Serum cystatin is not a marker of glomerular filtration rate in pregnancy

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Summary: The role of cystatin C (Cys-C) as a marker of glomerular filtration rate (GFR) in pregnancy is undetermined. Measurements of Cys-C and creatinine (Cr) were taken at 14–17⁺⁶, 18–23⁺⁶, 27–31⁺⁶ weeks' gestation, at delivery and 2–6 weeks postpartum in a prospective observational study of 27 women. There was no difference between Cys-C levels in early and late second trimester, but they were significantly higher in early third trimester ($P < 0.001$) than second trimester, despite no concurrent increase in Cr. Cys-C was also significantly higher at delivery than at all other times in pregnancy ($P < 0.001$) and fell to postpartum values higher than second trimester measurements ($P < 0.01$), but lower than delivery ($P < 0.001$). In conclusion, changes in Cys-C may be influenced by pregnancy-related changes in glomerular filtration and therefore we would advise against their use as a marker of GFR in pregnancy.

Keywords: nephrology, glomerular filtration, cystatin C, renal physiology

INTRODUCTION

Serum creatinine (Cr) is the most commonly used marker of renal function but has limitations. Cystatin C (Cys-C) is freely filtered at the glomerulus, actively reabsorbed and catabolized by tubular cells and is potentially a superior marker of glomerular filtration rate (GFR) than Cr. There is no correlation between fetal and maternal Cys-C measurements, nor has the utero-placental unit been shown to contribute to changes in maternal Cys-C, therefore Cys-C in pregnancy is likely to be predominantly determined by maternal renal handling. Studies of Cys-C have previously focused on the third trimester and its role in the diagnosis of preeclampsia. We undertook a prospective observational cohort study of 27 women at St Helier Obstetric Department, and measured Cys-C and Cr during gestation, at delivery and at postpartum.

METHODS

Ethical approval was granted by the local ethics committee. Twenty-seven women were recruited into the study. They had no history of preeclampsia, hypertension, diabetes, anti-phospholipid syndrome, systemic lupus erythematosus, renal disease, thrombophilia, body mass index (BMI) >27 or age >40 . Serial measurements of Cys-C and Cr were taken at 14–17⁺⁶, 18–23⁺⁶, 27–31⁺⁶, at delivery and 2–6 weeks after

delivery. Cys-C and Cr were measured using particle-enhanced turbidimetric immuno-assay (DAKO Ltd, Ely, UK) and Jaffe assay, respectively.

Statistical analysis was performed using SPSS v16. Median and interquartile range (IQR) are presented as not all data were normally distributed. Differences between time points were tested with Mann-Whitney U tests. P values <0.05 were considered statistically significant.

RESULTS

Cys-C and Cr are shown in Table 1. None of the women developed preeclampsia, or delivered before 37 weeks gestation. There was no difference between Cys-C levels in early and late second trimester, but they were significantly higher in early third trimester ($P < 0.001$) than in second trimester, despite no concurrent increase in Cr. Cys-C was also significantly higher at delivery than at all other times in pregnancy ($P < 0.001$) and fell postpartum to values higher than second trimester measurements ($P < 0.01$), but lower than delivery ($P < 0.001$).

DISCUSSION

During pregnancy, GFR rises from the luteal phase of the last menstrual period and by the end of the first trimester, it has reached 40–50% above non-pregnant values, peaks in the second trimester and is associated with an increase in renal plasma flow and reduced filtration fraction. Elevated GFR persists throughout the third trimester due to a rise in filtration

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Table 1 Cystatin C and creatinine at five gestation time points

Gestation weeks	Early 2nd trimester (14–17 ⁺⁶) (n = 27)	Late 2nd trimester (18–23 ⁺⁶) (n = 16)	Early 3rd trimester (27–31 ⁺⁶) (n = 14)	Delivery (37 ⁺² –42 ⁺¹) (n = 18)	Postpartum (3–9 ⁺⁰) (n = 11)
Cys C (mg/dL)					
Median	0.95	0.88	1.00*	1.27**	1.02***
IQR	0.89–1.03	0.82–0.98	0.97–1.08	1.13–1.39	0.90–1.06
Cr (μmol/L)					
Median	67.0	67.5	66.5	74.5 ^Φ	86.0 ^{ΦΦ}
IQR	64.0–69.0	64.0–71.0	60.5–69.3	69.0–86.0	77.0–95.0

Cystatin: Between late 2nd trimester and early 3rd trimester * $P = 0.006$

Between early 3rd trimester and delivery ** $P < 0.0001$

Between delivery and postpartum *** $P = 0.001$

Between delivery and early or late 2nd trimester: $P < 0.001$

Between late 2nd trimester and postpartum: $P = 0.009$

Creatinine: Between delivery and early 2nd trimester ^Φ $P = 0.001$

Between delivery and late 2nd trimester $P = 0.004$

Between delivery and early 3rd trimester $P = 0.003$

Between delivery and postpartum ^{ΦΦ} $P = 0.01$

Between early or late 2nd trimester and post-partum $P < 0.0001$

fraction and fall in renal blood flow, but others suggest GFR may fall from 34 weeks onwards.

In our study, Cys-C was significantly elevated at 27–31⁺⁶, despite no increase in Cr, and rose further at delivery, then fell postpartum to levels that were higher than during gestation. One longitudinal study reports a significant fall in Cys-C in the second trimester,¹ but this has not been reproduced by others.^{2–4} An increase in Cys-C has been described towards the end of the third trimester,² but our data suggest that Cys-C rises earlier. One study demonstrated a trend in increasing Cys-C from week 17 onwards.⁴

A relationship between GFR measured by iothexol clearance and Cys-C in the third trimester has been described in healthy pregnancies⁵ and those complicated by preeclampsia; however, in other reports, Cys-C levels in the third trimester tend to be higher than in non-pregnant subjects.^{2,3–5} This is inconsistent with formal measurements of GFR at this stage of gestation.

Given the absence of a contribution from fetal or uteroplacental sources, this suggests that renal handling of Cys-C is altered in pregnancy. A different correlation between GFR in non-pregnant and pregnant women has also been described.⁵ The renal clearance of β -2 microglobulin (12 kDa) and β -trace protein (23–29 kDa), which are similar sized molecules to Cys-C (13 kDa), also increase in the third trimester.³

Limitations of our study include the number of participants, incomplete Cys-C and Cr values for delivery and postpartum, and a lack of comparison with a gold standard measurement of GFR such as inulin clearance. Further work to identify a marker of renal function that is able to detect changes

at the higher GFRs recognized in pregnancy is urgently required.

We would, however, conclude that Cys-C levels may be influenced by differential renal handling during gestation, and we would advise against its use as a marker of GFR in pregnancy.

CONFLICTS OF INTEREST STATEMENT

The contents of this manuscript, whether verbatim or re-phrased, have not been published elsewhere and we confirm there are no potential conflicts of interest.

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