR>300mg/mmol or ACR >250mg/mmol) to define high-risk proteinuria in pregnancy for which there is expert consensus that thromboprophylaxis is warranted in pregnancy and the post-partum period in the absence of other risk factors (with risk reassessed at 6 weeks post-partum).

There is also consensus, but insufficient evidence, that sub-nephrotic levels of proteinuria confer a risk of thrombosis although the threshold level of proteinuria at which the risk of VTE is clinically significant remains unknown. Consequently, thromboprophylaxis in women with CKD varies across the UK and internationally. There are anecdotal data that regions with a higher threshold for thromboprophylaxis

do not report many/any thrombotic events attributable to proteinuria alone. In contrast, clinicians with a lower threshold for recommending thromboprophylaxis accept the compromise that maternal morbidity and mortality from thrombosis justifies the number needed to treat. In the light of this uncertainty, the guideline committee suggest that non-nephrotic range proteinuria (uPCR>100mg/mmol or uACR>30mg/mmol) be considered a risk factor for thrombosis and thromboprophylaxis with low molecular weight heparin be offered in the presence of additional risk factors. Recognised risk factors include gestation, other medical comorbidity (including active lupus), age, BMI, parity, smoking, gross varicose veins, pre-eclampsia, assisted reproduction, operative delivery, post-partum haemorrhage, still-birth, hyperemesis, infection, and immobility.[1] Renal disease aetiology, the trajectory of proteinuria and serum albumin concentrations may also inform the decision to offer thromboprophylaxis, although specific guidance on these factors is not possible due to insufficient evidence.

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4.6 Anaemia

Guideline 4.6.1

We recommend pregnant women with CKD are given parenteral iron if indicated (1C).

Guideline 4.6.2

We recommend erythropoietin-stimulating agents are given if indicated in pregnancy (1C).

Rationale

Gestational increases in plasma volume are higher than the corresponding increase in red blood cell mass, leading to haemodilution and lower haemoglobin levels in pregnancy. The lower reference limit for haemoglobin concentrations in pregnancy is 105g/L-110g/L depending on gestation[1,2], with values <85g/L associated with an estimated 62% increase in the risk of low birth weight (<2,500 g) and a 72% increase in the risk of preterm delivery before 37 weeks, across ethnic groups.[3].There are no data to guide the optimum target haemoglobin for women with CKD in pregnancy.

The most common cause of anaemia in pregnancy is iron deficiency, which is estimated to affect greater than 40% of pregnancies.[4] Markers of iron deficiency

include ferritin (<100µg/L), transferrin saturation (<20%), hypochromic red cells (>6%) and reticulocyte haemoglobin content (<25pg), although the specificity and sensitivity of these markers in pregnancy are unknown.[5] Oral iron is cheap and accessible, although the intravenous route may offer better bioavailability and tolerability in pregnancy, in women with CKD.[6] Parenteral iron is considered safe in pregnancy and breastfeeding[7-10], although there is a paucity of safety data on exposure in the first trimester.

Erythropoietin concentrations increase approximately two-fold during pregnancy.[11] As women with CKD may have insufficient capacity for a gestational increase in erythropoietin, supplementation with synthetic erythropoietin may be required, even in the context of mild or moderate renal impairment. For women who required erythropoietin prior to pregnancy, an increased dose requirement should be anticipated during pregnancy. As erythropoietin is a large molecule that does not cross the placental barrier, its use is considered safe in pregnancy and breastfeeding[12,13]; however, a theoretical risk of exacerbating pre-existing or new-onset hypertension exists.

Hypoxia-inducible factor (HIF) activators are an emerging class of drugs with a therapeutic role in the management of renal anaemia. However, the small size of these molecules potentially enables placental transfer, and HIF has multiple direct and indirect effects on developmental and physiological processes.[14] No formal recommendation has been made for the use of this class of drug in pregnancy, but on the basis of their molecular characteristics, the guideline committee would not recommend their use at conception or in pregnancy and lactation.

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4.7 Bone health

Guideline 4.7.1

We recommend women with CKD who are vitamin D deficient be given vitamin D supplementation in pregnancy (1B).

Guideline 4.7.2

We recommend calcimimetics are discontinued in pregnancy (1D).

Guideline 4.7.3

We recommend non-calcium based phosphate binders are discontinued in pregnancy (1D).

Rationale

Vitamin D deficiency is estimated to affect 13–64% of pregnant women[1] and is associated with increased incidences of pre-eclampsia and gestational diabetes. Although studies of the benefit of vitamin D on pregnancy outcome are inconsistent, meta-analysis demonstrates that oral vitamin D supplementation is associated with reduced risks of pre-eclampsia, low birth weight and preterm birth.[2,3] Optimal serum calcifediol (25(OH)-vitamin D) levels and optimal doses of colecalciferol and ergocalciferol are unknown. It is the clinical practice of the guideline committee to check serum calcifediol levels in pregnancy, and offer replacement (colecalciferol 20,000iu per week) until serum calcifediol is >20 ng/ml (>50 nmol/L). Although calcifediol is the major circulating form of vitamin D, it has low biological activity until converted to calcitriol ($1,25(OH)_2$-vitamin D). Serum calcitriol levels are approximately threefold higher in the first trimester and 5-6 times higher in the third trimester compared with those in non-pregnant women.[4] To what extent this increase is dependent on the 1α-hydroxylase enzyme activity in the kidney is unknown, as the enzyme is also found in colon, skin, macrophages and the placenta. In the absence of better evidence, the guideline committee suggests that, once serum calcifediol levels are replete, activated vitamin D analogues (alfacalcidol, calcitriol) can be continued in pregnancy at a dose that would be considered appropriate for maintenance treatment outside of pregnancy. For women with CKD who do not require activated analogues, a maintenance daily dose of vitamin D 400-1000iu can be given in pregnancy, depending on ethnicity and body mass index.

Calcimemtics (cinecalcet, etelcalcitide) and non-calcium phosphate binders (sevelamer hydrochloride, lanthanum carbonate) have insufficient safety data in pregnancy and should therefore be discontinued in advance of pregnancy and during lactation.

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4.8 Renal biopsy

Guideline 4.8.1

We recommend if a histological diagnosis will change management in pregnancy then renal biopsy can be performed in the first and early second trimester of pregnancy (1C).

Rationale

Published data on antenatal renal biopsy are limited by heterogeneity and cohort size. The most commonly described risk is bleeding. Contributory factors are thought to include the increased renal blood flow in pregnancy and the technical difficulty in performing a renal biopsy in the standard prone position at later gestations. A systematic review on renal biopsy in pregnancy including 39 studies published between 1980 and 2012, examined 243 antenatal biopsies compared with 1236 postpartum biopsies.[1] This showed that the risk of renal biopsy complications was significantly higher in antenatal biopsies compared with those postpartum (7% vs 1%, p=0.001). Complications, including macroscopic haematuria, perirenal haematomata, and the need for blood transfusion were described between 23-28 weeks' gestation. No serious complications occurred prior to 22 weeks' gestation.

Women who undergo renal biopsy in pregnancy have histological diagnoses spanning the spectrum of glomerular disease[2], although treatment options may be limited in pregnancy due to the teratogenicity and/or fetal toxicity of available treatments.[3] A change in management based on the results of a renal biopsy in pregnancy was reported in 39/59 (66%) of women.[1]

The decision to undertake renal biopsy in pregnancy must balance the increased risk of bleeding, the likelihood of a change in management based on the biopsy result, and the risks of either iatrogenic preterm delivery or a delay in management until a biopsy can be performed post-partum. It is the consensus of the guideline group that renal biopsy in pregnancy should be performed by the most experienced clinician available, under ultrasound guidance.

References

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4.9 Peripartum care

Guideline 4.9.1

We recommend women with CKD receive routine peripartum care, with additional specialist input (1D).

Guideline 4.9.2

We recommend women with CKD have observations taken and documented during any hospital admission. This includes temperature, heart rate, blood pressure, respiratory rate, and oxygen saturation. An early warning score should be calculated and actioned appropriately (1D)

Guideline 4.9.3

We recommend additional assessment for women with an elevated early warning score, for women considered to be high-risk, and for any women in whom there is any clinical concern. This includes examination of jugular venous pressure, lung auscultation and urine output monitoring (in-dwelling catheter not usually required) in addition to routine parameters (1D).

Rationale

The guideline committee endorses existing guidelines on Intrapartum Care for Healthy Women and Babies[1], Intrapartum Care for Women with Existing Medical Conditions or Obstetric Complications and their Babies[2], and recommendations from the Royal College of Anaesthetists on the care of the critically ill pregnant woman.[3]

Failure to recognise the signs of illness in obstetric patients is a recurrent feature of cases of maternal morbidity and mortality.[4-6] The use of early warning systems is established in non-obstetric acute care settings. Although evidence linking implementation of obstetric early warning scores to improved pregnancy outcomes is limited, recent ethnographic research shows that a modified obstetric early warning score is valuable in structuring the surveillance of hospitalised women with an established risk of morbidity.[7] At present, there are variation in obstetric early warning score thresholds used in the UK and the guideline committee endorses the view of the Royal College of Anaesthetists that there should be a move towards a national early warning system, modified for obstetrics.[3] It is hoped that the on-going Pregnancy Physiology Prediction Pattern study[8] will add valuable, gestation-specific, normal distribution data for physiological parameters in pregnancy, and inform trigger thresholds for future validation. Pregnant women demonstrate a capacity for physiological compensation before a potentially rapid deterioration. It was the consensus opinion of the guideline committee that an elevated early warning score in obstetrics should therefore trigger early senior review. The principle of a maternity warning score is intuitively sound, but should not overrule clinical judgement, hence

the recommendation for detailed assessment of any woman in whom there is any clinical concern.

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Guideline 4.9.4

We recommend women with CKD at risk of volume depletion or volume overload are highlighted by the MDT in advance of delivery (1D).

Guideline 4.9.5

We recommend that fluid balance is managed with the aim of maintaining normal fluid

volume, avoiding dehydration and pulmonary oedema, with input from clinicians with expertise in fluid balance and renal disease (1D).

Guideline 4.9.6

We recommend all clinicians are aware of the increased risk of pulmonary oedema in women with CKD and pre-eclampsia (1D).

Rationale

It is the experience of the guideline committee that fluid management for women with CKD is often complex and needs to be tailored to the individual. Women at risk of either volume depletion or fluid overload should be highlighted in advance of delivery to ensure that clinical review of fluid state is undertaken prior to being prescribed intravenous fluids, or the institution of a fluid restriction. On-going fluid balance review should then be performed during labour and in the immediate post-partum period with the aim of euvolaemia and the avoidance of both pulmonary oedema and superimposed kidney injury. Fluid balance assessment should be undertaken by a competent clinician with an understanding of the haemodynamic changes in pregnancy and the puerperium. This may include nephrologists, anaesthetists, obstetric physicians, and maternal medicine specialists.

The guideline committee endorses the NICE guideline on hypertension in pregnancy for the management of pre-eclampsia in pregnancy.[1] The risk of pre-eclampsia is higher in all stages of CKD compared to women without CKD.[2] Pre-eclampsia is complicated by capillary leak, reduced plasma oncotic pressure, and either reduced or increased cardiac output.[3–5] The complexity and dynamic nature of pre-eclampsia mean that there should be a plan in place for regular fluid balance review by a competent clinician with expertise in CKD and pre-eclampsia. The aim of fluid balance in pre-eclamspia is euvolaemia. Insensible losses should then be replaced (30 ml/hr) along with anticipated urinary losses (0.5–1 ml/kg/hr), whilst limiting overall fluid intake to 80–100 ml/hr to avoid the risk of pulmonary oedema.[6]

References

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Guideline 4.9.7

We recommend the timing of birth for women with CKD is determined by obstetric indications, with consideration of renal factors including deteriorating renal function, symptomatic hypoalbuminaemia, pulmonary oedema, and refractory hypertension (1D).

Rationale

In women with CKD mode and timing of birth is usually determined by obstetric factors. Where maternal complications arise, clinicians must balance the competing risks of preterm delivery and maternal wellbeing. Potential maternal complications, which may inform the decision for iatrogenic preterm delivery in women with CKD, include loss of maternal renal function, symptomatic nephrotic syndrome including pulmonary oedema, and refractory hypertension. If maternal complications develop before 34 weeks' gestation, attempts should be made to continue the pregnancy if possible, due to the reduction in adverse neonatal and developmental outcomes at gestations of 34 weeks' gestation and more[(1)], although this decision will depend upon maternal wellbeing and the availability and likely success of medical management options. The guideline committee acknowledges that the diagnosis of superimposed kidney injury is difficult in pregnancy due to gestational variation in serum creatinine concentrations, possible underlying disease progression, and an unpredictable physiological response to pregnancy in CKD. In women without CKD, serum creatinine concentrations fall to a nadir in the second trimester before rising back towards pre-pregnancy levels at term.[(2)] The guideline committee therefore suggest that women with serum creatinine concentrations in pregnancy that are greater than pre-pregnancy concentrations warrant discussion with and/or assessment by the MDT.

There is no evidence that mode of delivery affects maternal renal function. Mode of delivery should therefore be based on obstetric indications and maternal preference according to guidance in women without CKD.[(3)]

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4.10 Postnatal care

Guideline 4.10.1

We recommend that non-steroidal anti-inflammatories should not be given (1C).

Rationale

Given that the risk of renal side effects from short-term use of non-steroidal anti-inflammatory drugs in patients without pre-existing risk factors is considered to be rare, NSAIDs are currently recommended in the postpartum period for perineal pain when paracetamol provides insufficient relief of symptoms.[1] Although the risk profile of non-steroidal anti-inflammatory drugs is considered to be different in CKD, evidence supporting this is mixed. Historical case-control studies[2,3] show an increased rate of kidney injury and progression to end stage renal disease in patients taking non-steroidal anti-inflammatory drugs. In contrast, data from older-age cohorts taking high-dose NSAIDS are conflicting,[4-6] Questionnaire data from a female cohort showed no measurable association between NSAID use and renal function decline over 11 years, although the mean eGFR at study commencement was 88ml/min/1.73m^2.[7] There are no data examining non-steroidal anti-inflammatory drug use in women of reproductive age with risk factors for renal disease progression, in the context of peripartum haemodynamic change. The guideline committee therefore endorses existing recommendations that NSAIDs should be contraindicated in women with a (pre-pregnancy) eGFR <30mls/min/1.73m^2 (estimated to be equivalent to serum creatinine >150µmol/L in pregnancy) [8-9], and should be avoided where possible in all those with renal impairment due to the possibility of sodium and water retention and a deterioration in renal function.[8]

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Guideline 4.10.2

We recommend women with CKD have a planned early postpartum renal review (1D).

Rationale

There are no published data to guide post-partum surveillance on women with CKD. Whilst guidelines for the management of CKD do not require follow up secondary care for all patients, every woman with suspected kidney disease (acute or chronic) newly identified in pregnancy and all those with known CKD should have a clear plan in place for appropriate postpartum follow up.[1-3] Timing of postpartum follow-up should be determined by the MDT, guided by the level of and change in renal function, the aetiology of CKD, blood pressure, and the need for post-partum therapeutic drug monitoring. For women who are thought to have previously undiagnosed CKD in pregnancy, post-partum renal review should be arranged in order to facilitate diagnosis. This may not have been possible in pregnancy if a biopsy was not done, or due to difficulties interpreting renal function in the context of gestational change or in the face of superimposed preeclampsia. Appropriate treatment should be advised and a pathway for long-term care made clear both to the patient and her primary care physician. The key is to avoid women being lost to follow-up and presenting years later with what might have been avoidable, progressive kidney disease.

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Guideline 4.10.3

We recommend that women with CKD are prescribed medications that are compatible with breastfeeding whenever possible (1D).

Rationale

Women with CKD should be supported in their wish to breastfeed and be prescribed medications which are considered safe in lactation (see section 2) Currently, breastfeeding is not advised for infants of mothers taking mycophenolate mofetil as there are no data to confirm safety. If mycophenolate mofetil is deemed to be the only therapeutic option, then breastfeeding should be avoided.

Guideline 4.10.4

We recommend that women with CKD are offered safe and effective contraception post-partum and receive updated pre-pregnancy counselling before future pregnancies (1D).

Rationale

The provision of information and a choice regarding contraceptive method within seven days of delivery has been set as a quality standard in the UK, addressing a priority area for quality improvement in health and social care.[1] Safe and effective methods of contraception in women with CKD are detailed in section 3.1.3.

Events during pregnancy including obstetric complications, the development of superimposed pre-eclampsia, and a decline in maternal renal function will inform future obstetric risk, necessitating the need for new pre-pregnancy counselling to ensure informed decision-making regarding future pregnancy.

References

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5. Specific conditions

5.1 Renal transplantation

Guideline 5.1.1

We recommend women with renal transplants wait until their kidney function is stable on medications that are safe in pregnancy before conceiving, which is usually more than one year after transplantation (1D).

Rationale

Pregnancy rates are lower in women of reproductive age with renal transplants compared to the general population.[1-2] It is unclear whether this is due to reduced fertility or patient choice. Women with renal transplants usually have successful pregnancy outcomes, but maternal and neonatal complications remain higher compared to the general population.[3] A prospective UK cohort study of 105 pregnancies in 95 women with renal transplants compared with 1360 healthy controls, showed an increased risk of pre-eclampsia (adjusted odds ratio (aOR)=6.31), induction of labour (aOR=2.67) caesarean delivery (aOR=4.57), preterm delivery <37 weeks (aOR=12.57) and <32 weeks (aOR=4.15), and small for gestational age babies (aOR=2.92).[4]

There are few data supporting timing of pregnancy in women with renal transplants. Older reports suggested that a shorter interval from transplant to pregnancy was associated with worse pregnancy outcomes.[5-6] However, a meta-analysis of studies with mean transplant-to-pregnancy intervals of <2 years (3 studies), 2–3 years (10 studies), 3–4 years (14 studies) and >4 years (14 studies) concluded that a shorter time from transplant to conception was associated with a higher live birth rate and lower miscarriage rate, although rates of pre-eclampsia, gestational diabetes, caesarean section, and preterm birth were higher.[3] Impact of pregnancy on graft function related to the interval between transplantation and conception is variably reported. A recent study of Medicare data demonstrated that graft loss was significantly higher in women who conceived within two years of transplantation, but those who waited three years or more were not at greater risk of graft lost than women who did not have pregnancies.[7]

European Best Practice Guidelines (2001) recommended a delay of 24 months between transplantation and conception[8], but American guidelines (2005) subsequently advised 12 months if stable graft function.[9] Standard immunosuppression regimens in the UK routinely include mycophenolate mofetil in the first year after transplantation.[10] Due to the teratogenicity of mycophenolate mofetil, switching to alternative agents is recommended before pregnancy (see section 2), thus at least a year after transplantation is advised before attempting to conceive.

Other factors to consider regarding timing of pregnancy include recent episodes of rejection, stability and level of graft function, presence of cytomegalovirus, maternal

age, diabetes and blood pressure control, but direct evidence regarding impact of these factors on pregnancy and graft outcomes is limited.

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Guideline 5.1.2

We recommend that plans for delivery in a woman with a renal transplant are discussed with the local surgical transplant team (1D).

Guideline 5.1.3

We recommend that mode of delivery in women with renal transplants is based on obstetric indications and maternal preference (1D).

Guideline 5.1.4

We recommend that caesarean delivery in a woman with a renal transplant patient is performed by the most senior obstetrician available, ideally a consultant (1D).

Guideline 5.1.5

We recommend that women with kidney-pancreas transplants, kidney-liver transplants, and dual kidney transplants are managed during pregnancy and delivery by a multidisciplinary team including transplant physicians and surgeons, at a transplant centre (1D).

Rationale

The majority of women with renal transplants have caesarean deliveries.[1] However, renal transplantation is not a contraindication for vaginal delivery. Caesarean section is associated with increased bleeding risk, thromboembolism, infection, surgical complications (for example, ureteric injury) and renal transplant injury has been reported.[2] Vertical skin incision prior to horizontal uterine incision can theoretically be used to reduce the risk of allograft injury, although there are no data on the relative benefits and long-term outcomes of this technique.

Dual organ transplants are associated with higher rates of adverse pregnancy outcomes.[3] A small cohort study demonstrated increased rates of urinary tract obstruction in women with intraperitoneal grafts.[4] The complex anatomy of dual transplants is such that the guideline committee recommends management and delivery at a transplant centre whenever possible.

References

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5.2 Dialysis

Women receiving maintenance dialysis before pregnancy

Guideline 5.2.1

We recommend women established on dialysis prior to pregnancy receive pre-pregnancy counselling including the options of postponing pregnancy until transplantation (when feasible) and the need for long frequent dialysis prior to and during pregnancy (1C).

Guideline 5.2.2

We recommend women established on haemodialysis prior to pregnancy receive long, frequent haemodialysis either in-centre or at home to improve pregnancy outcomes (1C).

Guideline 5.2.3

We suggest women receiving haemodialysis during pregnancy have dialysis dose prescribed accounting for residual renal function, aiming for a pre-dialysis urea <12.5mmol/l (2C).

Guideline 5.2.4

We recommend women established on peritoneal dialysis prior to pregnancy should convert to haemodialysis during pregnancy (1D).

Rationale

Reported pregnancy outcomes for renal transplant recipients remain better than for dialysis recipients, and advice to wait for a renal transplant prior to pregnancy is appropriate for most women with established end stage renal disease.[1].

Evidence for the management of pregnancy in women receiving dialysis is limited to observational cohort studies, and prone to publication bias. Nevertheless, cohort studies and meta-analysis show an association between increased dialysis provision and improved fertility and pregnancy outcomes.[2–6] A cohort of women who received 48±5 hours of dialysis per week had a conception rate of 32 pregnancies per 1000 women/year compared with 5 per 1000 women/year in a separate cohort receiving fewer than 20 hours of dialysis per week.[2,7] Dialysis in pregnancy for 37-56 hour/week compared to fewer than 20 hours/week also resulted in a higher live birth rate (85% versus 48%), higher median gestational age at delivery (38 weeks versus 28 weeks) and a greater median birth weight (2600g versus 1800g).[4]

It is acknowledged that achieving 48±5 hours/week dialysis is not feasible for many women or dialysis centres in the UK. An alternative approach is an increase in haemodialysis provision guided by biochemical parameters. A retrospective observational study of 28 pregnancies in women on haemodialysis compared successful pregnancies in which the baby survived to one year with unsuccessful

pregnancies. Despite no overall difference in weekly dialysis hours between groups (19.2±3.3 versus 16.3±4.3 hours/week), maternal urea was measurably lower in the pregnancies with successful outcomes (16.2mmol/L versus 23.9mmol/L). In addition, maternal urea showed a negative correlation with both birth weight and gestation at delivery with a maternal serum urea <17.5mmol/L (48mg/dL) correlating with delivery after 32 weeks' gestation and birth weight greater than 1500g.[8] A graded increase in dialysis guided by residual renal function and biochemical parameters was also reported by Luders *et al.* Weekly hours of haemodialysis were initially prescribed according urine output (1L), time on dialysis prior to pregnancy (1 year) and weight (70kg), then increased according to mid-week pre-dialysis serum urea, blood pressure, weight gain, polyhydramnios and uraemic symptoms. Mean weekly dialysis was 17.6±2.9 hours/week. Multivariable linear regression identified a midweek pre-dialysis serum of urea 12.5mmol/L (BUN 35mg/dL) as discriminatory in determining successful pregnancy outcome. The use of Kt/V or equivalent renal clearance has not been validated in pregnancy and should not be used as measure of dialysis adequacy in pregnancy.[9] Expert consensus is that clinical assessment of the ultrafiltration target is performed at least weekly, in order to accommodate anticipated weight-gain in pregnancy of 300 g/week during the second trimester and 300–500 g/week in the third trimester,[9] with a post-dialysis blood pressure target <140/90mmHg, whilst avoiding intradialytic hypotension <120/70mmHg.[10]

The provision of long, frequent haemodialysis has implications for electrolyte and nutritional provision and pregnant women on dialysis should have access to nutritional assessment and dietary counselling. Nutritional support is considered in many publications on dialysis in pregnancy, although data are diverse with different nutrients reported across the various studies, and no consensus in the vitamins and microelements that should be routinely monitored.[9] Expert consensus is that diet of women receiving long, frequent haemodialysis should be unrestricted and rich in protein (1.5-1.8g/kg IBW/day[10]). Electrolytes including magnesium and calcium-phosphate balance should be monitored every 1-2 weeks.[10] Dialysate concentrations of potassium, calcium and phosphate may need to be increased. Magnesium supplementation may be required. Dialysate losses of folic acid and water-soluble vitamins need to be considered, with increased supplementation as required, including high-dose folic acid (5mg) pre-pregnancy (whenever possible) and in the first trimester.

There are inadequate data to confirm the efficacy, safety and equivalence of peritoneal dialysis in supporting pregnancy, compared to enhanced haemodialysis. A systematic review of 38 pregnancies in women receiving peritoneal dialysis prior to pregnancy reported fetal survival in 83% of pregnancies, with 39% delivering prior to 34 weeks and 65% of babies being small for gestational age.[5] Continuing peritoneal dialysis may be considered in the context of vascular access difficulties, logistical barriers to frequent haemodialysis and good residual renal function. Alternatively, a

combined approach of peritoneal dialysis supplemented by intermittent haemodialysis during pregnancy has been reported.[11,12]

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Initiating dialysis during pregnancy

Guideline 5.2.5

We suggest haemodialysis should be initiated in pregnancy when the maternal urea concentration is 17-20mmol/L and the risks of preterm delivery outweigh those of

dialysis initiation. Gestation, renal function trajectory, fluid balance, biochemical parameters, blood pressure and uraemic symptoms should be considered in addition to maternal urea concentration (2D).

Rationale

The guideline committee acknowledges that there are inadequate data to produce evidence-based recommendations for the initiation of dialysis during pregnancy. However a specific request from the UK renal community was received, for expert, opinion-based practice.

In pregnancy, concern regarding the fetotoxicity of urea is likely to precede maternal indications for dialysis, which are the same as outside of pregnancy: refractory hyperkalaemia, acidosis and/or fluid overload, and uraemic symptoms that impact upon daily living.[1] A recommendation to initiate dialysis when maternal urea concentration is greater that 17mmol/l is extrapolated from historical, observational data reporting high rates of fetal death in women with this level of renal dysfunction[2,3], although these data also reflect obstetric and renal practice from over 50 years ago. Contemporary practice is variable: from routine commencement of dialysis at a maternal urea above 17mmol/L[4], to consideration of dialysis only when the urea is consistently above 20mmol/L.[5] In addition to maternal serum biochemistry, fetal health (including growth profile and polyhydramnios) and maternal wellbeing (including fluid balance, biochemistry, blood pressure and nutrition) will influence initiation of dialysis in pregnancy. It was the consensus of the guideline committee that in the context of deteriorating renal function, a serum urea above 15mmol/L should initiate conversations about the risks, benefits and logistics of dialysis initiation in pregnancy, weighed with the risks of preterm delivery before dialysis initiation if the gestation is approaching or more than 34 weeks.

Residual renal function is hypothesised to contribute to improved pregnancy outcomes in women commencing dialysis during pregnancy, compared to women established on dialysis prior to pregnancy[6] and intensification of dialysis in pregnancy has not been shown to confer the same benefit in women initiating dialysis in pregnancy as it does for women established on haemodialysis prior to pregnancy.[5] Meta-analysis data demonstrating improved outcomes with intensification of dialysis do not include women starting dialysis after 20 weeks' gestation and cannot be generalised.[7] In the absence of evidence for intensive haemodialysis in women newly commencing dialysis in pregnancy, the guideline committee advocates a 'gentle' start to new dialysis in pregnancy (for example 2 hours, three times per week) with titration according to biochemical parameters and maternal and fetal wellbeing.

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5.3 Lupus nephritis and vasculitis

Guideline 5.3.1

We recommend that women with lupus or vasculitis should be advised to wait until their disease is quiescent for at least 6 months before conceiving (1B).

Rationale

Data from systematic reviews and a meta-analysis consistently report that having active lupus nephritis is associated with adverse pregnancy outcomes.[1,2] In addition, prospective studies have recently demonstrated that having quiescent disease is associated with good pregnancy outcomes in the majority of women with lupus nephritis.[3-5] The 2017 European League Against Rheumatism (EULAR) guideline recommends pre-pregnancy counselling for women with SLE to allow risk stratification and highlights active lupus nephritis, history of lupus nephritis, and the presence of antiphospholipid antibodies as major risk factors in pregnancy.[6] Quiescence is also required to enable the optimisation of medications prior to pregnancy.[7] Currently, induction therapy for acute lupus nephritis involves the use of teratogenic agents, namely cyclophosphamide or mycophenolate mofetil, and mycophenolate mofetil is favoured for maintenance therapy. Women should discontinue these medications three months prior to conception (see section 2) and in most cases need to be established on azathioprine for maintenance.[8] Additionally, women need to know

which medications should be established pre-pregnancy (for example, hydroxychloroquine), and ensure that their blood pressure is controlled.

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Guideline 5.3.2

We recommend that all women with lupus should be advised to take hydroxychloroquine in pregnancy unless it is contraindicated (1C).

Rationale

The guideline committee recommends that all patients with lupus should take hydroxychloroquine in pregnancy, endorsing EULAR[1–3] and British Society of Rheumatology (BSR)[4] guidance. In women with anti Ro antibodies, retrospective case-control data show the use of hydroxychloroquine is associated with a reduction in the risk of congenital heart block (OR=0.28; 95% CI 0.12-0.63)[5], including in the offspring

of women with previously affected infants (OR=0.23; 95% CI 0.06-0.92).[6] Hydroxychloroquine is associated with a lower risk of lupus flare.[4, 7] A recent prospective study has demonstrated that hydroxychloroquine is associated with less fetal growth restriction.[8]

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Guideline 5.3.3

We recommend that women with lupus be monitored for disease activity during pregnancy (1D).

Rationale

The guideline committee endorses EULAR and BSR guidance[1,2] that women should be monitored for symptoms and signs of clinical lupus flare. Optimal frequency of monitoring in pregnancy is not adequately addressed in current literature.[3] EULAR recommends that there is an assessment of lupus activity at every visit during pregnancy and that renal function is checked every 4-8 weeks, and in suspected flare.[1] Given the risk of lupus flare in pregnancy and the post-partum period, it is the opinion of the guideline committee that clinical assessment for possible flare including symptoms and urine testing should be performed opportunistically at all health care attendances during pregnancy. Increased surveillance for women with new or worsening clinical manifestations, those with serologically active disease, women with a recent change in treatment, and in any woman in whom there is clinical concern should be undertaken by the MDT, or by a clinician with expertise in managing lupus in pregnancy. Serology can be checked, but clinicians need to be aware that complement levels may rise in pregnancy so a fall within the normal range can herald a flare in pregnancy. There are pregnancy specific modifications for both BILAG2004 and SLEDAI scoring systems, which assess disease activity. Distinguishing a flare of lupus nephritis from preeclampsia can be challenging.[4] The MDT should oversee the care of all women with lupus nephritis during pregnancy due to the complexities of diagnosis, combined with the need for early recognition and timely therapy to maintain maternal and fetal health.

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Guideline 5.3.4

We recommend that women who are positive for anti-Ro (SSA) or anti-La (SSB) antibodies be referred for fetal echocardiography in the second trimester (1C).

Rationale

The guideline committee endorses the EULAR and British Society of Rheumatology (BSR) guidance recommending fetal echocardiography from week 16 for women who are positive for anti-Ro (SSA) or anti-La (SSB) antibodies.[1,2] However, there is debate as to the frequency of monitoring with suggested protocols ranging in their recommendations from weekly, to monthly, to not repeating if normal at 16-18 weeks.[3] The rationale is that surveillance will pick up early stages of heart block allowing timely intervention, yet the optimum treatment for fetal heart block remains unclear. Observational studies suggest that early changes in cardiac function may be reversible with dexamethasone[4], although there is an absence of evidence that increased immunosuppression is beneficial once complete heart block has developed. Open-label trials of intravenous immunoglobulin (IVIg) have failed to show therapeutic benefit.[5,6].

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Guideline 5.3.5

We recommend women with antiphospholipid syndrome and a history of a confirmed thromboembolic event or previous adverse obstetric outcome (excluding recurrent early fetal loss) receive low molecular weight heparin in pregnancy and for six weeks postpartum (1B).

Rationale

The guideline committee endorses recent expert guidance advising aspirin for all women with antiphospholipid syndrome, including those with recurrent early miscarriage; aspirin and low molecular weight heparin prophylaxis for those with of a history mid/late trimester pregnancy morbidity or loss; and high prophylactic or treatment dose low molecular weight heparin for those with prior thrombotic episodes.[1,2] A useful appraisal of the relevant evidence and a practical approach to treatment is available.[3]

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Guideline 5.3.6

We recommend that steroids, azathioprine, calcineurin inhibitors, intravenous immunoglobulin and plasma exchange can be used to treat lupus in pregnancy (1C).

Rationale

The safety of anti rheumatic drugs in pregnancy is comprehensively reviewed in the 2016 EULAR guideline.[1] Standard maintenance therapy for lupus and women with lupus nephritis who are planning pregnancy would be steroids and azathioprine. Non-fluorinated steroids (for example, prednisolone) are metabolized by the placenta, reducing fetal exposure, although the lowest effective dose should be used to prevent maternal side effects. There are data confirming the efficacy and safety of tacrolimus to maintain remission and treat flares of lupus nephritis in pregnancy.[2] The combination of tacrolimus and steroids is diabetogenic and women taking these drugs in isolation or combination should be screened for gestational diabetes. The role of intravenous immunoglobulin (IVIg) in treating immune cytopaenias is established

outside of pregnancy and is safe to use in pregnancy, especially when rituximab is avoided due to the risk of neonatal B-cell depletion (see section 2).[3] The use of IVIg is also described in case studies where infection risk precludes traditional immunosuppression.[4]

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5.4 Diabetic nephropathy

Guideline 5.4.1

We recommend that women with diabetic nephropathy have optimisation of blood glucose, blood pressure and proteinuria prior to conception (1C).

Guideline 5.4.2

We recommend that women with diabetic nephropathy continue angiotensin converting enzyme inhibitors until conception, with regular pregnancy testing during attempts to conceive (1C).

Guideline 5.4.3

We recommend that the schedule of care, surveillance and management of women with diabetic nephropathy should be untaken according to national guidelines for diabetes in pregnancy, in addition to specialist monitoring of renal disease in pregnancy (1D).

Rationale

Most women with diabetic nephropathy have successful pregnancy outcomes[1–4]. However, diabetic nephropathy in pregnancy is associated with an increased risk of adverse outcomes including pregnancy loss, congenital malformation, pre-eclampsia, preterm delivery, growth restriction and neonatal unit admission; with glycaemic control at the time of conception and the severity of underlying CKD contributing.[1,5-7]

Reassuringly, a European-wide cohort study including 163 pregnancies in women with type 1 diabetes compared to 630 women with type 1 diabetes who did not undertake a pregnancy, showed that pregnancy was not an independent risk factor for the development of microvascular complications.[8]

Pre-pregnancy counselling of women with diabetes is associated with improved glycaemic control prior to pregnancy and a reduction in rates of spontaneous pregnancy loss and congenital malformations.[9] Data from single arm studies (n=8-24) show that reduction of pre-pregnancy proteinuria with angiotensin converting enzyme inhibitors (ACEi) is associated with a reduction in proteinuria in pregnancy[10, 11]. Women with diabetes and proteinuria (n=7) treated with ACEi prior to pregnancy to achieve blood pressure <135/85mmHg and albuminuria <300mg/day have been shown to have pregnancy outcomes comparable to women with diabetes in the absence of nephropathy.[12] The periconceptual use of ACEi is described in section 3.3.5.

Proteinuria increases in pregnancy in the majority of women with diabetic nephropathy, including progression to the nephrotic range[1]. Low molecular weight heparin may be indicated for the prevention of venous thromboembolism, although the level of proteinuria at which the risk of venous thromboembolism becomes clinically significant is unknown (see section 4.5).

The guideline committee endorses national guidance for the management of diabetes in pregnancy.[13]

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5.5 Urinary Tract Infection (UTI)

Guideline 5.5.1

We suggest women with reflux nephropathy, congenital anomalies of the kidneys and urinary tract (CAKUT), women with CKD taking immunosuppression, and women with a history of recurrent UTI should be offered antibiotic prophylaxis during pregnancy after a single UTI in pregnancy, including asymptomatic bacteriuria (2D).

Guideline 5.5.2

We recommend pre-pregnancy UTI prophylaxis be continued in pregnancy using agents known to be safe (1D).

Rationale

Asymptomatic bacteriuria is estimated to occur in 2% to 7% of pregnancies with a risk of progression to acute pyelonephritis if untreated. A meta-analysis of studies to 2015 showed that treatment of asymptomatic bacteriuria reduced the incidence of pyelonephritis in pregnancy from 21% to 5% (RR 0.23, 95% CI 0.13-0.41), with some

poor quality evidence that antibiotic use also reduced the incidence of low birth weight babies and preterm delivery.[1] Screening of all pregnant women for asymptomatic bacteriuria is therefore recommended.[2] There are no data describing outcomes for women with CKD and asymptomatic bacteriuria in pregnancy.

The prevalence of UTI following renal transplantation varies from 23% to 75% according to diagnostic criteria, length of follow-up and antibiotic prophylaxis.[3] Registry data show that incidence within the first six months is 17% in women, with a cumulative incidence of 60% by three years post-transplantation.[4] Between 3 and 27% of renal transplant recipients experience recurrent UTI.[3,5,6] The reported incidence of UTI in pregnancy in women with renal transplants is variable with cohorts reporting incidences of between 14% and 42%.[7,8]. An increased incidence of UTI in pregnancy is also described in women with reflux nephropathy[9–11] and polycystic kidney disease.[12] There are no published data to guide the management and prophylaxis of urinary tract infection specifically in women with CKD in pregnancy.

In the absence of evidence specifically examining women with CKD, the guideline committee endorses generic guidelines for UTI in pregnancy.[2,13-15] It was the consensus opinion of the guideline committee that the following women with CKD have an increased risk of complicated and/or recurrent UTI in pregnancy: women with reflux nephropathy, women with congenital anomalies of the kidneys and urinary tract (CAKUT), women with CKD on immunosuppression including women with renal transplants, and women with a history of recurrent UTI prior to pregnancy. In the absence of evidence of harm, antibiotic prophylaxis should be offered to these women following a single confirmed UTI, with or without symptoms, in pregnancy. This decision should be informed by urine culture and antimicrobial sensitivities, and patient preference.

Women who have been commenced on UTI prophylaxis prior to pregnancy should continue prophylaxis in pregnancy with an antimicrobial that is considered safe as their risk of infection is likely increased in pregnancy due to gestational changes to the urinary tract including dilatation of the renal pelvis and ureter, decreased ureteral peristalsis, and reduced bladder tone.

Not all antimicrobials are considered safe in pregnancy. Penicillins, cephalosporins, fosfomycin, trimethoprim (not in first trimester) and nitrofurantoin (not at the end of pregnancy, not in glucose-6-phosphate dehydrogenase deficiency and ineffective if pre-pregnancy eGFR <45ml/min/1.73m^2) can be used.

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5.6 Reflux nephropathy and Congenital Abnormalities of the Kidney and Urinary Tract (CAKUT)

Guideline 5.6.1

We recommend women with previous bladder surgery (re-implantation of ureter, bladder reconstruction, all complex paediatric urology) should be discussed during pregnancy with a urologist with expertise in bladder reconstruction to evaluate options for delivery (1D).

Rationale

The majority of women with previous urinary tract surgery can have healthy, successful pregnancies without compromise to previous urinary tract reconstruction. No long-term adverse outcomes were identified in a case series of 29 pregnancies in the UK, although urinary tract infections (55%) and upper renal tract obstruction (10%) were common.[(1)] The anatomy of the lower urinary tract following reconstructive bladder surgery can be variable, and the risk of obstruction caused by the gravid uterus, or damage to bladder and ureters during caesarean section, should be anticipated. Caesarean section is not mandatory but can be performed, and when feasible, should be done with input from a urologist with experience in bladder reconstruction.[(2)]

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Guideline 5.6.2

We recommend that antenatally detected abnormalities in the fetal kidneys and/or urinary tract should be discussed with fetal medicine and paediatric nephrology specialists to determine appropriate neonatal management (1D).

Guideline 5.6.3

We recommend that children with antenatally detected abnormalities in the fetal kidneys and/or urinary tract should have specialist follow up if features of urinary tract infection are identified (1C).

Rationale

There are inadequate data to define an evidence-based management strategy for antenatally detected abnormalities of the urinary tract. Expert consensus, based on observational data, is that infants of mothers with urinary tract abnormalities, who had normal urinary tracts on antenatal ultrasound scans do not need further follow up

unless features of urinary tract infection are identified in childhood.[1] Neonatal management of antenatally detected abnormalities of the urinary tract will be dependent on the severity of the radiologically identified abnormality and clinical features in the newborn.

The inheritance pattern and penetrance of forms of CAKUT from parent to child is poorly defined. Heterogeneous multifactorial genetic traits are likely but monogenic forms of inheritance have also been described. Cohort studies report between 36% and 67% of children of patients with vesicoureteric reflux demonstrate reflux on a voiding cystourethrogram.[2,3] However, not all vesicoureteric reflux results in renal parenchymal damage and 80% of mild cases resolve by 5 years.[4]

References

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VI. LAY SUMMARY

Most women with chronic kidney disease (CKD) have successful pregnancies, but kidney disease can affect the health of both pregnant women and their babies. For that reason, experts in renal disease and pregnancy should be available to all women with kidney disease in the UK to offer advice before pregnancy and to help support, monitor and treat women with kidney disease when they are pregnant and after delivery.

Planning pregnancy is important for women with CKD. Women with kidney disease should have access to contraception until they are ready to become pregnant and the progesterone-only pill ('mini pill'), contraceptive implant and Mirena® coil are safe and effective. Women should let their nephrologist know that they would like to consider pregnancy before they stop using contraception. Women of reproductive age with CKD should have an opportunity to discuss the likely risks of a pregnancy for both herself and her baby, with a specialist. Risks include delivering her baby before the due date, her baby being small and needing admission to intensive care, and a worsening of her

kidney function in or after pregnancy. A woman's kidney disease and blood pressure should be treated before she conceives. Medications may need to be adjusted so that they are safe for a developing baby. Many drugs are safe in pregnancy including ciclosporin, tacrolimus, hydroxychloroquine and azathioprine. However mycophenolate is harmful to a developing baby and it is important that mycophenolate is swapped for an alternative medication (usually azathioprine) and a woman's kidney function to be monitored following this change before she tries to conceive. Blood pressure medications that end in 'pril' or 'sartan' also need to be stopped, either before pregnancy or as soon as possible in early pregnancy (before 12 weeks).

Women with CKD should have specialist care of kidney disease in pregnancy, in addition to routine antenatal care. This means that they will be seen by doctors (obstetricians) as well as midwives during their pregnancy, and they will have extra scans to check the growth and wellbeing of their baby. Many women with CKD will need treatment for their blood pressure in pregnancy and a number of different blood pressure medications are safe including labetalol, nifedipine, methyldopa. Pregnant women with CKD may need iron (which can be given by injection), and vitamin D. If women were taking erythropoietin ('Epo') before conceiving then the dose will need to be increased in pregnancy. Women with CKD, including women with renal transplants, can have a vaginal delivery. They can also breastfeed if they wish and can be given medications that are safe in breastfeeding if they need them.

Compared with women without CKD, women with CKD have a higher risk of a condition called pre-eclampsia. This condition only occurs in pregnancy and goes away after delivery. It causes high blood pressure, protein leak into the urine, headaches and abnormal blood tests. It can also affect the growth of the baby. It can be difficult to know if a woman with CKD has pre-eclampsia if she had high blood pressure and protein in her urine before pregnancy, and specialists should be available to help with diagnosis and treatment. If a woman develops pre-eclampsia, she will need close monitoring and she may need to deliver her baby early. All women with CKD should take low-dose aspirin in pregnancy. This is safe and reduces the risk of pre-eclampsia.

Women with kidney transplants, lupus and diabetes can have successful pregnancies. Timing of pregnancy in these conditions is particularly important in order to make sure kidney function is stable, and that lupus and diabetes are well controlled before pregnancy, in order to have the best chance of a healthy baby. Women who have congenital kidney disease and women who have had bladder surgery should have specialist advice on the best way to deliver their baby. Pregnancy while on dialysis has a very high risk of complications. Although the number of hours of dialysis can be increased in pregnancy, pregnancy outcomes are better for most women on dialysis if they can delay pregnancy until after successful kidney transplantatio

VII. The experience of pregnancy and renal disease

Experience 1: Multidisciplinary team

Pregnancy with CKD is significantly different from a normal pregnancy and for me it was critical that I was referred to a specialist care team. Within a week of knowing I was pregnant I was referred. The team at the hospital were fantastic, and it gave me great peace of mind to know that my care was in the hands of a multispecialty team who were aware of my health condition and could advise me accurately.

Experience 2: Multidisciplinary team

During the pregnancy I attended regular appointments with specialists in kidney disease in pregnancy. I found that I saw less of my usual renal team than I expected, however it was very clear the communication between all teams was excellent.

Experience 3: Multidisciplinary team

Possibly the thing of greatest importance was the immense emotional support that I received from the specialist team caring for me. This, I believe, was the most important aspect for my wellbeing during pregnancy. At any point if I was tense about anything, they would sit me down and listen to my concerns patiently. I remember I was under the care of a specialist obstetrician. In an appointment when my blood pressure was rising, he had to increase my dose of labetalol. I was very tense and I started weeping. He just looked into my eyes and said, “I promise it will be fine.” These words will stay with me in my grave. It touched me very deeply and it was like my tension had disappeared immediately.

Experience 4: Fertility

As a lupus and renal patient, I have gone through 6 known miscarriages, 3 failed IVF attempts and 2 successful pregnancies. The first successful pregnancy was after 15 years of marriage, which is a long time, I would imagine, by anyone’s standard.

Experience 5: Pre-pregnancy counselling

Women with CKD need significant support to understand if pregnancy is something that they should consider in the first place. I first got diagnosed with CKD in 2009. During a visit to the nephrologist in 2011 I was told that I should not think about pregnancy at all, because it would be fatal for me and the baby. I was not given detailed counselling at that point and it was very heart-breaking. However, when I met an expert in 2013 she presented the pros and cons of having a baby with underlying CKD in a very balanced manner. My major concern was my life expectancy and that of my baby and I was assured that shouldn't be a concern.

Experience 6: Pre-pregnancy counselling

Prior to falling pregnant I attended the pre-pregnancy appointment. At this appointment I met the renal transplant doctor who specialised in pregnant transplant patients, a high-risk obstetrician and a specialist in pregnant women with complex medical conditions. At this appointment, which lasted approximately one hour, my medical history was taken and my medication was reviewed. I was then informed of all the potential risks associated with falling pregnant and I was taken off all the medication that could be harmful to my unborn baby and these medications were changed to medication safe to use in pregnancy. I remember walking out of the appointment feeling more comfortable, and confident that I would be provided with appropriate care during my pregnancy, and even though I may encounter more problems than the average pregnant woman, I would have the support and medical care required. Some of the main pieces of information I remember very clearly are that I would be at higher risk for having a premature baby and I would be high-risk for pre-eclampsia, but I was happily surprised to hear that research suggests there would no effects on the baby secondary to me taking immunosuppressive medication in pregnancy. I never expected to be able to have children with a renal transplant.

Experience 7: Antenatal care

Regular check-ups were the most critical part in my entire journey through pregnancy. I believe it is important for every pregnant woman with CKD to have such detailed follow-up. I started with visiting the clinic once every month. As the pregnancy progressed, the check-ups were scheduled twice a month and towards the end, they were weekly. These meetings helped relieve a huge amount of anxiety that I had, especially towards the last few weeks of my pregnancy

Experience 8: Antenatal care

I spent approximately 8 weeks in hospital before and after I gave birth to my son. I was seeing one doctor or another at least weekly from the second trimester onwards. I also needed to leave work at about 28 weeks pregnant. At first, I felt guilty about work. However, they were extremely supportive and they were the ones to advise I take long-term sick leave. Once I didn't have to worry about work, I didn't mind spending time in hospital because I know it was what I needed to do to keep my baby and me safe and healthy.

Experience 9: Pre-eclampsia

When I was about 22 weeks pregnant, at the renal clinic, my blood pressure was high. When the consultant measured it again in his room it was still very high, about 180/120. I could see the panic in his eyes. He immediately took me to the delivery suite where I was informed I needed to be monitored. I was informed during this time that it was hard to differentiate between kidney disease and pre-eclampsia due to the symptoms being the same - high blood pressure and protein in the urine. I was also advised that if the risk remained I may need to give birth. I was informed at this stage the baby would have very little chance of survival and even if she did survive would most likely have developmental problems. I was further advised of the option of termination, as I was still under 24 weeks. This was devastating to me, as I had obviously heard of pre-eclampsia and that I was at risk, but had never contemplated it actually happening or its effect.

Experience 10: Peripartum care

My obstetrician had always encouraged and anticipated a natural birth but as both my health and the health of my son worsened towards the end of pregnancy I needed to have a C-section. In the end, I was fine with this decision because I felt so unwell that I didn't think I would be well enough to endure a long labour. I was very short of breath, my heart rate was high around 120-150 at times and I was very weak. I was anxious about losing blood and being able to lie flat for the C-section but I trusted the opinion of all the doctors involved which was reassuring.

Experience 13: Dialysis

Things didn't improve and my creatinine and urea kept creeping up. At that stage my creatinine was about 270 and urea 18. I was finally informed that I had two options: start dialysis whilst pregnant or give birth preterm, following which I may still need dialysis. After being reassured that dialysis would not affect my baby and in actual fact would keep her safe, I opted for the first option of starting dialysis whilst pregnant.

Following this decision I was immediately fitted with a catheter in my neck, which is something I had been dreading. It was done under local anaesthetic and although I didn't feel any actual pain, the procedure was still very uncomfortable. It took me quite some time to get used to having two wires sticking out of my neck and until now, I don't like to touch or feel the wires under my skin or to actually see them sticking out of my skin, so I ensure the nurses keep that area covered at all times.

The first time I had dialysis, I was really worried. Although I had been reassured it was pain free and that I wouldn't feel a thing, the actual thought of being hooked up to a machine that was filtering my blood scared me. Having seen kidney patients in the past, dialysis had always looked ominous to me. However, my first experience was good. I think I was in a good place for anybody to start dialysis for the first time. The nurses there were very sympathetic and experienced and I was amazed by the amount of emphasis on hygiene. I was always attached and taken off the machine by a sister, who was always happy to answer any questions I had. It has also given me a greater respect for nurses, as the ones I encountered were very pleasant whilst at the same time having immense knowledge regarding the whole dialysis process, the machines, and what patients should be doing. I was also amazed at the dialysis machine. How it was able to filter the blood, remove the toxins and then pump the blood back into my body. It also made me realise what an important job the kidneys do.

I soon got used to the process, which was 2 hours 3 times a week, then 2.5 hours 4 times a week. The effect of the dialysis however was very tiring and although sometimes I fell asleep during it, I still needed a good solid 2 hours sleep immediately afterwards. I would still feel exhausted for the remainder of the day with my body feeling very weak. I would then feel much better and rejuvenated the following day before being subjected to dialysis the day after. So it was up and down, feeling tired then very well, then very tired again. This made me wonder how people on dialysis manage to lead a normal life, which I was obviously not doing at that time.

VIII. Summary of clinical responsibility for elements of the guideline

Recommendations	Primary care and community	Secondary care	MDT
Structure of care			✓
Medication in pregnancy and lactation	✓	✓	✓
Contraception	✓	✓	✓
Fertility	✓	✓	✓
Pre-pregnancy counselling		✓	✓
Optimisation for pregnancy	✓	✓	✓
Assessment of renal function in pregnancy	✓	✓	✓
Antenatal care	✓	✓	✓
Pre-eclampsia prophylaxis	✓	✓	✓
Blood pressure management	✓	✓	✓
Venous thromboembolism	✓	✓	✓
Anaemia	✓	✓	✓
Bone health		✓	✓
Renal biopsy			✓
Peripartum care		✓	✓
Postnatal care	✓	✓	✓
Transplantation		✓	✓
Dialysis			✓
Lupus nephritis and vasculitis		✓	✓

Diabetic nephropathy	✓	✓	✓
Urinary tract infection	✓	✓	✓
Reflux nephropathy and CAKUT		✓	✓

IX. Ovid Medline search terms (1946 to 2018)

Pregnancy:

1. exp Pregnancy/
2. exp Pregnancy Complications/
3. exp Pregnancy Trimesters/
4. exp Pregnancy Outcome/
5. exp Pregnancy Maintenance/
6. exp Pregnancy, Multiple/
7. exp Pregnancy, High-Risk/
8. exp Pregnant Women/
9. exp Delivery, Obstetric/
10. exp Postpartum Period/
11. exp Peripartum Period/
12. exp Gravidity/
13. pregnan$.mp.
14. gravid.mp.
15. gestation$.mp.
16. c?esarean$.mp.
17. obstetric.mp.
18. peripartum.mp.
19. intrapartum.mp.
20. postpartum.mp.
21. (pregnan$ or gestation$ or pre-eclamp$ or preeclamp$ or pre eclamp$ or eclamp$ or HELLP or obstetric$ or postpartum$ or peripartum$ or intrapartum$ or antepartum$ or prepartum$ or antenatal$ or prenatal$ or postnatal$ or perinatal$ or internatal$ or cesarean$ or caesarean$).ti.
22. or/1-21
23. limit 22 to (English language and female)

CKD:

1. exp Renal Insufficiency/
2. exp Kidney Diseases/
3. exp Kidney Failure, Chronic/
4. ((Kidney* or renal*) adj4 (disease* or failur* or transplant* or insufficienc* or implant*)).tw.
5. CKD.tw.
6. kidney diseases/ and (chronic or end-stage or endstage).ti,ab.
7. renal insufficiency/ and (chronic or end-stage or endstage).ti,ab.
8. ((chronic or progressive) adj2 (renal or kidney)).ti,ab.
9. (chronic adj (kidney or renal) adj insufficienc*).ti,ab.
10. ckd.ti,ab.
11. ((renal adj3 insufficienc*) not (acute adj2 renal)).ti,ab.
12. ((renal or kidney) and chronic).ti,ab.

13. or/1-14

Transplant:

1. exp Kidney Transplantation/
2. ((kidney? or renal$) adj3 (transplant$ or graft$)).ti,ab.
3. or/1-2

Lupus and GN:

1. exp glomerulonephritis/
2. exp nephritis/
3. Glomerulonephritis.mp.
4. (glomerul$ adj3 nephritis).mp.
5. gn.mp.
6. (iga or berger$ or (focal adj3 glomerul$) or (segmental adj3 glomerul$) or fsgs or minimal change or (membran$ and glomerul$) or mgn or mcgn or dense deposit disease or mesangial proliferative glomerul$ or alport$ or hereditary nephr$ or (rapid$ progressive adj3 glomerul$) or crescentic gn).mp.
7. glomeruloneph$.ti,ab.
8. nephropath$.ti,ab.
9. (glomerul$ adj (sclerosis or nephritis)).ti,ab.
10. exp lupus nephritis/
11. lupus nephritis.mp.
12. or/1-9.

Dialysis (Iansavichus et al., 2015, #75528)**:**

1. ((dialy$ OR h?emodia$).mp.
2. ((end stage OR endstage) adj (kidney OR renal)).tw.
3. esrd.tw.
4. renal replacement.mp.
5. ur?emi$.mp.
6. ur?emi$.tw.
7. exp *Uremia/
8. capd.tw.
9. h?emofilt$.mp.
10. ur?emic patient$.tw.
11. intradialy$.tw.
12. tenckhoff$.tw.
13. ccpd.tw.
14. ur?emic.tw.
15. fistula$.mp
16. or/1-15

Contraception:

1. exp contraception/
2. exp contraception behavior/
3. exp contraceptive devices/
4. contracept$.mp
5. exp family planning/
6. family planning.mp
7. exp pregnancy, unplanned/
8. exp pregnancy, unwanted/
9. exp birth control/
10. birth control.mp.
11. (family planning or family-planning).mp.
12. contracept$.mp.
13. (sexual and reproductive health information).mp.
14. (family planning or planned parenthood or birth control or reproductive health).mp.
15. (birth regulat* or population regulat* or fertility regulat* or birth spacing or pregnancy inter*).mp.
16. fertility control.mp.
17. reproduct$ control.mp.
18. ((unplan* or unwant* or mistime* or wanted* or unintend* or intend*) adj pregnan*).mp.
19. safe sex.tw.
20. ((birth control or family planning or reproductive health) adj clinic).mp.
21. pregnan$ adj2 (prevent* or interrupt* or terminat*).mp.
22. exp contraception, barrier/
23. exp condoms/
24. (barrier method* or condom* or vaginal sponge* or cervical cap*).mp.
25. exp contraception, immunologic/
26. exp reproductive-control-agents
27. ovulat* adj2 (supress* or inhibit* or prevent*)
28. Birth control pill.mp.
29. Oral contracept$.mp.
30. (intrauterine device* or intra-uterine device* or IUD* or TCu380a or CuT-200 or gynefix or mirena or intrauterine system).mp.
31. exp contraception, postcoital/
32. morning after pill.mp.
33. emergency contracept$.mp.
34. ((contra* or family planning or pill or method) adj (method or failure or method failure or discontinuation)).mp.
35. ((female or woman or women) adj sterili*).mp.
36. periodic* abstinen* or sexual* abstinen* or coitus interruptus
37. or/1-36

Fertility:

1. (fertil* or steril* or infertile* or sub-fertil* or fecund* or subfecund* or sub-fecund* or assist* reproduce*).tw.
2. exp infertility/
3. Infertility, Female/
4. Anovulation/
5. anovulat*.tw.
6. (oligo-ovulation or "oligo ovulation" or oligoovulat*).tw.
7. exp fertility/
8. fertil$.ti,ab,sh,tw.
9. infertil$.ti,ab,sh,tw.
10. subfertil$.ti,ab,sh,tw.
11. exp ovulation induction/ or exp superovulation/
12. (ovulat$ adj2 induc$).tw.
13. (ovar$ adj2 stimulat$).tw.
14. superovulat$.tw.
15. or/1-14

Fluid Balance:

1. Fluid Therapy/
2. Fluid?.ti,ab.
3. Infusions, Intravenous/
4. ((intravenous$ or IV or drip?) adj3 infusion?).ab,ti.
5. Rehydration Solutions/
6. (re-hydrat$ or rehydrat$).ab,ti.
7. (type? adj3 (intravenous$ or IV or drip? or fluid?)).ab,ti.
8. ((rate? or amount? or volume?) adj3 (intravenous$ or IV or drip? or fluid? or admin$)).ab,ti.
9. Body Water/
10. Water-Electrolyte Balance/
11. Water-Electrolyte Imbalance/
12. ((body or bodies) adj2 water).ti,ab.
13. ((fluid? or water$ or electrolyte) adj3 (balanc$ or imbalanc$)).ti,ab.
14. Furosemide/
15. Dopamine/
16. Dopamine Agents/
17. Furosemide.mp.
18. Dopamine.mp.
19. or/1-18

Anaemia:

1. exp anemia/
2. (anemi* or anaemi*).ti,ab.
3. *Anemia/ OR an?emi$.ti.
4. erythropoietin$.mp.
5. or/1-4

Bone:

1. exp hyperparathyroidism, secondary/
2. ((renal adj2 osteo*) or ((renal or secondary) adj2 hyperparathyroidism)).ti,ab.
3. hyperparathyroidism.mp.
4. or/1-3

Diabetic nephropathy:

1. exp pregnancy in diabetics/
2. pregnancy in daibetics.mp.
3. (diabetic adj (kidney or renal) adj (disease* or failure)).ti,ab.
4. exp diabetic nephropathies/
5. diabetic nephropathy.mp.
6. or/1-6

Hypertension:

1. Chronic hypertensi*/or chronic hypertension in pregnanc*
2. exp Hypertension/
3. exp hypertension, renal/
4. exp Blood Pressure/
5. exp Blood Pressure Determination/
6. exp Antihypertensive Agents/
7. Hypertens*.mp.
8. pre-eclamp*.mp.
9. preeclamp*.mp.
10. toxemia*.mp.
11. toxaemia*.mp.
12. gestosis.mp.
13. antihypertensive*.mp.
14. ((high$ or rais$ or elevat$ or heighten$ or increas$) adj3 (blood pressure or diastolic pressure or systolic pressure or pulse pressure)).mp.
15. ((high$ or rais$ or elevat$ or heighten$ or increas$) adj3 (BP or DBP or SBP)).mp.

16. or/1-15

Urinary Tract Infection and Reflux:

1. exp urinary tract/
2. exp urinary tract infections/
3. exp cystitis/
4. vesico-ureteral reflux/
5. exp pyelonephritis/
6. exp Urinary Calculi/
7. exp Vesico-Ureteral Reflux/
8. exp Urogenital Abnormalities/
9. exp Urethritis/
10. (UTI or CAUTI or RUTI or cystitis* or bacteriuria* or pyelonephriti* or pyonephrosi* or pyelocystiti* or pyuri* or VUR or urosepsis* or uroseptic* or urosepses* or urethritis*).ti,ab.
11. ((urin* or renal* or kidney*) adj1 (system* or tract* or calculus or calculi* or stone* or sepsis*)).ti,ab.
12. ((bladder* or genitourin* or genito urin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen*) adj3 (infect* or bacteria* or microbial* or block* or obstruct* or catheter* or inflamm*)).ti,ab.
13. ((upper or lower) adj3 urin*).ti,ab.
14. ((vesicorenal* or vesicoureteral* or vesicoureteric* or vesico renal* or vesico ureteral* or vesicoureteric* or bladder* or cystoureteral* or ureter* or urether* or nephropathy*) adj3 (backflow* or reflux*)).ti,ab.
15. CAKUT.ti,ab.
16. or/1-12

Venous Thromboembolism:

1. pulmonary embolism/ or thromboembolism/ or venous thromboembolism/ or venous thrombosis/ or upper extremity deep vein thrombosis/
2. (((venous or vein) adj (thrombosis or thromboses or thrombus or thromboembolism)) or (dvt or vte) or ((pulmonary or lung) adj3 (embolism or emboli or embolus or emboliz* or thromboembolism))).ti,ab.
3. or/1-2

Proteinuria:

1. exp Proteinuria/
2. exp Albuminuria/
3. protein creatinine ratio.mp.
4. protein to creatinine ratio.mp.

5. protein: creatinine ratio.mp.
6. uPCR.mp.
7. spot urinary protein creatinine ratio.mp.
8. albumin creatinine ratio.mp.
9. albumin to creatinine ratio.mp.
10. albumin: creatinine ratio.mp.
11. uACR.mp.
12. spot urinary albumin creatinine ratio.mp.
13. microalbuminuria.mp.
14. exp Nephrotic Syndrome/
15. or/1-14

Biopsy:

1. exp Biopsy, Fine-Needle/
2. exp Biopsy/
3. exp Biopsy, Needle/
4. exp Biopsy, Large-Core Needle/
5. morphology.mp.
6. exp Pathology/
7. exp Pathology, Molecular/
8. exp Pathology, Clinical/
9. exp Histology/
10. or/1-9

Renal Function:

1. exp creatinine/
2. exp kidney function tests/
3. exp glomerular filtration rate/
4. kidney function.mp.
5. renal function.mp.
6. glomerular filtration.mp.
7. GFR.mp.
8. (CKDEPI or CKD-EPI or Chronic Kidney Disease Epidemiology).mp.
9. (MDRD or modification of diet in renal disease).mp.
10. Cockcroft.mp.
11. exp cystatin C/
12. ((equation or formula) AND (kidney function or renal function)).mp
13. or/1-12

Pre-pregnancy:

1. exp Prenatal Care/
2. exp Preconception Care/
3. pre-natal.ti,ab.
4. pre-concept*.ti,ab.
5. peri-concept*.ti,ab.
6. pre-gestation*.ti,ab.
7. pregestation*.ti,ab.
8. (pre-pregnancy or prepregnancy or prenatal or pre-natal or preconcept* or pre-concept* or periconcept* or peri-concept* or pre-gestation* or pregestation*).ti,ab.
9. ((Counsel* or advice* or education) adj3 (pre-pregnancy or prepregnancy or prenatal or pre-natal or preconcept* or pre-concept* or periconcept* or peri-concept* or pre-gestation* or pregestation*)).mp.
10. (pre-pregnancy or prepregnancy or prenatal or pre-natal or preconcept* or pre-concept* periconcept* or peri-concept* or pre-gestation* or pregestation*) AND (service* OR counsel* OR program* OR care OR education* OR clinic*).mp.
11. or/1-10

Antenatal:

1. exp Perinatal Care/
2. exp Obstetrics/
3. exp Maternal Health Services/
4. exp Home Childbirth/
5. ((midwif* or nurs* or obstetric* or medical*) adj (service* or care)).mp.
6. ((antenatal* or prenatal* or matern* or perinatal* or pregnan* or childbirth* or childbearing*) adj (service* or care)).mp.
7. exp Midwifery/
8. exp Nurse Midwives/
9. exp Birthing Centers/
10. ((nurs* or midwif* or obsteric* or medical*) adj model*).mp.
11. ((nurs* or midwif* or obsteric* or medical*) adj2 team*).mp.
12. (multidisciplinary adj team*).mp.
13. (shar* adj2 care).mp.
14. ((nurs* or midwif* or obsteric* or medical*) adj2 manag*).mp.
15. ((nurs* or midwif* or obsteric* or medical*) adj2 led*).mp.
16. or/1-15

Postnatal:

1. exp Postnatal Care/
2. exp Postpartum Period/
3. exp Peripartum Period/
4. postnatal.mp.
5. postpartum.mp.
6. peripartum.mp.
7. post adj2 pregnan*.mp.
8. or/1-8

Medication:

Generic and brand drug names (UK, EU and US) in conjunction with drug class were searched as multipurpose fields in conjunction with pregnancy search terms.