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Original Article

ORIGINAL ARTICLE

Defining normal serum creatinine in pregnancy—results from the AKID UK prospective cohort study

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ABSTRACT

Background. Abnormal kidney function in pregnancy may represent chronic kidney disease or pregnancy-associated acute kidney injury, both associated with adverse outcomes during and after pregnancy. Serum creatinine remains the standard biomarker for kidney function in pregnancy, but normal levels change dynamically through pregnancy and at term. Existing gestation-specific reference ranges for serum creatinine and recommendations to investigate for abnormal kidney function in pregnancy are based on limited data. Data describing trajectories of serum creatinine through pregnancy and the normal, physiological increase in serum creatinine at term are also lacking.

Methods. We recruited 476 healthy pregnant individuals aged 16 years or over, 2019–21, measuring serum creatinine in the first, second and third trimesters of pregnancy, at birth and postpartum. Clinical data were abstracted. Gestation-specific reference ranges for serum creatinine were defined as mean ± 1.96 × SD, after excluding those with adverse pregnancy outcomes. Trajectories of serum creatinine through pregnancy, and the change in serum creatinine at delivery were described.

Results. 1875 creatinine measurements were recorded. Reference ranges for serum creatinine in the first, second and third trimesters of healthy pregnancy were 37–67 μmol/l (0.42–0.75 mg/dl), 34–63 μmol/l (0.38–0.71 mg/dl), and 34–66 μmol/l (0.39–0.75 mg/dl). Increasing serum creatinine in early pregnancy was more common in those with hypertensive disorders of pregnancy, prior to disease onset. In healthy participants, median serum creatinine increase from 36 weeks to birth was 6.8% (95% CI 4.5%, 9.1%).

Conclusions. Investigation for abnormal kidney function in pregnancy should be considered at a lower creatinine threshold than currently recommended. Detecting abnormal creatinine trajectories may help early identification of high-risk pregnancies.

Keywords: Creatinine; pre-eclampsia; pregnancy; pregnancy-induced hypertension; reference range

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KEY LEARNING POINTS

What was known:

- Serum creatinine is the standard biomarker for monitoring kidney function during pregnancy, but kidney function changes dynamically through pregnancy.
- Existing reference ranges for serum creatinine in pregnancy are based on limited, historical data, limiting clinicians' ability to confidently detect abnormal kidney function in pregnancy. This may lead to under-detection of pregnancy-associated acute kidney injury or pre-existing chronic kidney disease, worsening outcomes through under-management of these conditions.
- Trajectories of serum creatinine through pregnancy may associate with adverse pregnancy outcomes, but this phenomenon is under-explored.

This study adds:

- In a contemporary cohort of UK healthy pregnant participants, we have defined reference ranges for serum creatinine as 37–67 μmol/l (0.42–0.75 mg/dl), 34–63 μmol/l (0.38–0.71 mg/dl), and 34–66 μmol/l (0.39–0.75 mg/dl), in first, second and third trimesters, respectively.
- The upper limit of these reference ranges lies below existing UK thresholds recommending investigation for abnormal kidney function.
- Individuals experiencing adverse pregnancy outcomes appear to have differences in the trajectory of serum creatinine through pregnancy, with an early increase in creatinine seen in the third trimester.

Potential impact:

- Investigation for abnormal kidney function in pregnancy should be recommended at a lower level of serum creatinine than described in current UK guidance.
- Validation of our findings with other cohorts, worldwide, would strengthen this recommendation.
- The utility of creatinine monitoring to predict adverse pregnancy outcomes warrants further investigation.

INTRODUCTION

Physiological adaptations to healthy pregnancy include a 50–85% increase in renal blood flow, increased glomerular pore size, and dilatation of afferent and efferent glomerular arterioles, resulting in a 50% increase in glomerular filtration rate (GFR) [1]. These adaptations (and their reversal) are reflected in dynamic changes in serum creatinine through pregnancy [2]. Serum creatinine decreases in the first trimester, plateauing in the second trimester, before rising again in the third trimester, reaching pre-pregnancy levels at term [3]. Creatinine-based estimated GFR calculations [4] adjust for age and sex to account for individual differences in creatinine production by muscle mass, but equations are not validated in pregnancy [1]. Routine clinical assessment of kidney function therefore relies on serum creatinine alone, but dynamic changes in serum creatinine through pregnancy complicate interpretation of results.

'Normal' kidney function based on serum creatinine in pregnancy is inadequately defined. While some gestation-specific reference ranges for creatinine in pregnancy have been published, these are based on limited data and were calculated based on small numbers of participants [5]. A current UK recommendation to suspect abnormal kidney function for those with a serum creatinine above 77 μmol/l (at any gestation) [6] is based on a meta-analysis including limited, historical data [5].

Detecting abnormal kidney function in pregnancy should prompt further investigation for chronic kidney disease (CKD) or pregnancy-related acute kidney injury (AKI), both of which have adverse consequences during and after pregnancy. CKD in pregnancy is associated with high risk of adverse pregnancy outcomes (APOs) [7] and increased lifetime cardiovascular and renal risk [8]. AKI is an independent risk factor for development of CKD, kidney failure, cardiovascular disease, and mortality in non-pregnant populations [9]. Outside pregnancy, AKI is defined as a ≥50% or ≥26 μmol/l rise in serum creatinine within 48 hours [10, 11, 12], but this definition is not applicable to pregnant populations because of normal dynamic changes in creatinine. Pregnancy-related AKI appears to be increasing in incidence [13] and is associated with APOs, both at the time of diagnosis [14] and in subsequent pregnancies [15]. Detecting AKI at term is challenging because reversal of physiological adaptations to pregnancy at this time already result in an increase in serum creatinine.

Contemporary, gestation-specific reference ranges for serum creatinine would have clinical utility in identifying individuals at risk of CKD or AKI in pregnancy, in order to implement monitoring and treatment aiming to reduce risk. Describing the trajectory of serum creatinine through pregnancy in individuals with and without APOs may identify trajectories associated with pathology or predictive of APOs [16]. Quantification of 'normal' increases in serum creatinine at term may aid identification of AKI.

We therefore conducted a prospective cohort study of healthy pregnant individuals, aiming to:

1. Derive gestation-specific reference ranges for serum creatinine in healthy pregnancy.
2. Describe the incidence of APOs overall, and for those with abnormal kidney function in pregnancy, as defined by our reference ranges, and by existing UK thresholds.
3. Describe the trajectory of serum creatinine through pregnancy in those with and without APOs.
4. Quantify the physiological increase in serum creatinine occurring at term.

MATERIALS AND METHODS

Study design and recruitment

The Acute Kidney Injury and Diabetes in pregnancy (AKID; IRAS ID 246444) was a prospective cohort study recruiting primiparous and multiparous pregnant individuals, aged 16

years or over, with singleton or multiple pregnancies, at a UK tertiary obstetric centre (approx. 6000 births/annum). Recruitment took place between December 2019 and October 2021, with a 6-month pause March–October 2020 during the COVID-19 pandemic. Potential participants were identified at appointments for 20-week fetal ultrasonography. Eligibility was confirmed from electronic pregnancy records. Written, informed consent was obtained by research midwives, electronically, after a telephone consultation or during an in-person consultation. Individuals with established diagnoses of CKD, type 1 or type 2 diabetes mellitus prior to pregnancy; without a stored, routinely collected first trimester serum sample; and those unable or unwilling to provide informed consent were excluded.

Data collection

Baseline data

Maternal age, body mass index (BMI), ethnicity, past medical history and medication data were collected from written and electronic pregnancy medical records.

Clinical data

Pregnancy and fetal outcomes were abstracted from electronic pregnancy records and/or hospital discharge summaries. APO data included pre-eclampsia , pregnancy-induced hypertension (PIH), and gestational diabetes mellitus (GDM) as defined by NICE [17], [18]; antepartum haemorrhage (any bleeding from or into genital tract after 24 weeks' gestation), postpartum haemorrhage (bleeding after birth, >500 ml), placenta praevia, instrumental delivery, emergency caesarean section, neonatal intensive care unit (NICU) admission, low birthweight (<2500 g), small for gestational age (SGA) <5th birth centile, and macrosomia (birthweight > 4000 g). APOs were diagnosed by the clinical teams responsible for participants' care.

Serum creatinine measurements

Our protocol included measurement of serum creatinine at 6–11, 26–32, 34–36 weeks' gestation, within 6 hours of birth and at 2–10 days postpartum. Retrospective measurement of serum creatinine was performed on serum samples already collected for routine virology testing between 6 and 11 weeks' gestation. Thereafter, additional blood samples for serum creatinine were collected solely for this study, at the above prespecified time points. Serum creatinine measurement using enzymatic assay was performed by clinical biochemistry services at North Bristol NHS Trust, UK.

Analyses

All analyses were performed in Stata 17 [19]. Participant characteristics are described using proportions for categorical variables, means (SD) for approximately normally distributed continuous variables, and median (interquartile range, IQR) for continuous variables that were positively skewed.

Calculation of reference ranges

Reference ranges for serum creatinine in healthy pregnancy were defined as mean ± 1.96 × SD [20]. Individuals with pre-eclampsia, PIH, GDM, preterm birth, SGA (<5th centile) or estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 by CKD-EPI equation [4] (which identifies CKD in non-pregnant individuals) were excluded from reference range calculations at all time points, irrespective of time of disease onset. After exclusions, the data used to calculate reference ranges came from singleton pregnancies only. While eGFR calculations are not validated for the diagnosis of CKD in pregnancy, given that serum creatinine is lower in healthy pregnancy than in the healthy, non-pregnant population, we used this equation as a sex- and age-corrected screen to identify and exclude abnormally elevated serum creatinine measurements from inclusion in pregnancy-specific reference ranges. Histograms of creatinine measurement in healthy pregnancy were plotted for each trimester.

The frequency of APOs in individuals with serum creatinine values outside these reference ranges was compared to those with creatinine values above the existing UK threshold for investigation of abnormal kidney function in pregnancy (serum creatinine > 77 μmol/l) [6].

Trajectory of serum creatinine through pregnancy in those with and without APOs

The distribution of serum creatinine at each time point was compared for those with or without PIH, pre-eclampsia, GDM, preterm, low birthweight, SGA, emergency C-section, NICU admission. These APOs were selected because of the plausible link with abnormal kidney function in pregnancy, whereas others (postpartum haemorrhage, placenta praevia, instrumental delivery, macrosomia) were not included in this analysis.

Multilevel models with random intercepts were used to estimate trajectories of serum creatinine through pregnancy to postpartum for participants with each APO (PIH, pre-eclampsia, GDM, preterm, low birthweight, SGA, emergency C-section, NICU admission, as compared to a reference group with none of these APOs). Multilevel fractional polynomials were used to allow for non-linear trajectories. The best-fitting model was chosen with up to 2 degrees. Models were controlled for age, BMI parity and ethnicity. We plotted predicted mean levels of creatinine by time since the start of pregnancy, with average levels of the included covariates (age of 31.6 years, BMI of 25 kg/m^2, parity of 0, white ethnicity).

Describing normal physiological increase in serum creatinine at term

The normal physiological increase in creatinine at term was described by calculating the mean percentage increase in serum creatinine between 36 weeks to birth after exclusion of participants with pre-eclampsia, PIH, GDM, SGA < 5th centile, preterm birth, CKD EPI eGFR < 60 ml/min/1.73 m^2, a postpartum haemorrhage (>1 l), emergency caesarean section or instrumental delivery. Individuals with a rise in serum creatinine at term over 1.5× baseline creatinine (the AKIN definition of AKI [12]) were identified and APO incidence described, in order to examine the utility of applying this definition to pregnant individuals at term.

RESULTS

Participant characteristics

The study recruited 476 participants, mean age 31.6 years. Other demographics and the incidence of APOs are shown in Table 1. Information on missing data is in Supplementary Table 1. A total of 1875 serum creatinine measurements were made, over five

Table 1: Baseline participant characteristics and adverse pregnancy outcomes. Small numbers (≤5) are suppressed to avoid identification of individual participants.

Participant characteristics	N (%), mean (SD) or median (IQR)
Age, mean (SD)	31.6 (4.8)
BMI, median (IQR)	25.1 (22.3, 29.0)
Ethnicity, *n* (%)	
Asian/Asian British	12 (2.5)
Black/African/Caribbean/Black British	5 (1.1)
Mixed/multiple ethnic groups	8 (1.7)
Other ethnic group	7 (1.5)
White	442 (93.3)
Parity, *n* (%)	
Primiparous	231 (48.7)
Multiparous	243 (51.3)
Number of regular medications, *n* (%)[a]	
0	320 (68.8)
1	117 (25.2)
2+	28 (6.0)
Not recorded	11
Deprivation index deciles, median (IQR)	7 ([4], [9])
Multifetal pregnancy	≤5 (≤1)
Adverse pregnancy outcomes, *n* (%)	
Pre-eclampsia	12 (2.7)
Pregnancy-induced hypertension (PIH)	23 (5.2)
Gestational diabetes (GDM)	13 (2.7)
Placenta praevia	<5
Antepartum bleeding	23 (5.2)
Postpartum haemorrhage (500–1000 ml)	113 (24.8)
Postpartum haemorrhage (>1000 ml)	49 (10.8)
Emergency caesarean section	97 (22.0)
Instrumental delivery	57 (13.0)
Preterm birth	20 (4.8)
Gestation at delivery, mean	39.4 weeks (1.5)
Small for gestational age (SGA)	7 (1.6)
Large for gestational age (LGA)	41 (9.5)
Neonatal intensive care (NICU) admission	27 (6.1)

[a]Excluding vitamin D, folic acid, iron and pregnancy multivitamins; list of most commonly used medications is in the Supplementary Material.

time points (Fig. 1). The distribution of creatinine values by gestational age is shown in Fig. 2.

Gestation-specific reference ranges for serum creatinine in healthy pregnancy

Data from 66 participants with pre-eclampsia, PIH, GDM, SGA < 5th centile, preterm birth and CKD-EPI eGFR < 60 ml/min/1.73 m^2 were excluded from reference range calculations. Creatinine measurements in the remaining participants were approximately normally distributed (Supplemental Fig. S1). The gestation at which serum creatinine readings were taken in each trimester differed from the protocolized ranges as follows: first trimester: 5–15 weeks; second trimester: 24–33 weeks; third trimester: 34–39 weeks. Reference ranges for serum creatinine in healthy pregnancy were calculated as 37.0–66.6 μmol/l, 33.5–62.6 μmol/l and 34.4–66.3 μmol/l for first, second and third trimesters, respectively (Fig. 1, Table 2). Serum creatinine reached a nadir in the second trimester (28 weeks' gestation). Mean serum creatinine in healthy participants at birth and postpartum was 53.2 μmol/l (SD 9.2) and 57.8 μmol/l (SD 9.7) (Table 2).

APO incidence and abnormal kidney function in pregnancy

Five participants (1%; Table 2) were identified as having abnormal kidney function in pregnancy based on a serum creatinine above 77 μmol/l. Of these, one had PIH and two had pre-eclampsia, four had emergency caesarean sections, there were two preterm births and two NICU admissions.

By contrast, a serum creatinine value above at least one of the reference range upper limits during pregnancy was seen in 33 participants (8%). Of these, one had GDM, two PIH and four pre-eclampsia. Four had instrumental deliveries and 12 had emergency caesarean sections. There were two episodes of low birth weight, one SGA, three preterm delivery and two NICU admissions.

Trajectories of serum creatinine in those with and without APOs

Figure 3 shows the trajectories of serum creatinine for individuals with and without several APOs. Participants with APOs had higher serum creatinine in the third trimester compared to those without. Participants with PIH ($n = 23$) had higher mean serum creatinine values throughout pregnancy, birth and postpartum, compared to normotensive participants ($n = 408$), although confidence intervals overlapped until 35 weeks' gestation; three weeks prior to the average gestation at PIH diagnosis (38 weeks) (Fig. 3). Participants with pre-eclampsia ($n = 12$) had higher mean serum creatinine values from 14 weeks' gestation through to postpartum, compared to normotensive participants ($n = 408$), although confidence intervals overlapped until 32 weeks' gestation; 6 weeks prior to the average gestation at pre-eclampsia diagnosis (38 weeks and 3 days) (Fig. 3b).

Quantifying physiological increases in serum creatinine at delivery

The median increase in serum creatinine from 36 weeks to birth in healthy participants was 6.8% (95% CI 4.5%, 9.1%). Ten participants had a >1.5× increase in serum creatinine (the AKIN definition of AKI [12]). In this group, the incidence of APOs was high, with one having pre-eclampsia, three PIH, two GDM, four postpartum haemorrhage (>1000 ml), four instrumental delivery, and five emergency caesarian sections. In all 10, serum creatinine values suggested recovery to a creatinine level below the peak creatinine but above the 36-week value, indicative of 'true' AKI.

DISCUSSION

In this large UK prospective cohort study, we analysed 1875 longitudinal creatinine measurements in a healthy cohort of 476 participants in order to define trimester-specific reference ranges of 37–67 μmol/l (0.42–0.75 mg/dl), 34–63 μmol/l (0.38–0.71 mg/dl), 34–66 μmol/l (0.39–0.75 mg/dl) in first, second and third trimesters, respectively.

A previous UK study of healthy pregnancies defined an upper limit of normal for serum creatinine as 85 μmol/l, 80 μmol/l and 90 μmol/l for first, second and third trimesters, respectively [21]. However, most creatinine measurements in this study were performed in the second trimester ($n = 271/430$), with only 20 creatinine measurements used to derive the first trimester limit. The upper limit of our serum creatinine reference ranges are over 10 μmol/l lower than the creatinine threshold (≥77 μmol/l)

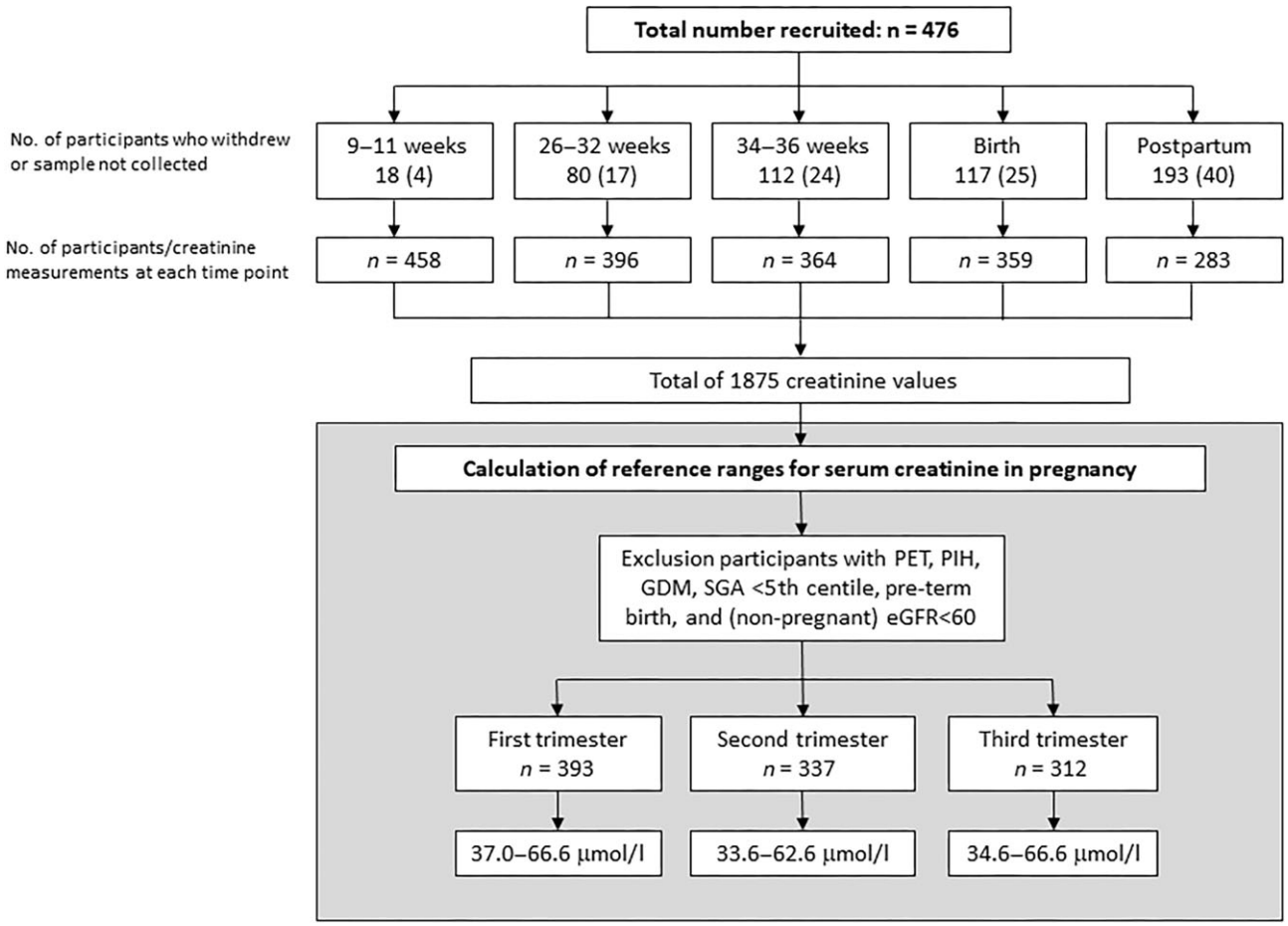

Figure 1: Recruitment and analyses flow diagram. Participant numbers: one creatinine measurement from each participant was taken at the prespecified time points (first, second and third trimesters; birth and 3–5 days postpartum) to provide a longitudinal series of creatinine values from the first trimester of pregnancy to postpartum for each participant. Number and percentage of missing data are as displayed. Calculation of references ranges for serum creatinine in pregnancy: participants who developed pre-eclampsia, pregnancy-induced hypertension (PIH), gestational diabetes (GDM), eGFR < 60 (as per non-pregnant CKD-EPI equation), small for gestational age (SGA) <5th centile or preterm birth (<37 weeks) were excluded from reference range calculations. Number of creatinine measurements included in reference range derivation are as displayed; 322 participants (68%) had all three creatinine measurements within pregnancy; 204 (43%) had all five creatinine measurements including delivery and postpartum measurements.

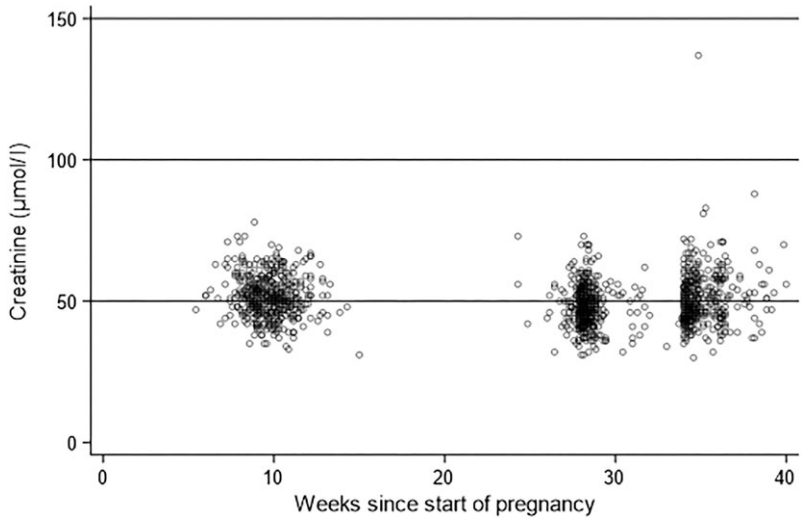

Figure 2: Scatter plot of serum creatinine by exact time of measurement.

Table 2: Distribution of serum creatinine during and after healthy pregnancy, with derived, gestation-specific reference ranges within pregnancy. Incidence of adverse pregnancy outcomes for those with serum creatinine outside these ranges, as compared to existing thresholds for abnormal serum creatinine.

	5–15 weeks	24–33 weeks	34–39 weeks	Birth	Postpartum
Reference range, μmol/l (mg/dl)	37.0–66.6 (0.42–0.75)	33.5–62.6 (0.38–0.71)	34.4–66.3 (0.39–0.75)		
Mean (SD)	51.8 (7.6)	48.1 (7.4)	50.3 (8.1)	53.2 (9.2)	57.8 (9.7)
Range	35–78	32–73	36–81	37–85	36–96
N	393	337	312	190	153
Number of participants above threshold for abnormal kidney function					
>77 μmol/l[a]	1 (0.2%)	0 (0%)	4 (1%)		
>Reference range[b]	12 (2%)	14 (4%)	19 (5%)		

[a]Recommended threshold for investigation of abnormal kidney function—Royal College of Physicians. Acute care toolkit 15: Managing acute medical problems in pregnancy. 2019.
[b]Reference range upper limit: 66.6 μmol/l for first trimester, 62.6 μmol/l for second trimester and 66.3 μmol/l for third trimester.

at which the UK Royal College of Physicians recommends investigation for abnormal kidney function in pregnancy [5], [6]. This recommendation is based on a systematic review that included three UK cohorts of low participant number (n = 10–13), two of which were conducted in the 1980s and hence are unlikely to be representative of the current UK pregnant population [5]. Although no comparable international guidance exists, recent prospective Chinese and Sri Lankan cohorts defined upper limit of normal (ULN) for serum creatinine as 68, 66 and 68 μmol/l or 70, 64 and 66 μmol/l in trimesters 1–3, respectively [22], [23]. Consistently, a 2019 meta-analysis of 29 studies proposed a ULN of 66 μmol/l [24]. Both our study and these larger international studies and meta-analyses suggest that a lower serum creatinine threshold to identify abnormal kidney function during pregnancy may be appropriate.

In addition to defining reference ranges for serum creatinine, our study identified trends in serum creatinine trajectories which may have clinical utility in identifying abnormal kidney function in pregnancy. First, we found a median increase in serum creatinine between 36 weeks and birth in healthy pregnancy of 6.8% (95% CI 4.5%, 9.1%). This may be used in clinical practice to identify abnormal rises in serum creatinine at term. Second, we described individuals meeting the AKIN definition of AKI (×1.5 increase in serum creatinine) at term, finding increased prevalence of APOs in this group, as well as the pattern of recovery of serum creatinine to a 'non-pregnant baseline'. This suggests that application of the AKIN definition of AKI may be appropriately applied to this group and may influence the interpretation of electronic AKI alerts in pregnant individuals. Third, creatinine trajectories among those with pre-eclampsia and PIH show a pattern of early increase in serum creatinine, as compared to those without APOs. This increase in serum creatinine appears to occur before clinical onset of pre-eclampsia or PIH and is in keeping with a recent retrospective study [25] using gestation-specific creatinine to predict pre-eclampsia, with measurements obtained at gestational weeks 14–16 having the greatest predictive power. Evidence in pregnant individuals with CKD suggests that failure of renal adaptation to pregnancy (<10% reduction in serum creatinine in early pregnancy) is associated with poorer pregnancy outcomes [7]. Thus, it is biologically plausible that detection of subtle second-trimester creatinine differences in seemingly healthy pregnancies identifies those with similarly impaired physiological adaptation to pregnancy who are predisposed to APOs. This finding warrants further evaluation in larger cohorts.

Our study illustrates the necessity for clearer clinical guidance on who should have serum creatinine measured and monitored in pregnancy. Current antenatal practice guidelines for the management of low-risk pregnancies in the UK, Europe and the USA do not recommend routine measurement of serum creatinine [26–28, 29]. Although measurement of serum creatinine in early pregnancy is recommended in those with known diabetes or CKD, this does not apply to other conditions commonly associated with CKD or higher-risk pregnancies, such as chronic hypertension or obesity [17, 30, 31]. Universal blood pressure, BMI, and pre-eclampsia screening at the first antenatal contact identifies high-risk pregnancies [29]. Given that significant overlap exists between the cardiometabolic risk factors that confer higher pregnancy risk, and those associated with kidney disease, routine creatinine measurement in the high-risk pregnant population may improve detection of CKD; however, the utility of universal testing of serum creatinine is unknown and remains an area of active research [28]. Clinical recognition of abnormality would support the provision of risk-stratified enhanced surveillance during and after pregnancy. This would include monitoring of kidney function and measures to reduce further risk in those with AKI, and future monitoring and treatment in those with CKD [32]. Given the association between kidney dysfunction (AKI and CKD) and future risk of pre-eclampsia [15], if subclinical AKI in pregnancy was identified through routine measurement, low-dose aspirin could be offered in future pregnancy as the only medication presently available to reduce likelihood of developing pre-eclampsia [33].

Our study's strengths include a large UK sample of healthy pregnant participants, with multiple serial serum creatinine measurements in each participant, collected routinely rather than according to clinical indication. The available clinical data are of high granularity. There are some limitations: recruitment was conducted during the COVID-19 pandemic, consequently a larger number of blood tests were omitted than would otherwise have been expected. The most significant proportion of missing data (38%) was in the postpartum period. The data collected (at 2–10 days postpartum) may represent a less healthy subset of the overall postpartum population, as those accessing healthcare during this time may have been more likely to have study bloods taken. The proportion of missing data within pregnancy was much lower (4–23%), hence, derived reference ranges are likely to accurately represent the studied population. Reflecting to some extent the population of our region, the cohort was less ethnically diverse than the overall UK population. White

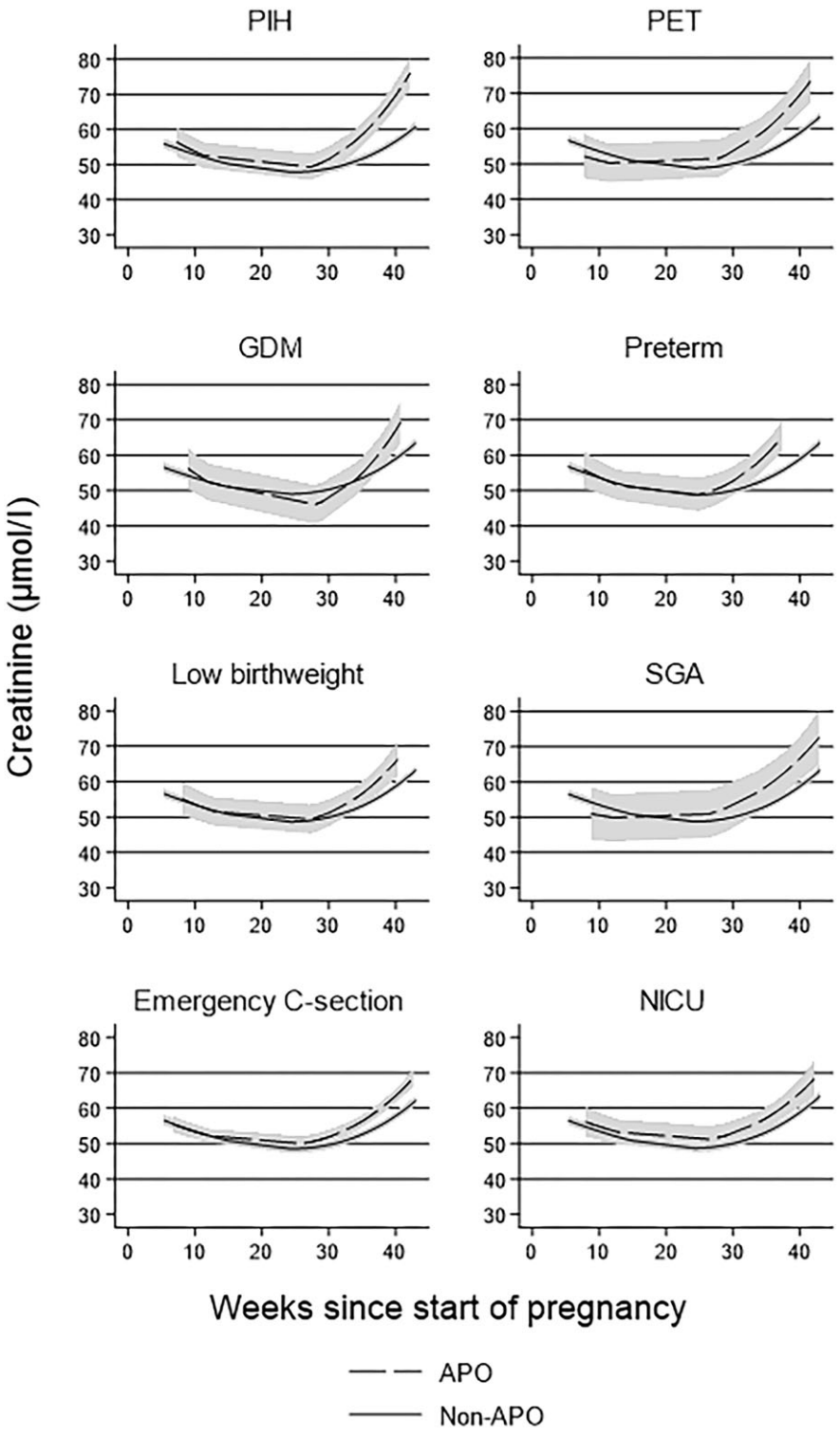

Figure 3: Comparison of creatinine trajectories between those with adverse pregnancy outcomes and a comparator group (with no adverse pregnancy outcome). Shaded areas represent 95% confidence intervals. Estimations derived using multilevel fractional polynomials. PIH: pregnancy-induced hypertension; GDM: gestational diabetes; SGA: small for gestational age; NICU: neonatal intensive care admission.

participants were overrepresented in our study (comprising 93%, as compared to 78% of those giving birth in England and Wales in 2018–2019) and Black and Asian participants underrepresented (1.1% and 2.5%, respectively, as compared to 11% and 5% nationally) [34]. As such, the confidence with which we can extrapolate our findings to more ethnically diverse groups is diminished, given the significantly elevated risk of in-pregnancy complications (including death) in Black and Asian populations [35]. The age of the cohort was representative of pregnant individuals in Western Europe, but less representative of low- and

middle-income countries. Deprivation rates were comparable to those of the general UK population (with 11% of participants in the most deprived quintile, as compared to 15% nationally) [34]. In future work, we aim to validate our reference ranges in comparable UK and international cohorts with significantly greater representation of Black and Asian participants to ensure generalizability of our results to those at highest risk of APOs.

The pregnancy-specific serum creatinine reference ranges defined here provide the most currently applicable reference ranges for populations of high-income countries. Our reference ranges suggest that investigation for abnormal kidney function in pregnancy should be considered at a lower creatinine threshold than that in current UK obstetric guidance. Validation of our findings in more diverse cohorts is required to further examine associations between creatinine values and APOs, and to inform future national and international guidance on monitoring of serum creatinine in pregnancy.

SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

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DATA AVAILABILITY STATEMENT

The data set used to produce this manuscript included single-participant clinical details relating to pregnancy and other clinical information, so are not shared. Further, anonymized, summary statistics are available on request by contacting the authors.

CONFLICT OF INTEREST STATEMENT

None of the authors have any conflicts of interest to declare.

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