Gestational period-specific renal functions: Evidence from a large, community-based, prospective cohort in rural Sri Lanka

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Abstract

Objective To estimate the gestational age-specific serum creatinine (sCr) in pregnancy. Design A population-based prospective cohort study. Settings Anuradhapura district, Sri Lanka Population or sample Study group: Healthy pregnant women with a period of gestation less than 12 weeks and without pre-existing medical conditions. Comparison group: A sample of non-pregnant reproductive age females from a population-based renal screening. Methods Baseline data were compared among pregnant and non-pregnant groups and the pregnant women were followed-up until the end of the second trimester. Main Outcome Measures Gestational period-specific sCr. Results A total of 2,259 pregnant women and 2.012 non-pregnant women were recruited. The mean (SD) sCr of the 2,012 nonpregnant women was 62.8(12.4) µmol/L, with the 97.5th percentile of 89.0 µmol/L. The mean (SD) eGFR was 105.1(27.9) mL/min/1.73 m2. At 4-7, 8-9, 10-12, 24-27 and 28-30 weeks of pregnancy, the mean sCr was 55.1, 52.7, 51.0, 47.2, and 49.3, while the 97.5th percentile for sCr was 72.4, 69.2, 69.3, 63.9, and 66.0 µmol/L, respectively, in the sample of pregnant women. In the first and second trimesters, the average sCr value was 84.7% and 76.4% of that of the nonpregnant group, respectively. The mean eGFR increased up to 129.4 mL/min/1.73 m2 in the 24th week of gestation. The analysis of cohort data clearly confirmed a significant reduction in sCr with advancing pregnancy ($p<0.001$). Conclusions This study confirms that the precise normative data needs to be considered in the interpretation of sCr in pregnancy, based on the period of gestation.

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Running title: Renal functions in pregnancy

Abstract

Objective

To estimate the gestational age-specific serum creatinine (sCr) in pregnancy.

Design

A population-based prospective cohort study.

Settings

Anuradhapura district, Sri Lanka

Population or sample

Study group: Healthy pregnant women with a period of gestation less than 12 weeks and without pre-existing medical conditions. Comparison group: A sample of non-pregnant reproductive age females from a population-based renal screening.

Methods

Baseline data were compared among pregnant and non-pregnant groups and the pregnant women were followed-up until the end of the second trimester.

Main Outcome Measures

Gestational period-specific sCr.

Results

A total of 2,259 pregnant women and 2.012 non-pregnant women were recruited. The mean (SD) sCr of the 2,012 nonpregnant women was 62.8(12.4) μmol/L, with the 97.5th percentile of 89.0 μmol/L. The mean (SD) eGFR was 105.1(27.9) mL/min/1.73 m2. At 4-7, 8-9, 10-12, 24-27 and 28-30 weeks of pregnancy, the mean sCr was 55.1, 52.7, 51.0, 47.2, and 49.3, while the 97.5th percentile for sCr was 72.4, 69.2, 69.3, 63.9, and 66.0 μmol/L, respectively, in the sample of pregnant women. In the first and second trimesters, the average sCr value was 84.7% and 76.4% of that of the nonpregnant group, respectively. The mean eGFR increased

up to 129.4 mL/min/1.73 m2 in the 24th week of gestation. The analysis of cohort data clearly confirmed a significant reduction in sCr with advancing pregnancy (p<0 .001).

Conclusions

This study confirms that the precise normative data needs to be considered in the interpretation of sCr in pregnancy, based on the period of gestation.

Key words : renal functions, pregnancy, serum creatinine, threshold,

Introduction

Owing to the alteration of the renin-angiotensin-aldosterone system (RAAS) and other maternal hormonal changes, systemic vascular resistance decreases during pregnancy, leading to lower blood pressure and an increase in renal plasma flow[1]. Studies using inulin, paminohippurate clearances[2] and 24-hour creatinine clearance[3] suggest that with augmented blood flow, renal vasodilatation and volume expansion up to 70%, a progressive increase in glomerular filtration occurs during pregnancy. Due to the rapid and dynamic changes in renal physiology during pregnancy, assessing renal functions and deciding on thresholds for normal and abnormal values is a major challenge in clinical practice.

Assessing renal functions in routine obstetric practice is a challenge. Both cystatin C- and serum creatinine (sCr)-based equations have been shown to systematically underestimate the glomerular filtration rate (GFR) in pregnancy [4-7]. Thus, 24-hour urine collection remains the standard method for estimating GFR, while sCr is used in clinical settings as a more feasible test for the assessment of renal functions in routine practice[8]. Nevertheless, both sCr- and sCr-based eGFR were shown to be predictive of adverse outcomes in pregnancy[9-11], although the latter was proven to be an inaccurate estimate of renal functions in pregnancy[12].

In a recent study using electronic data from 243,534 pregnancies showed that sCr rapidly decreases from 60 µmol/L prepregnancy to approximately 47 µmol/L at 16-32 weeks[13]. This observations is consistent with the findings of two recent systematic reviews[14, 15]. One review[14] included 49 studies with 4,421 serum creatine measurements. The authors proposed 85%, 80%, and 86% of the nonpregnant sCr upper limit in sequential trimesters as the standards for deciding "abnormal" values. Another systematic review[15] included 29 studies in the analysis and showed that sCr reduction was most prominent at 15-21 weeks of gestation, with a 23.2% reduction, slightly more than the percentage estimated in the previous systematic review. Both systematic reviews discussed a number of limitations in published literature including small samples size, heterogeneous nature of studies, retrospective/ secondary data use and use of sCr values, which were requested based on clinical grounds.

Against the backdrop of these important evidence gaps, the present study was designed to assess the renal function of pregnant women using a population-based prospective cohort design with comparable reference data drawn from the same reference population without sampling bias.

Methods

Study setting

This study was a component of the Rajarata Pregnancy Cohort (RaPCo)[16]. The study was performed in Anuradhapura, the largest district (geographically) in Sri Lanka. All pregnant women newly registered from July to September 2019 and residing in Anuradhapura were invited to participate in RaPCo and it recruited more than 90% of newly registered pregnant women in the district.

Out of the total of 3,407 pregnant women recruited for the RaPCo study, all pregnant women more than 18 years of age with a period of gestation (PoG) less than 12 weeks at recruitment were included in the present study. PoG was confirmed retrospectively after the dating ultrasound scan. The exclusion criteria included pregnant women with uncertain dates; a history of physician-diagnosed renal diseases, hypertension, diabetes mellitus, ischaemic heart diseases, hyperlipidaemia, autoimmune diseases, and thyroid dysfunctions; pregnant women with any renal disorders, hypertensive disorders and hyperglycaemic conditions in previous

pregnancies and multiple pregnancies. At the baseline assessment, a 75 g OGTT was performed, and all pregnant women with fasting plasma glucose greater than 126 mg/dL and 2-hr plasma glucose greater than 200 mg/dL were excluded. Pregnant women with systolic blood pressure greater than 140 mmHg and/or diastolic blood pressure greater than 90 mmHg at the first visit (screened using Omron OMRON HEM-7320) were also excluded. A follow-up assessment was performed towards the end of the second trimester. Study participants were invited to participate in the follow-up clinic at approximately 24-28 weeks of gestation. Only those who attended the clinics at 24-30 weeks were included in the follow-up analysis.

A sample of venous blood was collected in a plain tube by a qualified nursing officer. All collected samples were stored at -80°C for further analysis. Serum creatinine was assessed using a creatinine-sarcosine oxidase method (CREA-S) assay kit in a fully automated Mindray BS-240 clinical chemistry analyser. For the estimation of eGFR, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula was used.

A sample of healthy non-pregnant females of reproductive age participating in a large community-based chronic kidney disease (CKD) screening programme in Anuradhapura in 2015-16 were recruited as the comparison group[17]. To define the age groups (nonpregnant women) and PoG groups (pregnant women) for the analysis, a homogenous subset identification table of ANOVA was used. A one-way, two-way or repeated-measures ANOVA was used as appropriate for the analysis. The proposed threshold for 'abnormal' sCr was based on the 97.5th percentile.

Results

Renal functions of nonpregnant women of reproductive age

Data from 2,012 nonpregnant women of reproductive age were available for the comparison group. The mean (SD) age of this group was 35.9 (8.2) years. The mean (SD) sCr of the group was 62.8 (12.4) µmol/L with a 97.5th percentile of 89.0 µmol/L. The mean (SD) eGFR was 105.1 (27.9) mL/min/1.73 m^2 with a median of 100.8 (IQR 85.5-118.4) mL/min/1.73 m^2. The distribution of sCr and eGFR showed that the sCr values were fairly normally distributed (skewness of 0.182), while eGFR was skewed to the right (skewness of 1.21). However, the Kolmogorov-Smirnov statistics showed a violation of normality for both parameters ($p<0.001$). Age-disaggregated mean sCr and eGFR values were compared to identify homogenous subsets of age groups using one-way ANOVA. Based on the ANOVA results, two subgroups for sCr and three subgroups for eGFR were identified (Table 1). Although the mean sCr was significantly different, the 95th percentile for sCr was almost similar.

The pregnancy cohort

A total of 2,259 pregnant women were included in this analysis. The mean (SD) age of the study sample was 28.4 (5.3) years. The numbers of pregnant women in their first, second and third pregnancies were 508 (22.5%), 834 (36.9%) and 619 (27.4%), respectively. sCr in the pregnancy cohort was reasonably normally distributed (skewness 0.067) with a mean (SD) of 53.2 (8.7) µmol/L. The 97.5thpercentile for the SC in the first trimester was 70.9 µmol/L. The mean (SD) eGFR was 123.4 (10.7) mL/min/1.73 m^2, with a median of 123.5 (IQR 118.1-144.0) mL/min/1.73 m^2. During the follow-up at 24-30 weeks of PoG (992 pregnant women), the mean SC (SD) was 48.0 (8.2) µmol/L, with a slightly skewed distribution (skewedness 1.9). The 97.5th percentile for sCr from 24-30 weeks was 65.2 µmol/L. The mean (SD) eGFR was 127.4 (9.6) mL/min/1.73 m^2 , with a median of 127.9 (IQR 122.4-133.8) mL/min/1.73 m^2.

From the 4th-5th week of PoG, SC continued to decrease steadily until the completion of 12 weeks (Figure 1). At the 24th week, a further decline in sCr was observed, and it started to increase after the 25thweek. The respective eGFR values followed the inverse pattern, with the highest value at approximately the 24th week. Homogenous subsets of sCr values according to PoG were prepared for further analysis using one-way ANOVA (Table 2). In these groups, a one-way between-group ANOVA was conducted to explore the impact of PoG on sCr. There was a significant difference in sCr for the three groups [$F(4,3250)=95.703$, $p<0.001$]. The effect size calculated using eta squared was 0.105 (medium to large effect). Post hoc comparisons using Tukey's HSD test indicated that the mean sCr for each PoG group was significantly different from that of

other adjacent groups.

As age showed an effect on sCr in the nonpregnant cohort, the values of the pregnancy cohort were further analysed according to age categories. After the initial descriptive analysis and subset analysis, participants were divided into two groups according to their age (Group 1: less than 35 years; Group 2: 35 years and above). Using a two-way ANOVA for age and PoG, the interaction effect between PoG and age group was found to be marginal [F(4,3251)=2.331, p=0.054]. There was a statistically significant main effect for PoG [F(4,3251)=45.112, p<0.001], and the effect size was small to medium (partial eta squared=0.052). Post hoc comparisons using Tukey's HSD test indicated that even after including age in the model, the mean sCr for each PoG group was significantly different from that of the adjacent groups. The main effect of age [F(1,3251)=5.760, p=0.016] was also significantly different across age groups, with a small effect and higher sCr for the age group of 35 years and above.

To further assess the changes in renal functions using the cohort design, a one-way repeated-measures ANOVA was conducted. This analysis was conducted only for those who had follow-up data at 24-27 weeks of PoG, in which the lowest sCr was observed (n=524). Three groups were defined according to the PoG at the time of recruitment as above. The mean (SD) values of the first and second measures are presented in Table 3. There was a significant reduction in sCr with advancing pregnancy [Wilks' Lambda=0.71, F(1,521)=211.202, p<0.001, multivariate partial eta squared=0.288]. This analysis showed that despite having different mean values based on the PoG, at 24-27 weeks, the PoG values were concentrated around a mean value of 47 µmol/L.

Discussion

In this prospective cohort study, we systematically recruited a population-based sample of women with singleton pregnancies, excluding all comorbidities, to generate proper "normality data" for sCr in pregnancy. This prospective study, probably one of the largest reported so far for the first trimester renal function assessment in pregnancy with 2,259 pregnant women and with 992 follow-ups, provides evidence to confirm the previous observation and to enhance the precision estimates probably valid across the South Asian region.

Different upper normal limits for sCr have been proposed without consensus for many years. The suggested values varied, with different studies reporting 72 µmol/L[18], 89 µmol/L[19], 80 µmol/L[20] and 95 µmol/L[21] as upper limits. A similar study performed recently in China also published higher upper values of 68, 66, and 68 µmol/L for the first, second, and third trimesters, respectively[22]. In 2019, the Renal Association comprehensively reviewed the published guidelines from the National Institute of Health and Care Excellence (NICE), UK Consensus Group on Pregnancy in Renal Disease, and Kidney Disease Outcomes Quality Initiative (KDOQI) and searched Ovid Medline (1946 to 2018) for "Clinical practice guideline on pregnancy and renal disease"[8]. This guideline used the two most recent reviews: the Canadian study[13] and the systematic review published in 2019. In comparison with the 95thpercentile reported in the Canadian study, the 95thpercentiles observed in our study cohort in the first and second trimesters were slightly higher. In weeks 4-7, 8-9, 10-12, 24-27 and 28-30, a previous study reported 70, 65, 61, 59 and 59 µmol/L, respectively, as the 95th percentile, while our study reported 69.5, 66.7, 65.4, 59.6 and 63.4 µmol/L, respectively. Compared with the systematic review, which reported 85% and 80% of prepregnancy sCr values in the first and second trimesters, we observed values of 84.7% and 76.4% compared with the nonpregnant group, respectively, showing a slightly higher decrease at the end of the second trimester. In our study, we tried to overcome the listed limitations in both studies by using a prospective design and including all "healthy pregnant women".

Sri Lanka is a country with an ongoing epidemic of chronic kidney disease of unknown origin (CKDu)[23, 24]. Anuradhapura, where the present study was performed, is one of the most affected districts[25]. A previous study performed in the same study area among pregnant women showed a mean eGFR of 145.5 mL/min/1.73 m^2 [26], which is higher than the numbers presented in the present study (122-130 mL/min/1.73 m^2). That particular study was not conducted specifically among healthy pregnant women; thus, the eGFR estimates may be slightly different. In the same study area, early renal damage among children was proposed[27], raising the question of whether CKDu is partly due to an early enviormental impact. Based on these observations, a

higher prevalence of renal problems might be expected even among pregnant women showing high mean sCr values. Nevertheless, the use of the nonpregnant comparison group and application of percentage increase will overcome this issue when generalizing the results.

CKD-EPI was used in this study to estimate the eGFR. While this formula has been shown to underestimate eGFR during pregnancy[28], CKD-EPI has good performance postpartum and outside pregnancy, and the current evidence does not suggest that a superior formula is available for eGFR estimation in pregnancy[29].

To strengthen the observations and to evaluate the utility of the proposed normality data, a long follow-up of the same cohort is required with proper assessment of maternal and foetal outcomes. Although the sCr-based eGFR is not an accurate estimate during pregnancy, previous studies have shown that it could be used as a predictor of adverse pregnancy outcomes[9, 10]. As the normality data generated through this study are almost similar to the values observed in the previous secondary data analysis, these values seem universally valid across geographical regions [13].

Conclusions

This prospective cohort study confirms the previous observations on changes in sCr values in pregnancy with thresholds for normal and abnormal values almost similar to those observed in completely different geographical and ethnic settings. The rapid decrease in early pregnancy sCr and differences across trimesters need to be taken into account during clinical practice while interpreting sCr in pregnancy. Extension of prospective studies from early pregnancy to late infancy will provide confirmatory data on the upper threshold values for sCr as a biomarker of adverse pregnancy outcomes.

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Disclosure statement

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Contribution to Authorship

SBA conceptualized the study, analysed and interpreted data and prepared the initial draft of the manuscript. SBA, TCA and NDW design the study. GSA, JNW, AUH, IUJ, ISK and PLKA participated in planning field work, data collection including clinical assessments and examinations. SMS and FNS involved in planning the biochemical assessments, sample collection, laboratory procedures and revising the relevant components in the manuscript. All authors approved the final version of the manuscript. All authors have agreed to be accountable for the authors own contributions and to ensure questions related to the accuracy or integrity of any part of the work are appropriately investigated, resolved, and the resolution documented in the literature.

Ethics approval

Ethical clearance for the RaPCo study was obtained from the ethics review committee of the Faculty of Medicine and Allied Sciences, Rajarata University of Sri Lanka (ERC/2019/07).

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Disclosure of interests

We have no conflict of interests to declare.

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Figure and table legends

Table 1. Distribution of serum creatinine and eGFR values by age among nonpregnant females of reproductive age in North Central Province, Sri Lanka

Table 2. Distribution of serum creatinine and eGFR by period of gestation (grouped) in 2,259 pregnant women during the first trimester and follow-up in Anuradhapura, Sri Lanka

Table 3. Results of paired sample serum creatinine among 524 pregnant women with follow-up measurements performed between 24-27 weeks

Figure 1. Distribution of serum creatinine and eGFR by the period of gestation in 2,259 pregnant women during the first trimester and follow-up at 24-30 weeks

Table 1. Distribution of serum creatinine and eGFR values by age among nonpregnant females of reproductive age in North Central Province, Sri Lanka

Age (years)	N	Mean	Std. Deviation	Std. Erro
Serum creatinine (µmol/L)	**Serum creatinine** (µmol/L)			

Age (years)	**N**	**Mean**	**Std. Deviation**	**Std. Erro**
<35	920	60.93	12.383	0.408
35 and above	1,092	64.45	12.222	0.370
eGFR (mL/min/1.73 m^2)	**eGFR** (mL/min/1.73 m^2)	**eGFR** (mL/min/1.73 m^2)		
<30	534	118.7	30.533	1.321
30-34	386	107.19	25.624	1.304
35 and above	1,092	97.72	24.418	0.739

Table 2. Distribution of serum creatinine and eGFR by period of gestation (grouped) in 2,259 pregnant women during the first trimester and follow-up in Anuradhapura, Sri Lanka

PoG (Weeks)	**N**	**Σερυμ ςρεατινινε μμολ/Λ**	**Σερυμ ςρεατινινε μμολ/Λ**	**95% CI for Mean**	**95% CI**
		Mean	**SD**	**Lower**	**Upper**
4-7	830	55.1	8.5	54.5	55.7
8-9	871	52.7	8.3	52.2	53.3
10-12	558	51.0	8.9	50.3	51.7
24-27	708	47.2	7.3	46.6	47.7
28-30	284	49.3	9.9	48.1	50.5

Table 3. Results of paired sample serum creatinine among 524 pregnant women with follow-up measurements performed between 24-27 weeks

		Σερυμ ςρεατινινε μμολ/Λ	**Σερυμ ςρεατινινε μμολ/Λ**	**Σερυμ ςρεατινινε**
		1st trimester (4-12 weeks)	**1st trimester (4-12 weeks)**	**End of 2nd trimeste**
PoG at the first visit	**N**	**Mean**	**SD**	**Mean**
4-7 weeks	150	54.4	8.7	47.2
8-9 weeks	238	52.8	8.6	47.5
10-12 weeks	136	49.6	8.9	47.0
Total	524	52.4	8.9	47.3