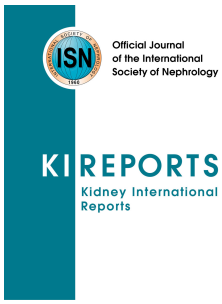
DOI:
10.1016/j.ekir.2018.10.015

Document Version
Peer reviewed version



Serum creatinine in pregnancy: a systematic review

Dr Kate Wiles, MSc MRCP, Dr Kate Bramham, PhD MRCP, Paul T. Seed, MSc CStat, Professor Catherine Nelson-Piercy, FRCP FRCOG, Professor Liz Lightstone, PhD FRCP, Professor Lucy C. Chappell, PhD FRCOG

PII: S2468-0249(18)30286-9

DOI: https://doi.org/10.1016/j.ekir.2018.10.015

Reference: EKIR 450

To appear in: *Kidney International Reports*

Received Date: 9 August 2018

Revised Date: 18 October 2018

Accepted Date: 22 October 2018

Please cite this article as: Wiles K, Bramham K, Seed PT, Nelson-Piercy C, Lightstone L, Chappell LC, Serum creatinine in pregnancy: a systematic review, *Kidney International Reports* (2018), doi: https://doi.org/10.1016/j.ekir.2018.10.015.

a. Title: Serum creatinine in pregnancy: a systematic review

b. Authors and affiliations:

- Dr Kate Wiles MSc MRCP
  NIHR Doctoral Research Fellow
  Department of Women and Children's Health
  King's College London

- Dr Kate Bramham PhD MRCP
  Clinical Lecturer and Consultant Nephrologist
  Department of Renal Medicine
  King's College Hospital

- Paul T Seed MSc CStat
  Senior Lecturer in Medical Statistics
  Department of Women and Children's HealthKing's College London

- Professor Catherine Nelson-Piercy FRCP FRCOG
  Professor of Obstetric Medicine
  Guy's and St. Thomas' NHS Foundation Trust and Imperial Healthcare NHS Trust

- Professor Liz Lightstone PhD FRCP
  Professor of Renal Medicine
  Section of Renal Medicine and Vascular Inflammation
  Imperial College London

- Professor Lucy C Chappell PhD FRCOG
  NIHR Research Professor in Obstetrics
  Department of Women and Children's Health
  King's College London

c. Name and address for correspondence:

Dr Kate Wiles
Department of Women's and Children's Health, 10th Floor North Wing
St. Thomas' Hospital
London SE1 7EH
+447779781815
kate.wiles@kcl.ac.uk

d. Sources of support requiring acknowledgment: National Institute for Health Research Rare Diseases Translational Research Collaboration (NIHR RD-TRC) and the Biomedical Research Centre at Guy's & St Thomas & King's College London.

Running title: Serum creatinine in pregnancy

PROSPERO registration: CRD42017068446

Abstract

Introduction

Standard assessment of renal function in pregnancy is by measurement of serum creatinine concentration 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.

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 concentration in a pregnant cohort, with either a reported local laboratory reference range or matched quantification in a 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.

Results

Forty-nine studies were identified. Data synthesis included 4421 serum creatinine values in pregnancy, weighted according to 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 centile (upper limit of the 95% reference range) for serum creatinine in pregnancy was 85%, 80% and 86% of the non-pregnant upper limit in sequential trimesters.

Conclusions

Based on a non-pregnant reference interval of 45-90µmol/L [0.51-1.02mg/dL], a serum creatinine of >77µmol/L [0.87mg/dL] 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 concentration.

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 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 function and should not be used.[1] eGFR calculations based on Modified Diet in Renal Disease (MDRD) calculations underestimate GFR in pregnancy by up to 41ml/min/1.73m^2 compared with inulin clearance.[2] 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 with inulin and creatinine clearance.[2,3]

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 [0.81mg/dL],[4] 80µmol/L [0.90mg/dL],[5] 89µmol/L [1.00mg/dL][6] and 95µmol/L [1.07mg/dL].[7] 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 concentration includes only 29 healthy pregnant women.[7] Contemporaneous

statements regarding creatinine concentration in pregnancy are largely based on expert opinion including a 'normal' range of 35-71µmol/L [0.40-0.80mg/dL],[8,9] an 'average' creatinine in pregnancy of 53µmol/L [0.60mg/dL],[10] and a recommendation that serum creatinine in pregnancy greater than 75µmol/L [0.85mg/dL] should raise suspicion of kidney injury.[11]

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.

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 for first publication to July 2017. Search terms included creatinine, glomerular filtration, GFR, MDRD, Cockcroft, renal function, kidney function, biochemistry, clinical chemistry in combination with pregnan$, trimester,

gestat$. Specific search strategies are detailed in the supplementary material. 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 relevant local laboratory reference ranges for the creatinine assay used at the time their study was conducted.

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 creatinine data according to trimester. Studies that included pregnant women with kidney disease (upper reference range for creatinine in control population >125µmol/L [1.41mg/dL]), vascular disease, diabetes and adverse pregnancy outcome including pre-eclampsia

were excluded. Any study that did not adequately describe the health of population studied was excluded, as 'normality' in the population could not be presumed. Studies were also excluded if serum creatinine concentrations were assessed in a non-pregnant cohort at less than 6 weeks post-partum.

Methodological quality of the studies was scored using the Newcastle-Ottawa scale for observational cohort studies.[12] This included measures of how representative both the pregnant and non-pregnant cohorts were of 'average' women of childbearing 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 measures of data spread (standard deviation/error or centile) were recorded. Where cohort ethnicity was not given, 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 both in non-pregnant[13-16] and pregnant[6,17] cohorts. Mean creatinine concentrations in the pregnant and non-pregnant cohorts 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 within the data, 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 concentration in pregnancy were converted to a proportion (percentage) of the equivalent value from either the non-pregnant cohort described in each study, 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.

Statistical analysis was performed using Stata version 14.2. We used the calculation of the I^2 statistic[18,19] 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 between studies was 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. 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.[20] Data from the included studies 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 revealed 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.[21]

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

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 pre-eclampsia, and did not include serum creatinine measurement. Studies of amniotic, fetal or neonatal creatinine measurement were also excluded. A further 185 sources were excluded after full-text review (Figure 1). Four studies were included after contacting the authors to provide local laboratory reference ranges at the time of their study .

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 1.

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 spectometry (IDMS) reference, according to current recommendation.[22]

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,[23] 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 2).

Data synthesis included all studies which had a matched 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, Figure 2).

Discussion

Data synthesis from this systematic review creates a mean and upper reference limit 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 [0.51-1.02mg/dL],[24] this equates to mean serum creatinine values of 56µmol/L [0.63mg/dL], 52µmol/L [0.59mg/dL] and 54µmol/L [0.61mg/dL] in sequential trimesters, whilst serum creatinine values greater than 76µmol/L [0.86mg/dL] in the first trimester, 72µmol/L [0.81mg/dL] in the second trimester, and 77µmol/L [0.87mg/dL] in the third trimester should be considered to be outside the upper limit of normal for pregnancy. A serum creatinine greater than 77µmol/L [0.87mg/dL] in pregnancy should raise the possibility of either acute kidney injury (AKI), 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 which 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 concentration 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 in 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[20] 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. [25-28]

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.[29] 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 concentration. 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.[30] Confirmation of the findings of this systematic review using IDMS traceable creatinine assay methods[22] 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, [26-28] followed by a decrease in creatinine clearance during the third trimester[25] leading to an increase in serum creatinine concentration towards term. This study suggests that the normal range for creatinine in pregnancy is either comparable to,[4] or lower[5-7] 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 [0.51-1.02mg/dL]. This is

derived from 269 healthy, Red Cross blood donors.[24] Although gender specific, this reference interval is not specific for women of child-bearing age as the reference population is 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,[31] with minimal effect on absolute serum creatinine values. Indeed, serum creatinine values have been shown to be stable in female, white European populations between the ages of 20 and 70 years.[14] 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.

Acute kidney injury occurs most commonly during pregnancy in the third trimester, predominantly due to the development of hypertensive disorders and puerperal pathologies including sepsis and haemorrhage.[32-35] 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.[36] 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 [1.02mg/dL],[24] a new serum creatinine of >77µmol/L [0.87mg/dL] 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.[37] 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.

Financial Disclosure

KW is funded by the National Institute for Health Research Rare Diseases Translational Research Collaboration (NIHR RD-TRC) and the Biomedical Research Centre at Guy's & St Thomas & King's College London.
KB has received consultancy fees from Alexion, and lecture fees from Alexion and Otsuka.
CNP has received consultancy fees from Alliance Pharma and UCB, and lecture fees from UCB and Sanofi.
LCC is supported by a Research Professorship from the National Institute for Health Research, RP-2014-05-019.

Supplementary Material

Supplementary material: Electronic Search Strategy (Word document .docx)

Supplementary information is available at KI Report's website

References

1. Koetje PMJL, Spaan JJ, Kooman JP, et al. Pregnancy reduces the accuracy of the estimated glomerular filtration rate based on Cockroft-Gault and MDRD formulas. *Reprod Sci*. 2011;18(5):456-62.

2. Smith MC, Moran P, Ward MK, et al. Assessment of glomerular filtration rate during pregnancy using the MDRD formula. *BJOG.* 2008;115(1):109-12.

3. Alper AB, Yi Y, Rahman M, et al. Performance of estimated glomerular filtration rate prediction equations in preeclamptic patients. *Am J Perinatol.* 2010;28(06):425-30.

4. Larsson A, Palm M, Hansson LO, et al Reference values for clinical chemistry tests during normal pregnancy. *BJOG.* 2008;115(7):874-81.

5. Abbassi-Ghanavati M, Greer LG, Cunningham FG. Pregnancy and laboratory studies: a reference table for clinicians. *Obstet Gynecol.* 2009;114(6):1326-31.

6. Girling JC. Re-evaluation of plasma creatinine concentration in normal pregnancy. *J Obstet Gynaecol.* 2000;20(2):128-31.

7. Lokitch G. *Handbook of Diagnostic Biochemistry and Haematology in Normal Pregnancy*. Boca Raton: CRC Press; 1993.

8. Fischer MJ. Chronic kidney disease and pregnancy: maternal and fetal outcomes. *Adv Chronic Kidney Dis.* 2007;14(2):132-45.

9. Maynard SE, Thadhani R. Pregnancy and the kidney. *J Am Soc Nephrol.* 2009;20(1):14-22.

10. August P. Preeclampsia: a nephrocentric view. *Adv Chronic Kidney Dis*. 2013;20(3):280-6.

11. Lightstone L. Kidney disease and pregnancy. *Medicine.* 2015;43(9):550-5.

12. Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions.* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from: www.handbook.cochrane.org.

13. Mussap M, Dalla Vestra M, Fioretto P, et al. Cystatin C is a more sensitive marker than creatinine for the estimation of GFR in type 2 diabetic patients. *Kidney Int.* 2002;61(4):1453-61.

14. Pottel H, Vrydags N, Mahieu B, et al. Establishing age/sex related serum creatinine reference intervals from hospital laboratory data based on different statistical methods. *Clin Chim Acta.* 2008;396(1-2):49-55.

15. Huang M, Yang JJ, Yang JJ, et al. Reference intervals for serum creatinine levels in the healthy geriatric population. *Clin Biochem.* 2013;46(15):1419-22.

16. Pottel H, Hoste L, Delanaye P. Abnormal glomerular filtration rate in children, adolescents and young adults starts below 75 ml/min/1.73m^2. *Pediatr Nephrol.* 2015;30(5):821-8.

17. Kristensen K, Lindström V, Schmidt C, et al. Temporal changes of the plasma levels of cystatin C, beta-trace protein, beta2-microglobulin, urate and creatinine

during pregnancy indicate continuous alterations in the renal filtration process. *Scand J Clin Lab Invest.* 2007a;67(6):612-8.

18. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ.* 2003;327(7414):557-60.

19. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med.* 2002;21(11):1539-58.

20. Scott A, Wu C. On the asymptotic distribution of ratio and regression estimators. *J Am Stat Assoc.* 1981;76(373):98-102.

21. DiCiccio T, Efron B. Bootstrap confidence intervals. *Stat Sci.* 1996;11(3):189-212.

22. Myers GL, Miller WG, Coresh J, et al. Recommendations for improving serum creatinine measurement: a report from the laboratory working group of the national kidney disease education program. *Clin Chem.* 2006;52(1):5-18.

23. McPhetters ML, Kripalani S, Peterson NB, et al. *Closing the gap: revisiting the state of the science (Volume 3: Quality Improvement interventions to address health disparities).* Agency for Healthcare Research and Quality. Evidence Reports/Technology Assessments No.208.3, August 2012.

24. Mazzachi BC, Peake MJ, Ehrhardt V. Reference range and method comparison studies for enzymatic and Jaffé creatinine assays in plasma and serum and early morning urine. *Clin Lab.* 2000;46(1-2):53-5.

25. Davison JM, Dunlop W, Ezimokhai M. 24-hour creatinine clearance during the third trimester of normal pregnancy. *BJOG.* 1980;87(2):106-109.

26. Davison JM, Noble MCB. Serial changes in 24 hour creatinine clearance during normal menstrual cycles and the first trimester of pregnancy. *BJOG*. 1981;88(1):10-7.

27. Roberts M, Lindheimer MD, Davison JM. Altered glomerular permselectivity to neutral dextrans and heteroporous membrane modeling in human pregnancy. *Am J Physiol*. 1996;270(2 Pt 2):F338-43.

28. Chapman AB, Abraham WT, Zamudio S, et al. Temporal relationships between hormonal and hemodynamic changes in early human pregnancy. *Kidney Int*. 1998;54(6):2056-63.

29. Ross JW, Miller WG, Myers GL, Praestgaard J. The accuracy of laboratory measurements in clinical chemistry: a study of 11 routine chemistry analytes in the College of American Pathologists chemistry survey with fresh frozen serum, definitive methods, and reference methods. *Arch Pathol Lab Med*. 1998;122(7):587-608.

30. Delanghe JR, Speeckaert MM. Creatinine determination according to Jaffe: what does it stand for? *NDT Plus* 2011;4(2):83-6

31. Shlipak MG, Katz R, Kestenbaum B, et al. Rate of kidney function decline in older adults: a comparison using creatinine and cystatin C. *Am J Nephrol*. 2009;30(3):171-8.

32. Prakash J, Pant P, Prakash S, et al. Changing picture of acute kidney injury in pregnancy: study of 259 cases over a period of 33 years. *Indian J Nephrol* 2016;26(4):262-7.

33. Gopalakrishnan N, Dhanapriya J, Muthukumar P, et al. Acute kidney injury in pregnancy: a single center experience. *Ren Fail.* 2015;37(9):1476-80.

34. Hildebrand AM, Liu K, Shariff SZ, et al. Characteristics and outcomes of AKI treated with dialysis during pregnancy and the postpartum period. *J Am Soc Nephrol*. 2015;26(12):3085-91.

35. Liu YM, Bao HD, Jiang ZZ, et al. Pregnancy-related acute kidney injury and a review of the literature in China. *Intern Med*. 2015;54(14):1695-703.

36. Wiles KS, Banerjee A. Acute kidney injury in pregnancy and the use of non-steroidal anti-inflammatory drugs. *The Obstetrician & Gynaecologist*. 2016;18(2):127-35.

37. Fitzpatrick A, Mohammadi F, Jesudason S. Managing pregnancy in chronic kidney disease: improving outcomes for mother and baby. *Int J Womens Health.* 2016;8:273-85.

38. Afolabi BB. Plasma Volume in Normal and Sickle Cell Pregnancy. Thesis submitted to the University of Nottingham 2011. Available from: eprints.nottingham.ac.uk/12073/1/FINALTHESISSUBMITTED060611.pdf [accessed 14th Feb 2018].

39. Akbari A, Lepage N, Keely E, et al. Cystatin-C and beta trace protein as markers of renal function in pregnancy. *BJOG.* 2005;112(5):575-8

40. Al-Kuran O, Al-Mehaisen L, Beitawi S, et al. Validation of reportable indices of haematology, liver and renal function in pregnancy for the middle eastern population. *J Obstet Gynaecol.* 2012;32(7):639-42

41. Babay Z, Al-Wakeel J, Addar M, et al. Serum cystatin C in pregnant women: reference values, reliable and superior diagnostic accuracy. *Clin Exp Obstet Gynecol*. 2005;32(3):175-9.

42. Babu R, Venugopal B, Sabitha K, et al. Comparative study of liver and kidney biochemical parameters in normal and pre-eclamptic gestation. *J Curr Trends Clin Med Lab.* 2013;1(3):26-30.

43. Collins PA. Serum constituents in pregnancy including 4 cases with elevated alkaline phosphatase levels. *Clin Biochem.* 1981;14(2):98-101.

44. Djordjevic A, Spasic S, Jovanovic-Galovic A, et al. Oxidative stress in diabetic pregnancy: SOD, CAT and GSH-Px activity and lipid peroxidation products. *J Matern Fetal Neonatal Med.* 2004;16(6):367-72.

45. Duvekot JJ, Cheriex EC, Pieters FA, et al. Maternal volume homeostasis in early pregnancy in relation to fetal growth restriction. *Obstet Gynecol.* 1995;85(3):361-7.

46. Fasshauer M, Seeger J, Waldeyer T, et al. Serum levels of the adipokine adipocyte fatty acid-binding protein are increased in preeclampsia. *Am J Hypertens.* 2008a;21(5):582-6.

47. Fasshauer M, Waldeyer T, Seeger J, et al. Serum levels of the adipokine visfatin are increased in pre-eclampsia. *Clin Endocrinol (Oxf).* 2008b;69(1):69-73.

48. de Flamingh JP, Van der Merwe JV. A serum biochemical profile of normal pregnancy. *S Afr Med J.* 1984;65:552-5.

49. Guo HX, Wang CH, Li ZQ, et al. The application of serum cystatin C in estimating the renal function in women with preeclampsia. *Reprod Sci*. 2012;19(7):712-7.

50. Hanna B. The role of calcium correction during normal pregnancy at third trimester in Mosul. *Oman Med J.* 2009;24(3):188-94.

51. Heguilén RM, Liste AA, Bellusci AD, et al. Renal response to an acute protein challenge in pregnant women with borderline hypertension. *Nephrology.* 2007;12(3):254-60.

52. Iqbal SA, Ansari AK, Akhtar MS. Assessment of renal function during various stages of pregnancy in women. *Proc Pak Acad Sci.* 2003;40(2):165-72.

53. Järnfelt-Samsioe A, Eriksson B, Waldenström J, et al. Some new aspects on emesis gravidarum. *Gynecol Obstet Inv.* 1985;19(4):174-86.

54. Jiang H, McGiff JC, Fava C, et al. Maternal and fetal epoxyeicosatrienoic acids in normotensive and preeclamptic pregnancies. *Am J Hypertens.* 2013;26(2):271-8.

55. Kametas N, McAuliffe F, Krampl E, et al. Maternal electrolyte and liver function changes during pregnancy at high altitude. *Clin Chim Acta.* 2003;328(1-2):21-9.

56. Klajnbard A, Szecsi PB, Colov NP, et al. Laboratory reference intervals during pregnancy, delivery and the early postpartum period. *Clin Chem Lab Med.* 2010;48(2):237-48.

57. Knopp RH, Bergelin RO, Wahl PW, et al. Clinical chemistry alterations in pregnancy and oral contraceptive use. *Obstet Gynecol.* 1985;66(5):682-90.

58. Kristensen K, Wide-Swensson D, Schmidt C, et al. Cystatin C, beta-2-microglobulin and beta-trace protein in pre-eclampsia. *Acta Obstet Gynecol Scand.* 2007b;86(8):921-6.

59. Lain KY, Markovic N, Ness RB, et al. Effect of smoking on uric acid and other metabolic markers throughout normal pregnancy. *J Clin Endocrinol Metab.* 2005;90(10):5743-6.

60. Lohsiriwat S, Imrittha N. Effect of posture on creatinine clearance in late pregnancy and after pregnancy. *J Obstet Gynaecol Res.* 2008;34(3):337-42.

61. Mahendru AA, Everett TR, Wilkinson IB, et al. A longitudinal study of maternal cardiovascular function from preconception to the postpartum period. *J Hypertens*. 2014;32(4):849-56.

62. Majewska AK, Janus T, Ronin-Walknowska E, et al. 1-H magnetic resonance spectroscopy of urine for the assessment of renal dysfunction in healthy pregnant women. *Adv Clin Exp Med.* 2010;19(2):177-83.

63. Makuyana D, Mahomed K, Shukusho FD, et al. Liver and kidney function tests in normal and pre-eclamptic gestation: a comparison with non-gestational reference values. *Cent Afr J Med.* 2002;48(5-6):55-9.

64. Matteucci E, Giampietro O. Na(+)-H+ exchange activity throughout pregnancy: the proper experimental approach. *Ann Ist Super Sanita.* 1997;33(3):371-4.

65. Milman N, Bergholt T, Byg KE, et al. Reference intervals for haematological variables during normal pregnancy and postpartum in 434 healthy Danish women. *Eur J Haematol*. 2007;79(1):39-46.

66. Milne JEC, Lindheimer MD, Davison JM. Glomerular heteroporous membrane modeling in third trimester and postpartum before and during amino acid infusion. *Am J Physiol Renal Physiol.* 2002;282(1):F170-5.

67. Miri-Dashe T, Osawe S, Tokdung M, et al. Comprehensive reference ranges for hematology and clinical chemistry laboratory parameters derived from normal Nigerian adults. *PLoS One*. 2014;9(5):e93919.

68. Ogueh O, Clough A, Hancock M, et al. A longitudinal study of the control of renal and uterine hemodynamic changes of pregnancy. *Hypertens Pregnancy*. 2011;30(3):243-59.

69. Pahl MV, Culver BD, Strong PL, et al. The effect of pregnancy on renal clearance of boron in humans: a study based on normal dietary intake of boron. *Toxicol Sci.* 2001;60(2):252-6.

70. Saxena AR, Ananth Karumanchi S, et al. Correlation of cystatin-C with glomerular filtration rate by inulin clearance in pregnancy. *Hypertens Pregnancy.* 2012;31(1):22-30.

71. Schoenmakers I, Jarjou LM, Goldberg GR, et al. Acute response to oral calcium loading in pregnant and lactating women with a low calcium intake: a pilot study. *Osteoporos Int.* 2013;24(8):2301-8.

72. Siddiqui JA, Rana IA. Mineral and parathyroid hormone inter-relationships in normal pregnancy and pregnancy-induced hypertension. *J Pak Med Assoc*. 1993;43:92-5.

73. Strevens H, Wide-Swensson D, Torffvit O, et al. Serum cystatin C for assessment of glomerular filtration rate in pregnant and non-pregnant women: indications of altered filtration process in pregnancy. *Scand J Clin Lab Invest*. 2002;62(2):141-7.

74. van Buul EJ, Steegers EA, Jongsma HW, et al. Haematological and biochemical profile of uncomplicated pregnancy in nulliparous women: a longitudinal study. *Neth J Med.* 1995;46(2):73-85.

75. Vural P, Akgül C, Canbaz M. Urinary PGE-2 and PGF-2alpha levels and renal functions in preeclampsia. *Gynecol Obstet Invest.* 1998;45(4):237-41.

76. de Weerd S, Steegers-Theunissen RP, de Boo TM, et al. Maternal periconceptional biochemical and hematological parameters, vitamin profiles and pregnancy outcome. *Eur J Clin Nutr.* 2003;57(9):1128-34.

77. Weissberg N, Shemesh O, Schwartz G, et al. The rise of serum creatinine levels during labor. *Arch Gynecol Obstet*. 1991;249(1):33-7.

Author	Year	Country/ Ethnicity	Longitudinal or cross-sectional	Control			Trimester 1			Trimester 2			Trimester 3			Creatinine assay method	Assessment of pregnancy normality*	Normal pregnancy outcome confirmed	Newcastle-Ottowa grade
				n	Mean Cr	ULN	n	Mean Cr	ULN	n	Mean Cr	ULN	n	Mean Cr	ULN				
Afolabi[38]	2011	Nigeria	C	15	58 [0.65]	80 [0.90]				9	61 [0.69]	93 [1.05]	3	57 [0.64]	104 [1.18]	Jaffe	1		6
Akbari[39]	2005	Canada	C	13	74 [0.84]	86 [0.97]				68	52 [0.59]	69 [0.78]	68	54 [0.61]	78 [0.88]	Not stated	2		7
Al Kuran[40]	2012	Jordan	L	LRR	70 [0.79]	96 [1.10]	797	67 [0.76]	97 [1.10]	797	64 [0.72]	100 [1.13]	797	72 [0.81]	132 [1.4]	Jaffe	2		6
Babay[41]	2005	Saudi Arabia	C	40	58 [0.66]	71 [0.80]	54	56 [0.63]	75 [0.85]	53	57 [0.64]	81 [0.92]	50	52 [0.59]	70 [0.79]	Not stated	3	Yes	8
Babu[42]	2013	India	C	LRR	71 [0.80]	78 [0.88]							25	52 [0.59]	70 [0.79]	Not stated	3		4
Chapman[28]	1998	WE:AC=10:1	L	13	71 [0.80]	88 [1.00]	10	65 [0.74]	77 [0.87]	8	53 [0.60]	73 [0.83]	8	49 [0.55]	68 [0.77]	Jaffe	3		8
Collins[43]	1981	Canada	C	65	71 [0.80]	88 [1.00]							350	53 [0.60]	71 [0.80]	Jaffe	1		6
Davison[25]	1980	UK	L	10	69 [0.78]	104 [1.18]							10	60 [0.68]	104 [1.18]	Enzymatic	3	Yes	9
Davison[26]	1981	UK	L	9	72 [0.81]	85 [0.96]	9	64 [0.72]	77 [0.87]	9	57 [0.64]	69 [0.78]				Enzymatic	3	Yes[+]	8
Djordjevic[44]	2004	Serbia-Montenegro	L	30	61 [0.69]	83 [0.94]	30	65 [0.74]	91 [1.03]							Not stated	1		7
Duvekot[45]	1995	Netherlands	L	10	56 [0.63]	63 [0.71]	10	53 [0.60]	68 [0.77]							Not stated	1	Yes	6
Fasshauser[46]	2008a	Germany	C	LRR[$]	76 [0.86]	104 [1.18]							20	55 [0.62]	79 [0.89]	Not stated	1		5
Fasshauser[47]	2008b	Germany	C	LRR[$]	76 [0.86]	104 [1.18]							20	54 [0.61]	79 [0.89]	Not stated	3		5
de Flamingh[48]	1984	South Africa	C	16	74 [0.84]	88 [1.00]	10	61 [0.69]	75 [0.85]	10	55 [0.62]	71 [0.80]	40	54 [0.61]	93 [1.05]	Not stated	3		4

Girling[6]	2000	47% WE, 21% AC, 10% Med	C	LRR[$]	88 [1.00]	120 [1.36]	20	68 [0.77]	84 [0.95]	271	63 [0.71]	125 [1.41]	68	54 [0.61]	97 [1.10]	Jaffe	3		6
Guo[49]	2012	China	L	LRR[$]	89 [1.00]	115 [1.30]				96	42 [0.48]	52 [0.59]	96	54 [0.61]	70 [0.79]	Jaffe	3		4
Hanna[50]	2009	Iraq	C	40	84 [0.95]	121 [1.37]	40	83 [0.94]	118 [1.33]	40	75 [0.85]	94 [1.06]	40	54 [0.61]	92 [1.04]	Jaffe	3		7
Heguilén[51]	2007	Argentina	C	8	82 [0.93]	102 [1.15]				5	66 [0.75]	88 [1.00]				Not stated	3		4
Iqbal[52]	2003	Pakistan	C	26	72 [0.81]	89	18	65 [0.74]	95	22	70 [0.79]	94	23	69 [0.78]	94	Jaffe	1		6
Järnfelt-Samsioe[53]^	1985	Sweden	C	LRR	80 [0.90]	110 [1.24]				37	68 [0.77]	94 [1.06]	34	66 [0.75]	94 [1.06]	Not stated	2	Yes[+]	4
Jaing[54]	2013	Italy	C	19	53 [0.70]	66 [0.75]							29	42 [0.48]	58 [0.66]	Not stated	1	Yes	7
Kametas[55]#	2003	Peru	C	13-15	55-63 [0.62-0.71]	68-80 [0.77-0.90]				77-80	47-56 [0.53-0.63]	58-74 [0.66-0.83]				Jaffe	2	Yes	6
Klajnbard[56]	2010	Denmark (WE)	L	LRR	70 [0.79]	90 [1.02]				532	58 [0.66]	73 [0.83]	358	62 [0.70]	84 [0.95]	Enzymatic	2	Yes	7
Knopp[57]	1985	USA (WE)	C	77	67 [0.76]	88 [1.00]							546	51 [0.58]	78 [0.88]	Jaffe	1		5
Koetje[1]	2011	Netherlands (WE)	C	44	69 [0.78]	91 [1.03]	44	58 [0.66]	74 [0.84]							Jaffe	2		4
Kristensen[17]	2007a	Sweden	C	58	65 [0.74]	82 [0.93]	94	53 [0.60]	70 [0.79]	107	51 [0.58]	64 [0.72]	88	54 [0.61]	70 [0.79]	Enzymatic	3	Yes[+]	6
Kristensen[58]	2007b	Sweden	C	58	65 [0.74]	82 [0.93]							218	53 [0.60]	68 [0.77]	Enzymatic	3	Yes	6
Lain[59]	2005	USA	L	63	50 [0.57]	92 [1.04]	63	51 [0.58]	92 [1.04]	63	44 [0.50]	99 [1.12]	63	50 [0.57]	92 [1.04]	Enzymatic	2	Yes	9
Larsson[4]	2008	Sweden	L	51	67 [0.76]	86 [0.97]	50	49 [0.55]	62 [0.70]	51	46 [0.52]	62 [0.70]	52	47 [0.53]	72 [0.81]	Jaffe	2	Yes[+]	6

Lockitch[7]	1993	Majority WE	L	121	73 [0.83]	94 [1.06]	29	52 [0.59]	77 [0.87]	29	50 [0.57]	73 [0.83]	29	56 [0.63]	87 [0.98]	Enzymatic	2	Yes	6
Lohsiriwat[60]	2008	Thailand	L	26	72 [0.82]	90							26	64 [0.72]	84	Jaffe	3	Yes	9
Mahendru[61]	2014	91% WE	L	54	68 [0.77]	88 [1.00]	54	53 [0.60]	69 [0.78]							Not stated	2	Yes	7
Majewska[62]	2010	Poland	L	40	72 [0.81]	94 [1.06]	40	50 [0.56]	63 [0.72]	40	46 [0.52]	60 [0.68]	40	52 [0.59]	75 [0.85]	Not stated	3	Yes	8
Makuyana[63]	2002	Zimbabwe	C	LRR	78 [0.88]	121 [1.37]							72	52 [0.59]	70 [0.79]	Jaffe	3		6
Matteucci[64]	1997	Italy	L	18	82 [0.93]	102 [1.15]	18	64 [0.72]	82 [0.93]	18	62 [0.70]	78 [0.88]	18	65 [0.74]	77 [0.87]	Jaffe	2	Yes	4
Milman[65]	2007	Denmark	L	164	75 [0.85]	96 [1.09]				394	55 [0.62]	71 [0.80]	521	58 [0.66]	81 [0.92]	Jaffe	2	Yes	7
Milne[66]	2002	UK (WE)	L	11	65 [0.74]	95 [1.07]							11	75 [0.85]	78 [0.88]	Not stated	3	Yes	9
Miri-Dashe[67]	2014	Nigeria	C	127	79 [0.89]	118 [1.33]	43[±]	46 [0.52]	68 [0.77]	43[±]	46 [0.52]	59 [0.67]	43[±]	65 [0.74]	94 [1.06]	Enzymatic	1		6
Ogueh[68]	2011	UK	L	13	88 [1.00]	107 [1.21]	12	78 [0.88]	96 [1.09]	13	77 [0.87]	105 [1.19]	12	74 [0.84]	106 [1.20]	Jaffe	1	Yes	8
Pahl[69]	2001	USA	C	15	67 [0.76]	83 [0.94]				16	64 [0.72]	76 [0.86]				Enzymatic	3		7
Roberts[27]	1996	UK (WE)	L	11	74 [0.84]	88 [1.00]				16	54 [0.61]	66 [0.74]	11	53 [0.60]	63 [0.71]	Jaffe	3	Yes	9
Saxena[70]	2012	USA	L	12	71 [0.8]	101 [1.14]				12	53 [0.60]	77 [0.87]	12	62 [0.70]	80 [0.91]	Jaffe	1	Yes	8
Schoenmaker[71]	2013	Gambia	C	10	59 [0.67]	89 [1.00]							10	74 [0.84]	68 [0.77]	Enzymatic	1		5
Siddiqui[72]	1993	Pakistan	C	30	69 [0.79]	88 [1.00]							35	49 [0.64]	58 [0.76]	Jaffe	3		7
Strevens[73]	2002	Sweden	C	12	61 [0.69]	83 [0.94]							14	48 [0.54]	66 [0.75]	Enzymatic	3		6

Van Buul[74]	1995	Netherlands	L	LRR	70 [0.79]	90 [1.02]	66	59 [0.67]	70 [0.79]	66	59 [0.68]	70 [0.79]	66	59 [0.67]	75 [0.85]	Jaffe	3	Yes	8
Vural[75]	1998	Turkey	C	15	63 [0.72]	95 [1.07]							20	61 [0.69]	73 [0.83]	Jaffe	2		4
de Weerd[76§]	2003	Netherlands	L	96	70 [0.79]		188	62 [0.70]								Jaffe	2	Yes[+]	6
Weissberg[77]	1991	Israel	C	9	77 [0.87]	92 [1.04]							32	61 [0.69]	71 [0.81]	Jaffe	1		5

Table 1: Study characteristics. Creatinine values are given as µmol/L [mg/dL]. Cr= creatinine, ULN= upper limit of normal, LRR= laboratory reference range, WE=white European, AC=Afro-Caribbean, Med=Mediterranean *Assessment of pregnancy normality: 1=limited data, 2=exclusion of comorbidity associated with abnormal renal function eg pre-eclampsia, diabetes, vascular disease, 3=specific exclusion of renal disease, [+]but not excluded from study data, [$]=provided by study author/centre or available from an alternative source and appropriate for date of study, ^= women with emesis excluded from extracted data, [#]= includes 2 study cohorts at different altitude, [±]=Total 131 pregnant women, distribution between trimesters not recorded,[§]=mean creatinine data only, upper limit data not derived from interquartile range.

Variable	**Coefficient (95% confidence interval)**	**p-value**
Pregnant cohort size*	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 2010-2017): • 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

Table 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. [*=per 100 women]

Trimester	**1st**	**2nd**	**3rd**
Number of included studies	19#	22	30
Number of creatinine measures in pregnancy	816#	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*	**56µmol/L [0.63mg/dL]**	**52µmol/L [0.59mg/dL]**	**54µmol/L [0.61mg/dL]**
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*	**76µmol/L [0.86mg/dL]**	**72µmol/L [0.81mg/dL]**	**77µmol/L [0.87mg/dL]**

Table 3: Creatinine in pregnancy as a percentage of non-pregnant value according to trimester

*Example creatinine values are based on a typical value for non-pregnant females of 67.5µmol/L [0.76mg/dL], and an upper limit of 90µmol/L [1.02mg/dL].[12]

#19 studies (816 creatinine measures) inform the mean value and 18 studies (628 creatinine measures) inform the upper limit. CI=confidence interval.

Figure legends

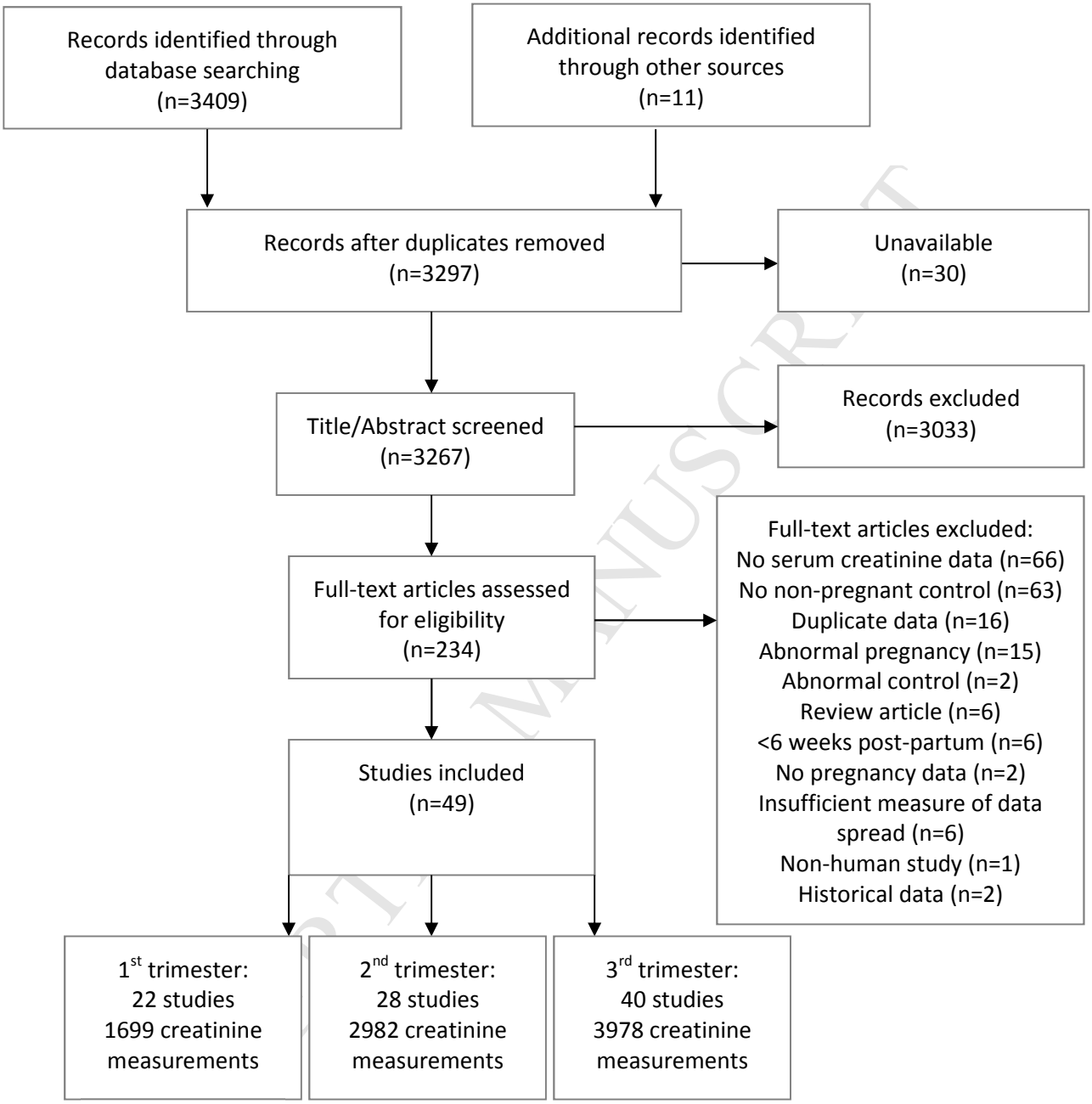
Figure 1: Flow diagram of the identification process for eligible studies

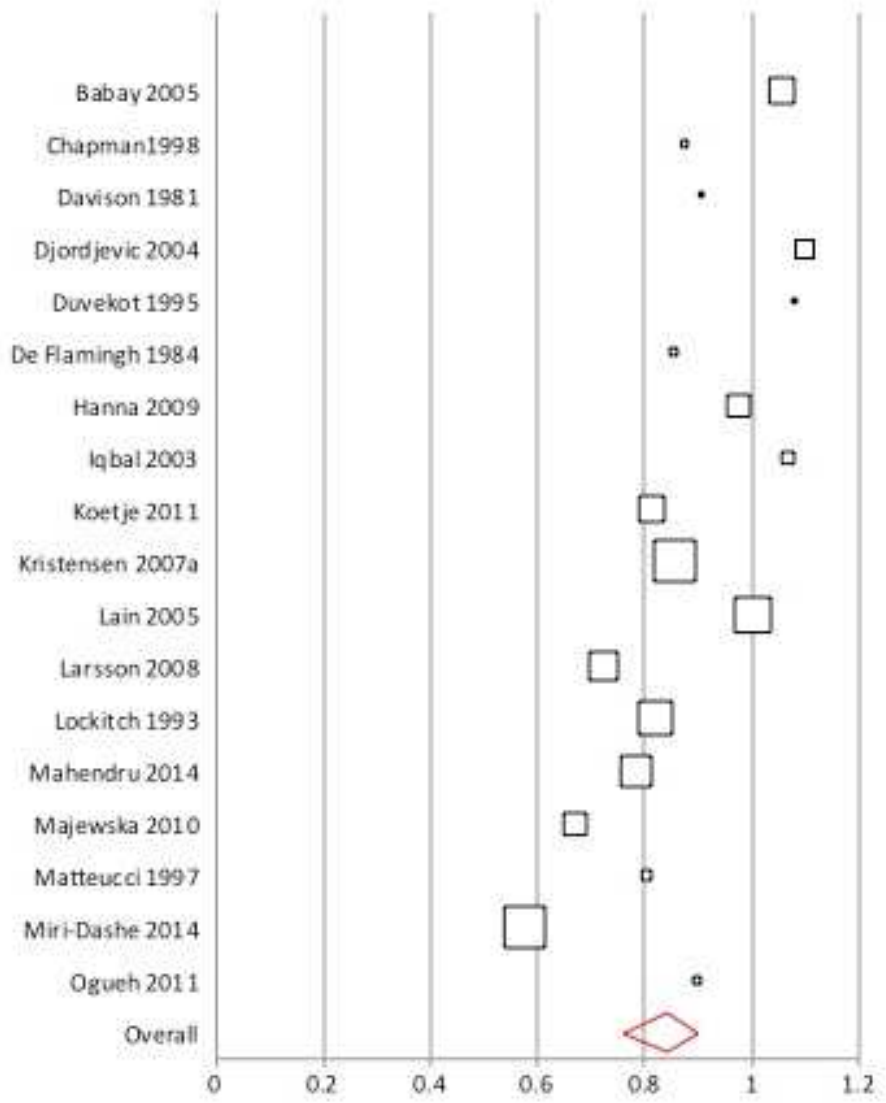
Figure 2: Pregnant:non-pregnant ratio for the upper limit of serum creatinine. Squares represent the point estimate of the ratio for each study, sized according to the study weight (geometric mean product of pregnant and non-pregnant sample size). Confidence intervals are not available due to the complexity of determining the precision of a ratio value. Overall is the summary value and 95% confidence interval generated by the bootstrapping technique for each trimester.

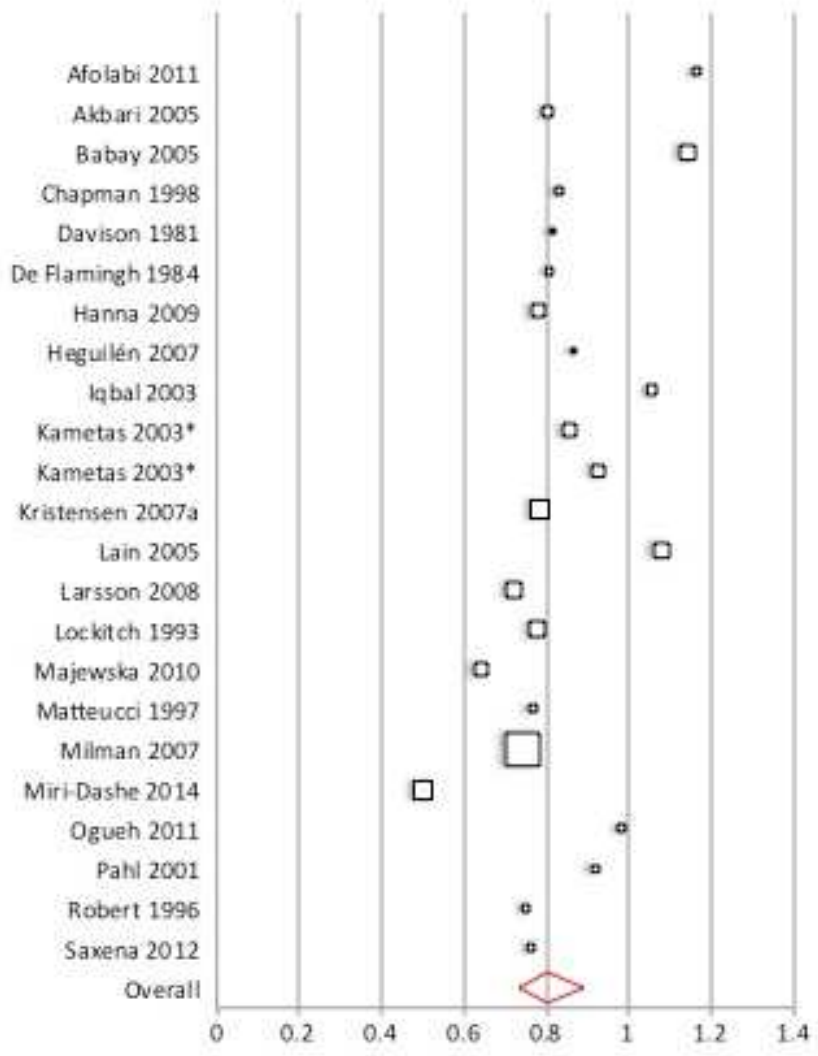
Acknowledgement

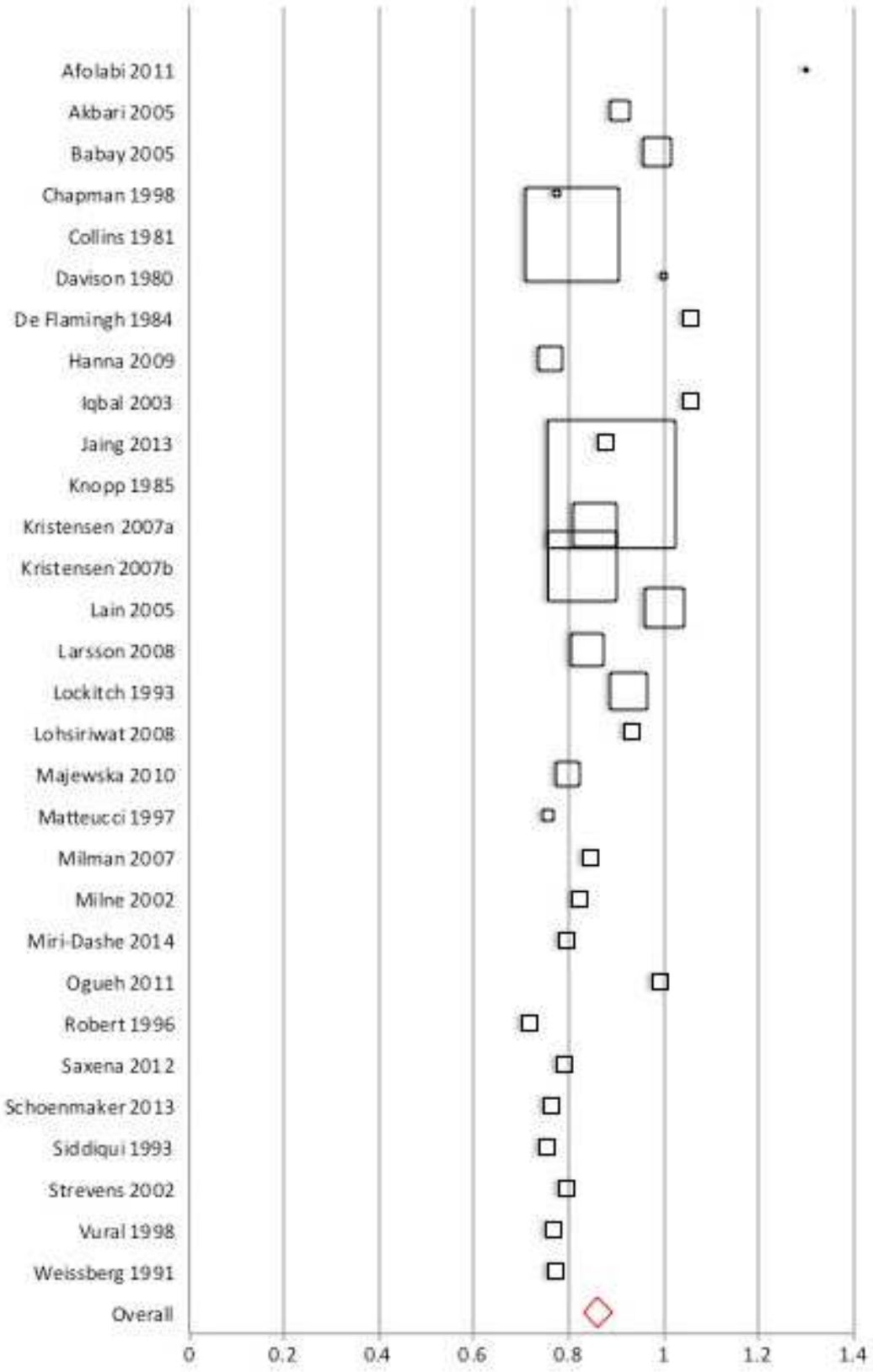
KW is supported by the National Institute for Health Research Rare Diseases Translational Research Collaboration (NIHR RD-TRC) and the Biomedical Research Centre at Guy's & St Thomas & King's College London. LCC is supported by a Research Professorship from the National Institute for Health Research, RP-2014-05-019. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Figure 1: Flow diagram of the identification process for eligible studies








Afolabi 2011
Akbari 2005
Babay 2005
Chapman 1998
Collins 1981
Davison 1980
De Flamingh 1984
Hanna 2009
Iqbal 2003
Jaing 2013
Knopp 1985
Kristensen 2007a
Kristensen 2007b
Lain 2005
Larsson 2008
Lockitch 1993
Lohsiriwat 2008
Majewska 2010
Matteucci 1997
Milman 2007
Milne 2002
Miri-Dashe 2014
Ogueh 2011
Robert 1996
Saxena 2012
Schoenmaker 2013
Siddiqui 1993
Strevens 2002
Vural 1998
Weissberg 1991
Overall
0
0.2
0.4
0.6
0.8
1
1.2
1.4