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Development of normal reference intervals for renal function in pregnancy: a secondary analysis of clinical trial data

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ABSTRACT

Background: Due to its potential nephrotoxicity, screening for pre-existing renal function disorders has become a routine clinical assessment for initiating Tenofovir diphosphate fumarate (TDF)-containing antiretroviral treatment (ART) or pre-exposure prophylaxis (PrEP) in pregnant and non-pregnant adults. We aimed to establish reference values for commonly used markers of renal function in healthy pregnant women of African origin.

Methods: Pregnant women ≥18 years, not living with HIV, and at 14–28 weeks gestation were enrolled in a PrEP clinical trial in Durban, South Africa between September 2017 and December 2019. Women were monitored 4-weekly during pregnancy until six months postpartum. We measured maternal weight and serum creatinine (sCr) at each visit and calculated creatinine clearance (CrCl) rates using the Cockcroft–Gault (CG) and Modification of Diet in Renal Disease (MDRD) formulae. Reference ranges for sCr and CrCl by CG and MDRD calculations were derived from the mean ± 2SD of values for pregnancy and postdelivery.

Results: Between 14-–and 40 weeks gestation, 249 African women not exposed to TDF-PrEP contributed a total of 1193 renal function values. Postdelivery, 207 of these women contributed to 800 renal function values. The normal reference range for sCr was 30–57 and 32–60 umol/l in the 2nd and 3rd trimesters of pregnancy. Normal reference ranges for CrCl using the MDRD calculation were 129–282 and 119–267 ml/min/1.73m^2 for the 2nd and 3rd trimesters, respectively. Using the CG method of calculation, normal reference ranges for CrCl were 120—304 and 123–309 ml/min/1.73m^2 for the 2nd and 3rd trimesters respectively. In comparison, the normal reference range for sCr, CrCl by MDRD and CG calculations postpartum was 40–77 umol/l, 92–201, and 90–238 ml/min/1.73m^2, respectively.

Conclusions: In African women, the Upper Limit of Normal (ULN) for sCr in pregnancy is approximately 20% lower than 6 months postnatally. Inversely, the Lower Limit of Normal (LLN) for CrCl using either MDRD or CG equation is approximately 35% higher than 6 months postnatally. We provide normal reference ranges for sCr and CrCl for both methods of calculation and appropriate for the 2nd and 3rd trimesters of pregnancy in African women.

ARTICLE HISTORY

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KEYWORDS

Renal function; serum creatinine; creatinine clearance

PLAIN LANGUAGE SUMMARY

Screening for pre-existing renal function disorders has become a routine clinical assessment for initiating TDF-containing antiretroviral treatment or pre-exposure prophylaxis in adults including pregnant women. Pregnancy inherently increases renal function, hence normal reference standards for non-pregnant adults cannot be used for pregnant women. In a secondary analysis of data from a healthy pregnant population not living with HIV who participated in a PrEP clinical trial, we established reference intervals for serum creatinine (sCr) concentration and creatinine clearance (CrCl) during pregnancy and postpartum in an African population. Using sCr and CrCl values for 249 healthy pregnant African women, we can confirm that the upper limit of normal for sCr in pregnancy is 20% lower than that for the 6-month postnatal period and recommend an upper limit of 57 umol/l and 60 umol/l in the second and third trimesters respectively to determine normal renal function in pregnant African women.

We further determined the lower limit of normal for creatinine clearance using two methods of calculation, which was 35% higher than that of the postnatal period. Using the modification of diet in renal disease calculation, we recommend a lower limit of 129 and 119 ml/min/1.73m^2 for the second and third trimesters respectively. Using the Cockcroft–Gault calculation, we recommend a lower limit of 120 and 123 ml/min/1.73m^2 for the second and third trimesters respectively. Using current standard cut-off values estimated for adults may lead to underreporting of abnormal renal function in African pregnant women.

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Introduction

High renal plasma flow associated with increased cardiac output during pregnancy is known to increase athe glomerular filtration rate (GFR) by 30 to 50% (Meah *et al*. 2016, Odutayo and Hladunewich 2012). In turn, increased GFR during pregnancy is accompanied by a decrease in serum creatinine (Harel *et al*. 2019). Generally, serum creatinine is mostly influenced by muscle mass, age, weight, and sex (Levey *et al*. 2020, Pottel *et al*. 2008), and remains the most commonly used marker of renal function in clinical practice. Creatinine clearance (CrCl) is also used to assess renal function and two formulae are commonly or interchangeably used to assess renal function in adults (Levey *et al*. 1999, Cockcroft and Gault 1976). The Modified Diet Renal Disease (MDRD) formula adjusts for age, sex, and ethnicity while the Cockcroft–Gault equation adjusts for age, sex, and weight and is reported as ml/min/1.73m adults (Levey *et al*. 1999, Cockcroft and Gault 1976).

Renal function is not routinely assessed during pregnancy and is generally only indicated in pregnancy-related hypertension or if patients present with a history of chronic kidney disease (Department of Health, South Africa, 2015). In such instances and generally feasible for patients with overnight stay at a health facility, creatinine clearance by 24-hour urine collection is the recommended standard for measurement of GFR, and clinicians have been strongly advised against using either the MDRD or Cockcroft-Gault equations appear to either underestimate or overestimate eGFR in pregnancy (Côté *et al*. 2010, Koetje *et al*. 2011).

However, in recent years renal function assessment has been recommended for all pregnant women receiving antiretrovirals as treatment (ART) or as preexposure prophylaxis (PrEP), since certain antiretrovirals particularly Tenofovir diphosphate fumarate (TDF) are known to have adverse effects on renal function (Yacoub *et al*. 2016). Hence, screening for pre-existing renal function disorders has become a routine clinical assessment for initiating TDF-containing ART or PrEP in adults (Department of Health, South Africa, 2019). For routine screening, creatinine clearance by 24-hour urine collection is not a practical option, hence the South African 2019 ART guidelines recommend initiating ART in adults whose eGFR using the MDRD equation is >50ml/min/1.73m^2 and for PrEP initiation eGFR >60ml/min/1.73m (Odutayo and Hladunewich 2012, Department of Health, South Africa, 2019). For pregnant women, serum creatine concentration <85 umol/l is considered safe to use TDF-ART or PrEP. While there are a handful of studies that describe changes in eGFR during pregnancy (Harel *et al*. 2019, Agampodi *et al*. 2023), there are no known studies that have generated normal reference values for eGFR using the MDRD or Cockcroft-Gault calculation for pregnant African women, and in addition there are no studies of sCr normal reference ranges for pregnant women living in high HIV burden countries where TDF-ART and PrEP are being widely prescribed (Wiles *et al*. 2018).

In a secondary analysis of data from a healthy pregnant population not living with HIV who participated in a PrEP clinical trial (Moodley *et al*. 2023), we established reference intervals for serum creatinine concentration and creatinine clearance during pregnancy and postpartum in an African population.

Methods

This is a secondary analysis of a large randomised controlled open-label clinical trial (RCT) investigating the safety of Tenofovir disoproxil fumarate/Emtricitabine when used as pre-exposure prophylaxis in healthy pregnant African women (Moodley *et al*. 2023). The RCT titled; 'Immediate or Deferred Pre-exposure Prophylaxis for HIV Prevention: Safe Options for Pregnant and Lactating Women, An Open-Label Randomised Control Study (UKZN Ethics Approval BFC243/16)' was conducted at a research clinic based at Prince Mshiyeni Memorial Hospital, Umlazi, Durban, South Africa. Pregnant women with no pregnancy complications at baseline were enrolled between September 2017 and November 2018 and randomised to either immediate PrEP or delayed PrEP until breastfeeding cessation. Women were enrolled in the 2nd trimester (between 14 and 28 weeks as assessed by ultrasonography) and followed up at 4 weekly intervals until 3 months postdelivery and thereafter three monthly until 18 months postpartum. For this secondary analysis, we included women not exposed to TDF-PrEP during pregnancy or lactation (Deferred Group) and followed up until 6 months postpartum.

At the enrolment visit, gestational age was measured by ultrasonography and physical examination included weight and height measurements. Weight measurements were repeated at 4 weekly intervals during pregnancy and until 6 months postpartum. Weight and height measurements were used to calculate Body Mass Index (BMI) at all study visits. Women were tested for HIV by point-of-care testing and 2.5 ml of blood was collected for serum creatinine at 4 weekly intervals. Serum creatinine (umol/l) was measured in real-time by a commercial laboratory using the conventional Jaffe assay on the Beckman Coulter Analyser.

The estimated GFR (CrCl) was calculated using the Cockcroft-Gault (CG) and Modification of Diet in Renal Disease (MDRD) equations.

Modification of Diet in Renal Disease equation (Levey *et al*. 1999)*:*

$$\mathrm{CrCl}\left(\mathrm{ml/min/1.73m^2}\right) = \left[186\times(\mathrm{sCr})^{-1.154}\times(\mathrm{age})^{-0.203}\right]\times 0.742 \text{ for female}$$

Cockcroft-Gault equation (Cockcroft and Gault 1976)*:*

$$\mathrm{CrCl}\left(\mathrm{ml/min/1.73m^2}\right) = \left[(140-\mathrm{age})\times \mathrm{weight}/(72-\mathrm{sCr})\right]\mathrm{x}\,0.85 \text{ for female}$$

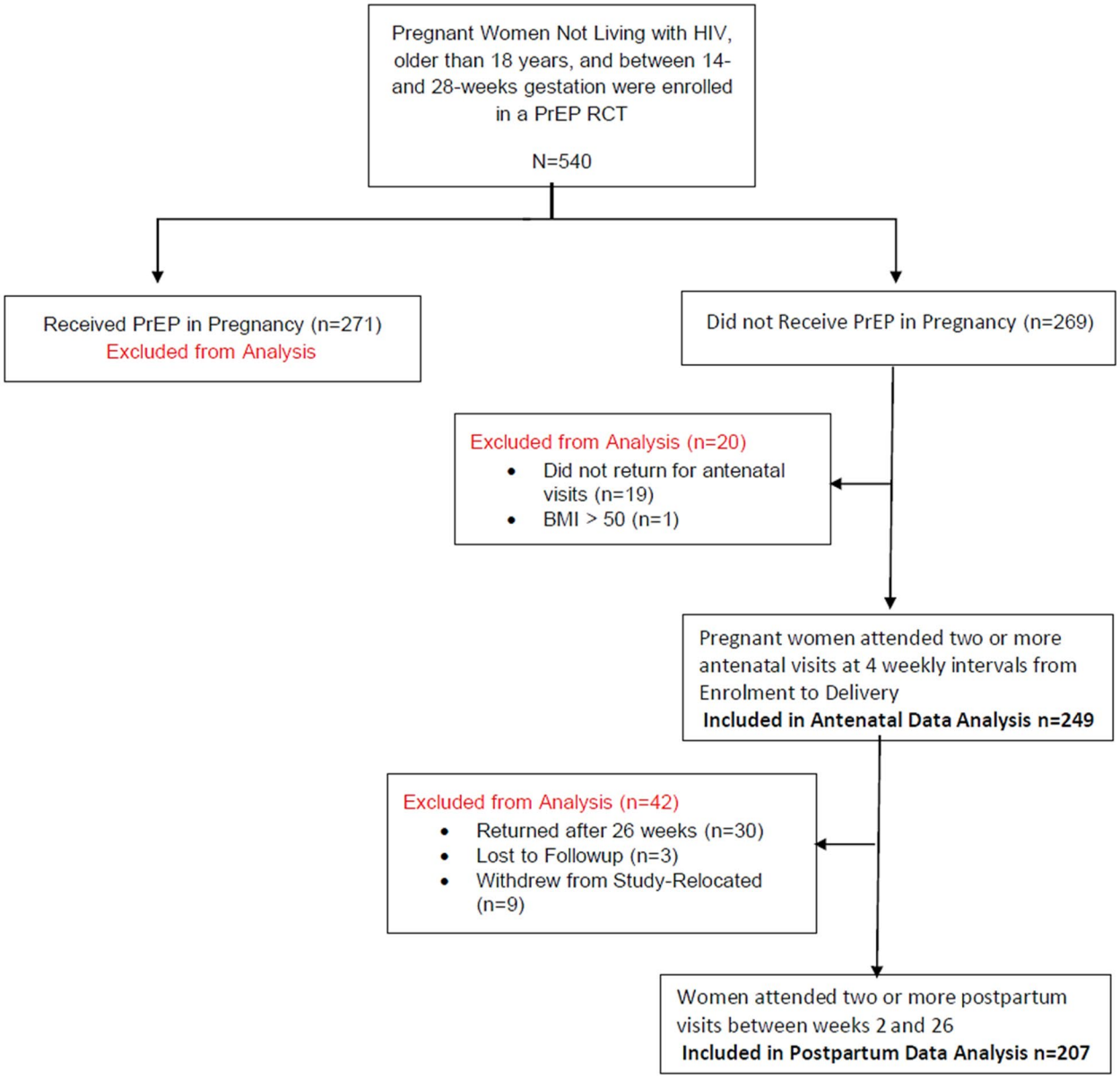
The Institutional Review Board of the University of KwaZulu-Natal approved the parent study (BFC 243/16) and this sub-study (BREC/00003765/2022). For this retrospective de-identified data analysis, the Institutional Review Board of the University of KwaZulu-Natal waived the need for informed consent (BREC/00003765/2022).

Statistical analysis

Data were analysed using SPSS version 25. Descriptive statistics such as frequencies and percentages were used to summarise categorical variables. Central tendency and dispersion of data were measured using means and standard deviations for normally distributed variables and medians and interquartile ranges for skewed variables.

The association of age and BMI with eGFR at enrolment during pregnancy was assessed using scatterplots and a lowess-nonparametric smoother. These graphs confirmed the use of linear terms for age and BMI in the regression models used for estimating the mean eGFR over time (gestational age). For both the eGFR approaches, a square root transformation was used to handle the slightly positive skewness in the data at all time points. A linear generalised estimation equations (GEE) model was used to model the square root of eGFR on non-linear gestational age (time effect) using fractional polynomials and linear effects for age and BMI, taking the repeated measures of each participant into account. The reference range was calculated using the predicted mean eGFR plus or minus 2x the standard deviation at each time point. The standard deviation of the transformed eGFR measurements for gestational age <30 weeks was used. The estimated reference range values were back-transformed to the original scale resulting in slightly asymmetric limits. The reference range analysis was done for gestational age <=40 weeks and BMI < 50.

For the postpartum analysis, the same approach as for the gestational age was used. It was established that time was linear for creatinine and eGFR and therefore linear mixed-effects models were used with time as a linear effect and the random effects using intercepts only. Creatinine was



PrEP Pre-exposure Prophylaxis, RCT Randomised Control Trial, BMI Body Mass Index

Figure 1. STROBE Flow Chart of Participants Included in Study Analysis.

modelled on the original scale whereas eGFR -MDRD was log-transformed and eGFR-CG using the inverse square root transformation. Time was not significant in any of the models, but it ensured a better fit across the time points.

Results

Of the 540 pregnant African women enrolled in the parent study, 249 women who did not initiate TDF-PrEP during pregnancy, with a median age of 23 years, enrolled between 14 and 28 weeks of gestation and attended two or more subsequent antenatal visits until delivery were included in this secondary analysis (Figure 1). Baseline characteristics are tabulated in Table 1. An estimated 47% of women were first-time pregnancies, and 47.8% had two or three pregnancies. Women booked for antenatal care at a median gestational age of 19 weeks (IQR 16; 22), with a median BMI of 26.6 (IQR 23.2; 31.1) at enrolment, and 31.7% (79/249) met the definition of Class II obesity (BMI of 35 to <40) (https://www.cdc.gov/obesity/basics/adult-defining.html). Clinically, three (1.2%) pregnant women developed pre-eclampsia, and one (0.4%) was diagnosed with gestational hypertension during the course of pregnancy. After delivery, 207 women attended two or more postpartum visits between 2 and 26 weeks and were in included in the postpartum data analysis (Figure 1).

Cumulatively, 249 pregnant women contributed a total of 1193 renal function results during pregnancy. In Table 2 we report the number of tests and mean and standard deviation for serum creatinine and creatinine clearance for every 2-week gestational intervals. Postdelivery, 207 of these women contributed to 800 renal function tests between 2 and 26 weeks postpartum, the number of tests and mean and standard deviation for serum creatinine and creatinine clearance are also tabulated (Table 2).

Serum creatinine levels remained constant from 14 weeks to 28 weeks gestation followed by a subtle increase in the 3rd trimester and postdelivery (Figure 2A). Creatinine clearance by Cockroft-Gault calculation remained consistently high (>200 ml/min/1.73m^2) throughout pregnancy while creatinine clearance by Modified Diet Renal Disease calculation decreased in the 3rd trimester from 32 weeks of gestation (Figure 2B). Creatinine clearance by both calculations decreased by 50 ml/min within 2 weeks post-delivery and remained constant until 6 months.

There was no significant difference in sCr or creatinine clearance between the small number of women with hypertensive disorders and normotensive women.

Estimated normal reference range in pregnancy

Reference ranges for creatinine clearance by Cockroft-Gault (CG) and Modified Diet Renal Disease (MDRD) calculations for use during pregnancy were derived from the mean and ± 2 standard deviations of values for each week of gestation from 14 weeks to 40 weeks after adjusting for age and BMI as shown in Figures 3B and C. The creatinine clearance is clearly stable over the first 30 to 33 weeks and then show a steady decline with both the MDRD and CG equations. Similarly, reference ranges for serum creatinine during pregnancy were derived from the mean ± 2 standard deviations of values for each week of gestation from 14 weeks to 40 weeks as shown in Figure 3A.

Based on the above inferences, the normal reference range for serum creatinine, and creatinine clearance by MDRD, and CG calculations during 14–33 weeks gestation and >33 weeks gestation in pregnancy and for 2 to 26 weeks postpartum are illustrated in Table 3. The reference range for serum creatinine does not differ much between 14 weeks of pregnancy until delivery but the upper limit of normal in pregnancy is

Table 1. Study population characteristics.

Characteristics	N = 249
Age (Years)	
Median (IQR)	23 (20; 27)
Gravidity Median (IQR)	
Gravidity n (%)	2 (1; 2)
1	117 (47.0%)
2-3	119 (47.8%)
>3	13 (5.2%)
Height (cm)	
Median (IQR)	158 (154; 162)
Weight at 1st Antenatal Visit (kg)	
Median (IQR)	66.8 (57.5; 78.6)
Gestational Age at 1st Antenatal Visit (Weeks)	
Median (IQR)	19 (16; 22)
Body Mass Index (BMI)at First Antenatal Visit	
Median (IQR)	26.6 (23.2; 31.1)
BMI Category n (%; 95%CI)	
Underweight	3 (1.2; 0.3-3.5)
Normal	95 (38.2; 32.1-44.5)
Overweight	72 (28.9; 23.4-35.0)
Obese	79 (31.7; 26.0-37.9)

SD: standard deviation; IQR: interquartile range.

Table 2. Mean values of serum creatinine and creatinine clearance by cockroft-gault and modified diet renal disease calculations stratified by gestational age and postpartum visits.

	Number of Tests	Serum creatinine (umol/l) Mean (SD)	CrCl (MDRD) ml/min/1.73m^2 Mean (SD)	CrCl (CG) ml/min/1.73m^2 Mean (SD)
Antepartum (Gestation)				
14 weeks	38	43.3 (7.4)	197.2 (33.9)	187.9 (40.9)
16 weeks	35	42.3 (6.2)	197.3 (35.8)	193.0 (39.7)
18 weeks	46	41.0 (6.8)	209.4 (39.9)	206.5 (43.2)
20 weeks	70	42.9 (8.3)	198.4 (41.3)	202.8 (46.7)
22 weeks	90	42.0 (6.8)	202.1 (37.0)	201.4 (51.3)
24 weeks	97	42.7 (7.1)	199.6 (39.5)	201.0 (45.2)
26 weeks	114	42.4 (6.7)	199.7 (41.8)	213.6 (51.3)
28 weeks	123	41.4 (6.7)	206.7 (41.3)	209.4 (50.1)
30 weeks	97	42.2 (7.1)	200.8 (42.4)	220.0 (53.4)
32 weeks	139	42.5 (7.0)	200.7 (39.4)	213.0 (50.3)
34 weeks	102	44.0 (8.1)	192.1 (40.0)	206.9 (50.7)
36 weeks	123	43.9 (7.3)	192.9 (38.0)	217.5 (50.4)
38 weeks	69	45.2 (8.1)	186.7 (38.8)	206.7 (50.2)
40 weeks	50	46.7 (8.6)	180.2 (38.5)	200.8 (41.9)
Postpartum				
2 weeks	154	57.7 (10.0)	140.9 (29.2)	146.3 (34.8)
10 weeks	132	59.2 (9.5)	135.7 (25.3)	139.4 (35.5)
14 weeks	138	58.2 (8.9)	138.5 (26.4)	142.9 (37.8)
18 weeks	132	57.9 (9.5)	139.0 (27.6)	144.8 (37.9)
22 weeks	128	57.1 (8.8)	140.0 (24.4)	147.4 (41.6)
26 weeks	116	57.7 (9.2)	138.8 (26.5)	148.2 (37.6)

SD: standard deviation; CrCl: creatinine clearance; MDRD: modified diet renal disease; CG: cockroft-gault.

approximately 20% lower than the upper limit of normal six months postnatally as a result of physiological changes in pregnancy. And inversely, the lower limit of normal for creatinine clearance using either equation is approximately 35% higher than the lower limit of normal six months postnatally.

Discussion

In this secondary analysis of clinical trial data for healthy pregnant African women, we can confirm renal function measured as eGFR (CrCl) remained consistently high (>200 ml/min/1.73m^2) throughout pregnancy and then decreased by 50 ml/min post-delivery, thereafter remaining constant until 6 months postdelivery. Both Cockcroft-Gault and MDRD calculations for estimating GFR were comparable during pregnancy and postpartum, with subtle differences in the 3rd trimester. We have also confirmed that eGFR in this African population was dependent on maternal age and body mass index. Serum creatinine levels remained constant between 40 and 46 umol/l throughout pregnancy and then increased to 58 umol/l postdelivery. The normal reference range for sCr does not vary much between 14 weeks of pregnancy and delivery but the ULN in pregnancy is approximately 20% lower than the ULN six months postnatally. And inversely, the LLN for CrCl using either Cockcroft-Gault or MDRD equation is approximately 35% higher than the LLN six months postnatally.

The 42–44% increase in GFR observed in our cohort of pregnant African women not living with HIV, is consistent with a meta-analysis of studies conducted in other pregnant population groups globally (40–50%) (Lopes van Balen *et al.* 2019). However, while the eGFR in the metanalysis peaked at ± 21 weeks, the eGFR by Cockcroft-Gault calculation in our study population peaked at ± 33 weeks gestation. eGFR by MDRD equation peaked at ±24 weeks which was closer to the observation made in the metanalysis. Seemingly eGFR in several studies included in the metanalysis may have been calculated using the MDRD equation. Variability in performance between the Cockcroft-Gault and MDRD equations may likely be attributed to an increase in body weight in the 3rd trimester of pregnancy. eGFR by Cockcroft-Gault equation is

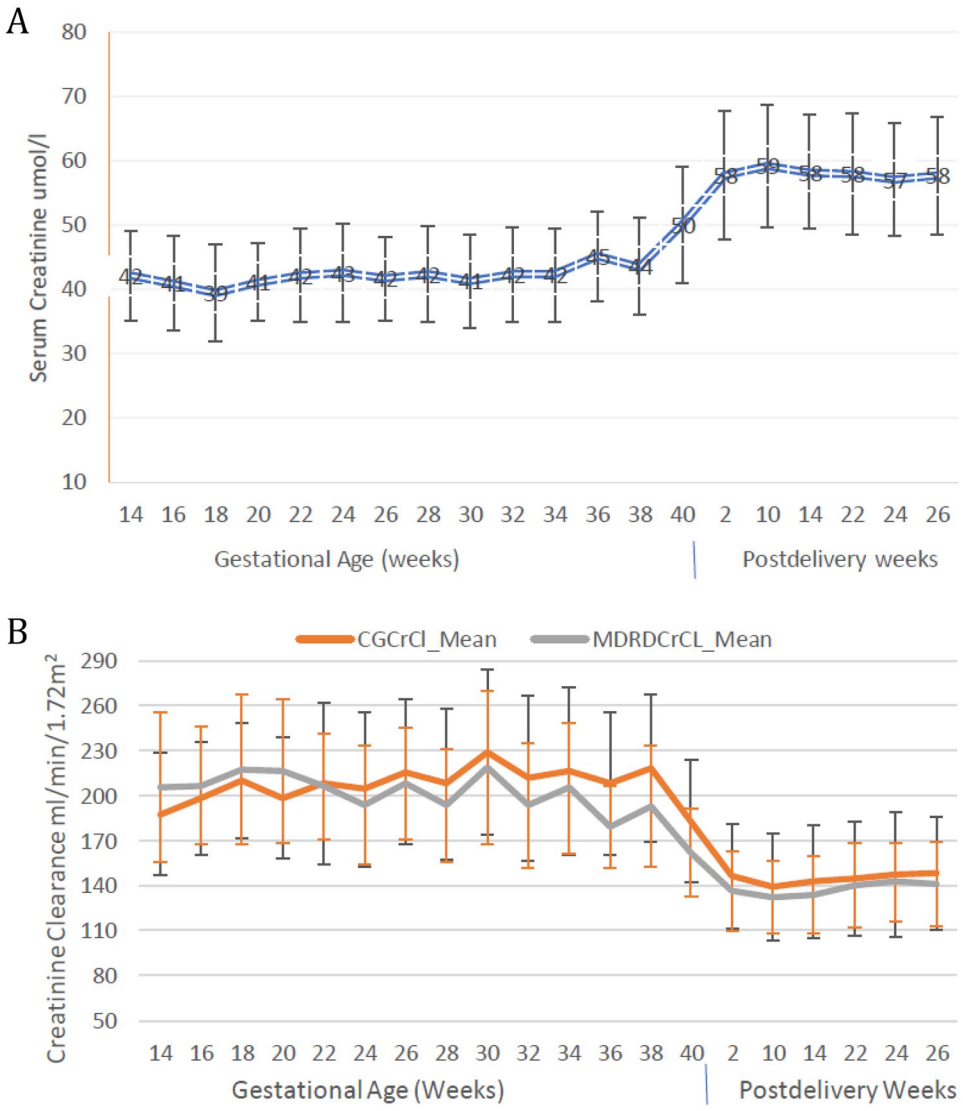


Figure 2. Change in Mean Serum Creatinine (A) and Creatinine Clearance (CrCl) by Cockroft-Gault (CG) and Modified Diet Renal Disease (MDRD) Calculations (B) during pregnancy and 6 months postdelivery.

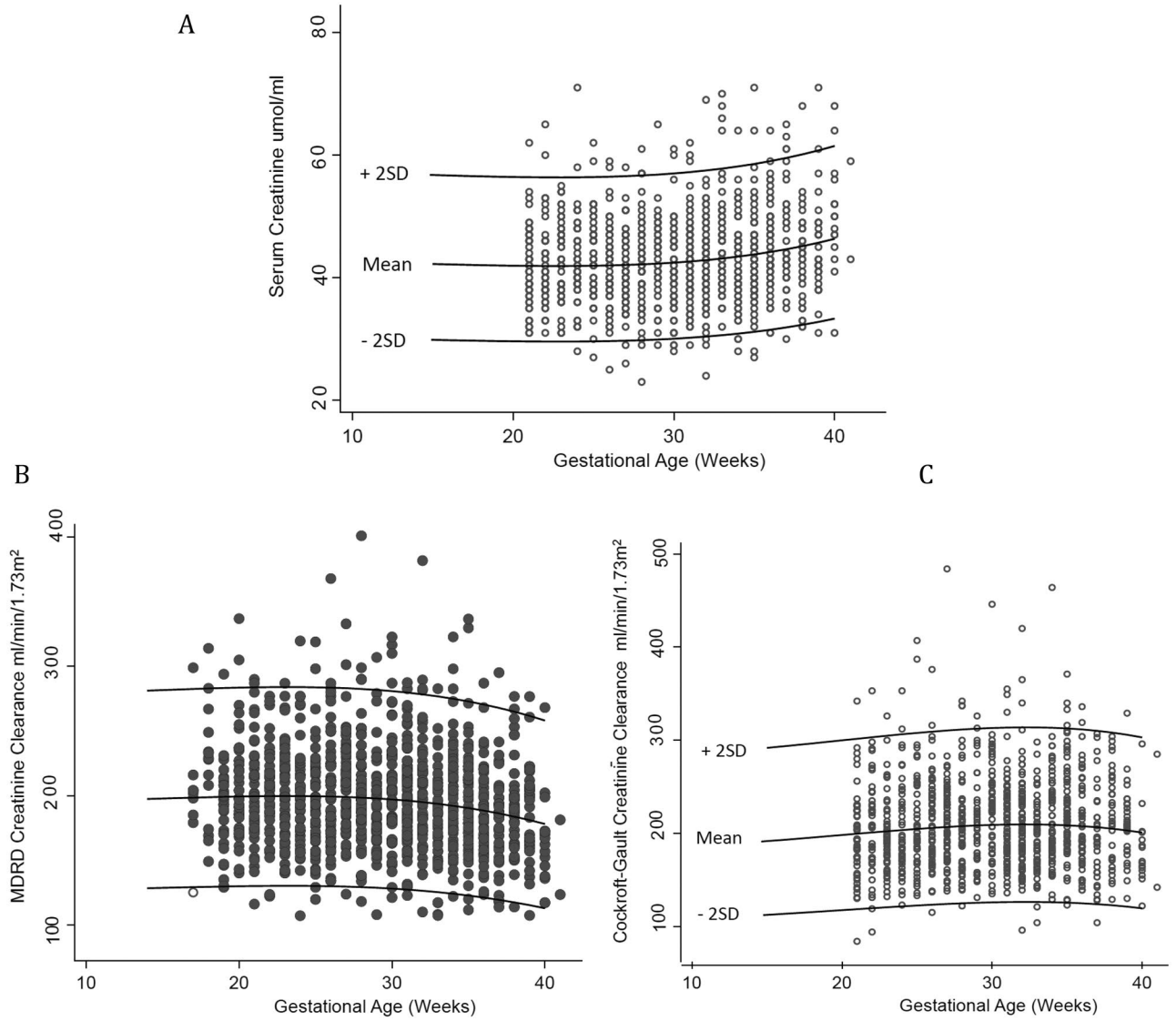


Figure 3. Estimated Normal reference range for Serum Creatinine (A), Creatinine Clearance by Modified Diet Renal Disease (MDRD) (B), and Cockroft-Gault Formula (C) between 14 and 40 weeks gestation.

proportional to body weight (De Waal *et al*. 2017, Chudleigh *et al*. 2008), as observed in our study as well. eGFR was also dependent on maternal age in our study; consistent with other studies of non-pregnant adults (De Waal *et al*. 2017, Michels *et al*. 2010). There was a tendency for older women to have much lower CrCl, although our pregnant population was a fairly young cohort and lower CrCl was not commonly observed. Other factors that could likely affect the sCr and eGFR in pregnancy and postpartum are gestational hypertension and pre-eclampsia. 15% of patients with pre-eclampsia will develop acute kidney injury (Conti-Ramsden *et al*. 2019). In our study, renal function measures for the handful of women with hypertensive disorders were not significantly different from normotensive women.

Derivation of the normal reference range for CrCl using both equations (CG and MDRD) and after adjusting for maternal age and BMI in our pregnant African population yielded values of minimal variability between study-defined gestational periods < 33 weeks and ≥ 33 weeks. We, therefore, propose the Lower Limit of Normal (LLN) of 129 and 119 ml/min/1.73m^2 for the 2nd and 3rd trimesters respectively when using the MDRD method calculation; and 120 and 123 ml/min/1.73m^2 when using the CG method of calculation. Based on the rate of change of approximately 40% reduction in GFR from pregnancy to six months postnatally, the recommended cut-off of 90 ml/min/1.73^2 as eligibility for TDF- containing ART or enhanced monitoring for nephrotoxicity in pregnant women as per most ART Guidelines (Department of Health, South Africa 2019, Schaefer *et al*. 2022) is equivalent to approximately 54 ml/min in the non-pregnant state, which would be considered a sign of moderate stage 3 chronic kidney disease in adults (Stevens and Levin 2013). Essentially both MDRD and Cockcroft-Gault equations overestimate eGFR during pregnancy, but could still be used within the context of pregnancy-derived normal reference ranges.

As a result of the physiological effects of pregnancy on renal function (eGFR) and the absence of guidance on what is

Table 3. Reference intervals for serum creatinine and creatinine clearance by cockroft-gault and modified diet renal disease calculations in pregnancy and up to 6 months postdelivery.

	Mean	Minimum	Maximum	−2 SD	+2 SD	Reference Interval
Serum Creatinine (umol/l)						
14–33 weeks gestation	42	25	87	30	57	30-57
> 33 weeks gestation	45	23	71	32	60	32-60
2 – 26 weeks postdelivery	58	35	76	40	77	40-77
CrCl MDRD (ml/min/1.73m^2)						
14–33 weeks gestation	198	87	368	129	282	129-282
> 33 weeks gestation	186	107	401	119	267	119-267
2 – 26 weeks postdelivery	136	94	232	92	201	92-201
CrCl CG (ml/min/1.73m^2)						
14-33 weeks gestation	202	76	484	120	304	120-304
> 33 weeks gestation	206	96	464	123	309	123-309
2 – 26 weeks postdelivery	138	84	272	90	238	90-238

SD: standard deviation; CrCl: creatinine clearance; MDRD: modified diet renal disease; CG: cockroft-gault.

considered to be normal in pregnancy, clinicians commonly depend on absolute serum creatinine (sCr) levels, but here again, there are no normative reference values for sCR in pregnancy. From our observation, sCr levels in pregnancy are ± 20% lower in pregnancy when compared to the postdelivery state and inversely related to eGFR confirming that pregnancy also affects systemic levels of Creatinine. Our findings concur with a systematic review by Wiles et al. 2018 reporting that mean serum creatinine in the first, second, and third trimesters of pregnancy were 16%, 23%, and 20% lower compared to nonpregnant adults. We propose an Upper Limit of Normal (ULN) of 57 and 60 umol/l in the 2nd and 3rd trimesters respectively and 77 umol/l postdelivery. The metanalysis by Lopes van Balen *et al*. (2019) proposed 66 umol/l be set as a cut-off in pregnancy.

Among pregnant women living with HIV in South Africa, Myer and colleagues reported <1% of pregnant women considered with moderate renal dysfunction compared to 7% in non-pregnant adults (Myer *et al*. 2013). Only 0.4% (1/238) of pregnant women had a CrCl, 50 ml/min/1.73m^2. The authors concluded that renal dysfunction is less common in pregnant women living with HIV when compared to non-pregnant adults using an sCr cut-off of 85 umol/l and CrCl of 50 ml/min/1.73m^2 across pregnant and non-pregnant adults. We believe, more pregnant women may have early signs of renal disease but were missed using renal marker thresholds for non-pregnant adults. Extrapolating from our data, the ULN for sCr in pregnancy should have been set 20% less than the cut-off for the postnatal group and the LLN for CrCl should have been set 40% higher.

Our study has a few limitations. Firstly, we did not use the gold standard of measuring renal sufficiency which would require 24-hour urine collection to calculate Creatinine Clearance. Nonetheless, we evaluated more practical and commonly used formulae to assess estimated GFR. Secondly, our study population did not include non-pregnant women who would have served as a true control group for comparison with the pregnant group. Thirdly, our study population only included African women and our derived normal reference ranges may not apply to other ethnic groups. Finally, we were unable to use the derived reference ranges in the same study population to determine the prevalence of renal adverse events, given that these pregnant women contributed to the normal reference range.

In conclusion, the Upper Limit of Normal (ULN) for sCr in pregnancy is approximately 20% lower than the ULN postnatally up to 6 months. Inversely, the Lower Limit of Normal (LLN) for CrCl using either equation is approximately 35% higher than the LLN postnatally up to 6 months.

Acknowledgements

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Ethical approval and consent to participate

The Institutional Review Board of the University of KwaZulu-Natal approved the parent study (BFC 243/16) for which participants provided written informed consent. The substudy (Ref BREC/00003765/2022) which was a retrospective analysis of de-identified data was also approved by the Institutional Review Board of the University of KwaZulu-Natal, who also waived the need for informed consent. This research was conducted in accordance with the relevant guidelines and regulations in the Declaration of Helsinki.

Consent for publication

Not applicable.

Authors' contributions

ZL, DM and MS conceptualised the study, interpreted the data for the study, and drafted the manuscript. MN collected and interpreted the data for this study. CL analysed the data and provided statistical guidance to interpret and present the findings. GG contributed to the collection and interpretation of data for this study. All authors provided a critical review of this manuscript, approved the final version to be published, and agreed to be accountable for all aspects of the work.

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Data availability statement

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

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