Serum cystatin C in pregnant women: Reference values, reliable and superior diagnostic accuracy

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Summary

Background: A simple, endogenous, accurate and minimally invasive marker of glomerular filtration rate (GFR) is much desired in clinical nephrology. Cystatin C fulfills all criteria to be a marker for GFR. For early detection of renal impairment in pregnant women, it is necessary to determine serum cystatin C reference values and the correlation with GFR. The present study was therefore undertaken.

Method: Healthy pregnant women were followed during pregnancy and the postnatal period. Patient demographics included age, height, weight, BMI, parity, total blood count, LFT, urea, creatinine, Na, K, and blood sugar. Serum cystatin C was estimated using particle enhanced nephlo-immunoassay method. All the parameters were recorded at the start of pregnancy and then in each trimester and the postnatal period. Regression analysis correlation coefficient, ANOVA and the Student's t-test were used for analysis using the SPSS statistical package.

Results: A total of 197 pregnant women were included. Mean serum cystatin C for all the women was 0.82 ± 0.184 mg/l. Serum cystatin C levels were high – 0.89 ± 0.12 mg/l in the first trimester, decreased significantly to 0.651 ± 0.14 mg/l during the second trimester ($p = 0.0000$ compared to first trimester), and increased again to 0.82 ± 0.191 mg/l in the third trimester. After delivery the level rose to 0.94 ± 0.12 mg/l. A strong correlation was found between serum cystatin C and serum creatinine. A strong negative correlation was found between GFR and cystatin C values in the women ($r = -0.546$, $p = 0.000$). A linear relationship was found between GFR and cystatin C levels. A significant increase in the GFR was noted with the progression of pregnancy from 128.06 ± 29.7 ml/min in the first trimester to 155.2 ± 29.59 ml/min during second trimester ($p = 0.006$). A decline in the level of cystatin C exactly parallel to the increase in the GFR was noted with the progression of pregnancy. Interestingly cystatin C was found to have a strong negative correlation with gestational age ($r = -0.663$, $p = 0.000$).

Conclusion: Our results indicate that the mean serum cystatin C levels reflect changes in the GFR during the entire pregnancy and also in the postnatal period. Moreover, serum cystatin C levels are independent of age, height, weight, or blood sugar level. Cystatin C can be used for close supervision and early diagnosis of renal impairment in pregnant patients. Cystatin C is a reliable, useful and promising marker of GFR in pregnant women.

Key words: Pregnant women; Serum cystatin C.

Introduction

Normal pregnancy is characterized by a rise in the total blood volume under the influence of placental hormones, rennin, and aldosterone to meet the demand of the growing fetus [1]. An increase of 50%-80% in cardiac output and the glomerular filtration rate (GFR) is also noted [1]. This increase in GFR leads to increased filtration of glucose, amino acids, and folic acid which occasionally exceeds the maximum tubular threshold, thus producing glucosuria, proteinuria and loss of folic acid and often pregnancy-induced hydronephrosis and hypertension [2, 3]. All these factors may render further damage in the susceptible kidney [3]. Unsuspected kidney diseases are present in 24% of otherwise normal pregnant women and may be accelerated during pregnancy [3]. Therefore, evaluation of kidney function is of major concern during pregnancy, not only in patients with a history of diabetes, hypertension, preeclampsia, or renal impairment to avoid adverse outcomes in the mother and the fetus, but also to detect asymptomatic renal impairment in otherwise normal pregnancies. Estimation of GFR is necessary and indicated in patients with underlying renal disease, in addition to primigravidas, patients with gestational hypertension and gestational diabetes. Serum creatinine is used as an endogenous marker for estimation of GFR [4]. Creatinine level depends on the muscle mass and its concentration is influenced by the dietary intake of meat and physical exercise, furthermore, it is unstable in stored samples [5, 6]. The estimation of creatinine is affected by the presence of glucose, fructose, bilirubin, and antibiotics. Creatinine though freely filtered at glomerulus, is also secreted in the tubules. Contribution of secreted creatinine in the urine increases significantly with decreasing GFR rendering it less sensitive. An alternative to creatinine is cystatin C. Cystatin C is a 13-KD protease inhibitor which is produced at a constant rate by all nucleated cells. Inflammatory processes, gender, dietary intake of meat and body muscle mass does not influence the level of cystatin C [7]. Thus, its measurement is supposed to be an alternative and a more sensitive marker of GFR than serum creatinine [8]. Cystatin C can be easily estimated in the serum and may reflect physiological changes during

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pregnancy in a better way. The effect on serum cystatin C levels during pregnancy has not been studied. The present study was undertaken to evaluate cystatin C as a marker of renal function during pregnancy and determine its reference values.

Method

This prospective study was conducted between January 2001 and June 2003. A total 197 pregnant women were followed during the first, second and third trimester of pregnancy and postnatally. Twenty-three women women were excluded from the final analysis due to the presence of gestational diabetes, gestational hypertension, UTI, abortion or a malformed fetus (Figure 1). Only healthy pregnant patients with no history of diabetes, hypertension, pre-eclampsia or clinically detected renal disease were included. Subjects were recruited from the Obstetrics Clinic at King Khalid University Hospital, Riyadh, Saudi Arabia. An informed consent was given by all patients. Patient demographic data included age, height, weight, body mass index (BMI), parity and history of infection or medications at the time of sampling. Blood samples were obtained at each trimester and the postnatal period. Total blood count, liver function test, urea, creatinine, Na, K, and fasting blood glucose were performed for all patients. Serum cystatin C levels were estimated by particle-enhanced nephlometric immunoassay (PENIA). This assay employs antibody coated latex particles which react with cystatin C (antigen) in the specimen in a reaction cell of an automated nephlometer. Venous blood was collected under aseptic conditions and the serum was separated according to the standard protocols. Sera were either processed immediately or stored at –30°C until the assay was performed. Serum cystatin C was measured using a BN 100 Nephlometer and N Latex cystatin C assay kits (Dade Behring, Germany) according to the procedure recommended by the manufacturer. Briefly, all the reagents and the serum samples were brought to room temperature. About 250-300 ml of sera were placed in sample cups and loaded onto the sample rocks. Serial dilutions of samples (1:10 and 1:100) were prepared by the built-in-auto-diluter. Seventy-five microliters of diluted sample and 7.5 µl of N latex cystatin C reagent (lyophilized polystyrene particles coated with rabbit antibodies to human cystatin C) were mixed together in a reaction cuvette.

The reaction cell was monitored for a fixed time of six minutes and intensity of the light scattered by the Ag-Ab complex was indirectly proportional to the concentration of cystatin C in the sample, and was measured at 840 nm. The scattered signal was converted to concentration units by utilizing stored calibration curve in the nephlometer. This method is highly sensitive and specific [9, 10]. Serum creatinine and serum urea were estimated by an enzymatic method on clinical chemistry auto-analyzers. Sodium and potassium were measured using third generation automated clinical chemistry Dimension® RxL analyzer by Dade Behring, Germany. Urine dipstick analysis was performed according to the standard procedures.

All the parameters were recorded at the time of sampling in each trimester, and postnatal period. GFR was calculated by the Cockcroft and Gault formula [11]. Recently the Cockcroft and Gault formula was compared with 24-hour urine creatinine clearance for estimation of GFR in pregnant women and found to have a good correlation [11]. We therefore used the Cockcroft and Gault formula to estimate the GFR and compare cystatin C. Regression analysis, ANOVA, correlation coefficient and the Student's t-test were used for analysis, using BMDP and SPSS 10.0 for Windows statistical packages.

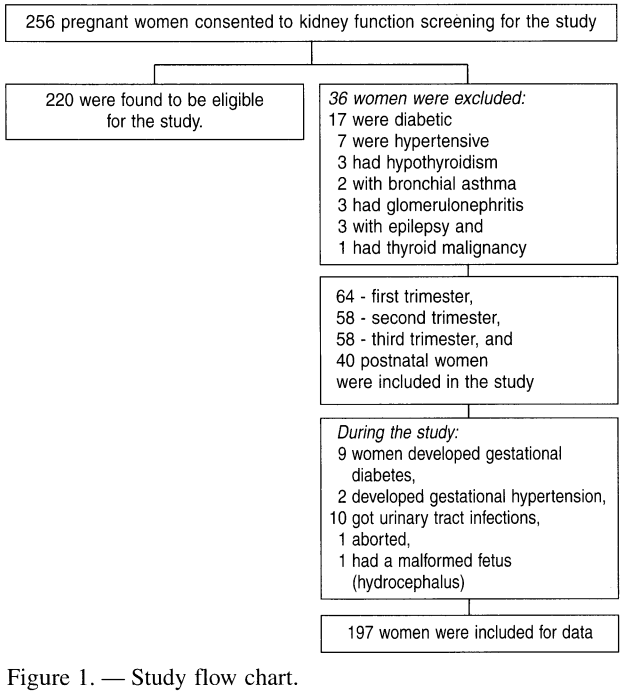

Figure 1. — Study flow chart.

Results

A total of 197 pregnant women were included. At the time of admission to the study, 54 women were in the first trimester of pregnancy, 53 in the second trimester, 50 in the third trimester, and 40 in the postnatal period (Figure 1).

The mean age of the pregnant women was 29.63 ± 6.54 years (range 18-47) in the first trimester, 30.3 ± 6.5 years (range 19-43) in the second trimester, 32.3 ± 6.63 years (range 22-44) in the third trimester, and 29.05 ± 6.5 years (range 19-41) in the postnatal group. Six percent of pregnant women were below 20 years of age while the majority (47.8%) ranged between 20-30 years, 39.1% between 31-40 years. Only 7.1% of the women were above the age of 40 (Table 1). The mean gestational age in the first trimester was 10.98 ± 1.11weeks (range 9-13 wks), 19.1 ± 3.4 weeks (range 14-26 wks) in the 2nd trimester, and 32.20 ± 2.5 weeks (range 27-37 wks) in the third trimester.

Table 1. — *Demographics and clinical characteristics of the healthy pregnant women.*

Parameters	Gestational period (Mean ± SD)			
	1st trimester (n = 54)	2nd trimester (n = 53)	3rd trimester (n = 50)	Postnatal (n = 40)
Age (years)	29.63 ± 6.54	30.3 ± 6.5	32.31 ± 6.63	29.05 ± 6.5
BMI	29.7 ± 4.36	31.8 ± 7.3	32.9 ± 8.3	29.4 ± 4.1
SBP (mmHg)	111.27 ± 7.69	108.9 ± 12.83	115.2 ± 12.3	113.62 ± 10.48
DBP (mmHg)	67.09 ± 8.6	65.64 ± 8.9	69.12 ± 11.17	64.95 ± 9.17
Gestational age (weeks)	10.98 ± 1.1	19.15 ± 3.4	32.20 ± 2.5	–

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure.

The mean height of all the pregnant women was 155.33 ± 4.86 cm (range 142-167 cm) while mean body weight was 70.41 ± 11.28 kg. Mean BMI of the first trimester patients was 29.7 ± 4.36 kg/m^2 (range 20.1-37.8), 31.8 ± 7.3 kg/m^2 (range 17.9-50.86) in the second trimester, and 32.94 ± 8.3 kg/m^2 (range 19.43-49.8) in the third trimester, while in postnatal patients it was 29.47 ± 4.14 kg/m^2 (range 21.6-44.8) (Table 1).

Variations in BP are also shown in Table 1. There was no case of pre-eclampsia in our patients neither at the time of recruitment nor during the entire study period. A total of nine patients developed gestational diabetes later during the study period, while ten developed urinary tract infections (UTI) and were not included in the final analysis (Figure 1).

Levels of serum creatinine, cystatin C, and GFR during pregnancy are shown in Table 2.

Mean serum cystatin C for all the patients (n = 197) was 0.82 ± 0.184 mg/l (range 0.51-1.19). Table 3 shows the levels of other renal markers during pregnancy. The serum cystatin C levels had no correlation with age (r = 0.037, p = 0.601), blood sugar (r = 0.135, p = 0.07), hemoglobin (r = .081, p = .257), WBC (r = 0.06, p = 0.25), weight (r = 0.068, p = 0.345). However, Serum cystatin C levels had a negative correlation with gestational age (r = -663, p = .000) (Table 4). Serum cystatin C levels were higher 0.89 ± 0.12 mg/l (range 0.57-1.1) in the first trimester, decreased significantly to 0.651 ± 0.14 mg/l (range 0.51-1.19) during the second trimester (p = 0.0000 compared to the first trimester), and increased again to 0.82 ± 0.19 mg/l (range 0.56-1.2) in the third trimester. After delivery (1-7 days) they rose to 0.94 ± 0.12 mg/l (range 0.68-1.1) (Table 2). The overall mean serum creatinine was 55.82 ± 9.5 umol/l (range 35-88). Unlike serum cystatin C, the values of serum creatinine did not change significantly during early pregnancy. The mean serum creatinine in the first trimester was 56.07 ± 9.78 umol/l (range 32-86), 57.46 ± 12.15 umol/l (range 38-88) in the second trimester, and it was 52.48 ± 9.106 umol/l (range 35-68) during the third trimester, while in postnatal patients it was 57.66 ± 6.97 umol/l (range 44-74) (Table 2). A total of ten (6.25%) women had UTI. Serum cystatin C concentrations in these ten patients were within the normal reference range of 0.58-1.1 mg/l. A total of nine (5.63%) women developed gestational diabetes during pregnancy in the study period (Figure 1). The serum concentration of cystatin C in these patients was 0.95 ± 0.193 mg/l (range 0.62-1.34) and the serum creatinine level was 55.3 ± 7.41 umol/l (range 41-64).

A strong correlation was found between serum cystatin C and serum creatinine. Also a strong negative correlation was found between GFR and cystatin C values in the patients (r= -0.546, p = 0.000). A linear relationship was found between GFR and cystatin C levels. Overall point to point corresponding change (decline) in the serum cystatin levels was observed with change (increase) in the GFR during pregnancy and in the postnatal period (Table 4). A significant increase in the GFR was noted with the progression of pregnancy from 128.06 ± 29.7 ml/min in the first trimester to 155.2 ± 29.59 ml/min during the second trimester (p = 0.006). Exactly parallel to increased GFR a decline in the level of cystatin C was noted with the progression of pregnancy being 0.89 ± 0.12 mg/l in the first trimester and 0.651 ± 0.14 mg/l in the second trimester (p = 0.000) (Table 2).

Other renal markers: *Serum urea:* The mean serum urea in our 197 healthy patients during the entire pregnancy till the second day of the delivery remained within normal reference range with a mean concentration of 2.98 ± 0.986 mmol/l (range 1.0-6.9). In the first trimester, the mean serum urea concentration was 3.06 ± 0.92 mmol/l (range 1.1-5), which did not change much in the second trimester 3.12 ± 0.87 mmol/l (range 3.1-4.9), however, it reduced slightly to 2.8 ± 1.2 mmol/l (range 1.0-6.9), and to 2.9 ± 0.97 mmol/l (range 1.2-5.9) in the 3rd trimester (p = 0.183) and postnatal period (p = 0.235), respectively (Table 3).

Serum sodium: The mean serum sodium in the 1st trimester was 139.2 ± 3.36 mmol/l (range 131-147) and the concentration remained almost the same in the second trimester 138.58 ± 2.87 mmol/l (range 130-147). In the third trimester it was 139.1 ± 2.8 mmol/l (range 132-147) and in the postnatal period 140.6 ± 3.4 mmol/l (range 134-146). The overall mean sodium of the total sample was 139.23 ± 2.7 mmol/l (134.4-147.0), which showed minor changes when compared with the mean of the 1st, 2nd and 3rd trimesters and postnatal period (Table 3).

Serum potassium: The mean serum potassium among the 197 healthy patients during the pregnancy and after the delivery was 3.98 ± 0.38 mmol/l (range 3.10-4.9), reflecting negligible changes with the progression of the

Table 2. — *Correlation of serum cystatin C levels, GFR and serum creatinine.*

Parameters (mean ± SD)	1st trimester	2nd trimester	3rd trimester	Postnatal
GFR (ml/min)	128.06 ± 29.7*	155.2 ± 29.59*	144.24 ± 28.2	140.33 ± 18.45
Cystatin C (mg/l)	0.89 ± 0.12**	0.651 ± 0.14**	0.82 ± 0.19	0.94 ± .12
Creatinine (µg/l)	56.07 ± 9.78	57.46 ± 12.15	52.48 ± 9.106	57.66 ± 6.97

*p = 0.006; **p = 0.0000.

Table 3. — *Frequency distribution of serum cystatin C and other renal markers.*

Parameters	1st trimester	2nd trimester	3rd trimester	Postnatal
Creatinine (µmol/l)	56.07 ± 9.78	57.46 ± 12.15	52.48 ± 9.1	57.66 ± 6.9
Urea (mmol/l)	3.06 ± 0.92	3.2 ± 0.87	2.8 ± 1.2	2.9 ± 0.97
Sodium (µmol/l)	139.2 ± 3.6	138.58 ± 2.8	139.1 ± 2.8	140.6 ± 3.4
Potasium (µmol/l)	3.93 ± 0.44	4.1 ± .41	3.9 ± 0.39	4 ± 0.31

Table 4. — *Correlation of serum cystatin C levels and other variables.*

Variables	Correlation coefficient	p value
Age	.037	.601
Blood sugar	.135	.070
Hemoglobin	- .081	.257
WBC	.080	.250
Weight	.068	.345
Gestational age	-.663	.000

pregnancy. The mean potassium level recorded in the first trimester was 3.93 ± 0.44 mmol/l (range 3.1-5), which did not change significantly in the 2nd trimester-4.1 ± 0.41 mmol/l (range 3.1-4.3) and 3rd trimester-3.9 ± 0.39 mmol/l (range 3.2-4.8) or in the postnatal period 4.0 ± 0.31 mmol/l (range 3.5-4.8) (Table 3).

Discussion

Human cystatin C is a basic protein, freely filtered by the glomerulus and almost completely reabsorbed by the proximal tubular cells [9, 10, 12]. Cystatin C has recently been designated as a new sensitive marker of GFR estimation [13, 14]. Serum cystatin C was shown to reflect GFR reliably in pregnant women [15], elderly persons with various renal diseases such as chronic renal failure due to various causes [17], patients with hepatorenal syndrome [19], fetuses with obstructive uropathies [20], renal transplant patients where it is more sensitive than creatinine [21], and during eclampsia [22]. The objective of the present study was to determine the serum cystatin C reference values and the correlation to GFR in normal cases. Our results show that the serum cystatin C levels were slightly higher than for normal non pregnant counterparts; however, they were within the normal range. Cystatin C level responded very well to increased GFR during pregnancy, resulting in a significant fall of cystatin C levels in the second trimester as compared to the levels at the start of the pregnancy ($p = 0.0000$) which is in agreement with the earlier reports [22, 23].

Serum cystatin C levels (based on the Cockcroft-Gault equation) were found to have a significant negative correlation with GFR ($r= -0.54552$, $p < 0.001$).

The regression equation for prediction of GFR from cystatin C values is: $Y = -0.0057 X + 1.67$ (Figure 2). This change in GFR and cystatin C is compatible with the physiological variation in GFR during pregnancy and to changes in blood volume which are increased several fold, clearing substances and hence decreasing their levels in the serum. Our results show a significant decrease in the serum cystatin C levels with the progression of pregnancy mostly in the second trimester ($p = 0.0000$). In addition, serum cystatin C levels decreased much earlier and corresponded with the increased GFR in pregnancy thus indicating better sensitivity as an endogenous marker for changes in GFR. Calculated GFR by cystatin C and the Cockcroft-Gault equation has been validated previously. Although this is an observation which needs to be validated by gold standard methods of measurement of GFR as insulin clearance. These gold standards of GFR estimation are however not practiced during pregnancy, and 24-hr creatinine clearance or GFR estimation with cystatin (Cockcroft and Gault formula) are more reliable. Our findings are in agreement with other researchers who found better accuracy of cystatin C [20].

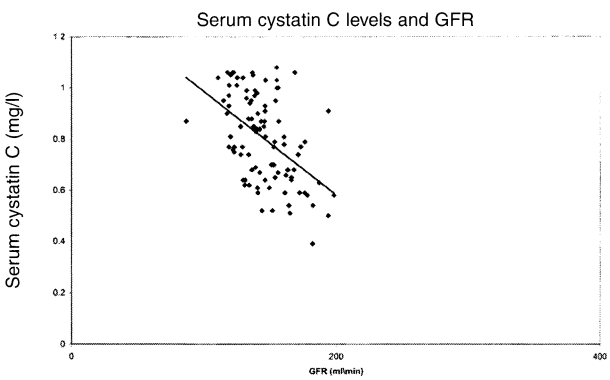

Figure 2. — Relationship between serum cystatin level & GFR.

In pregnant women who had UTI during various periods of pregnancy, cystatin C levels were no different than for other pregnant women (not included in the final analysis) and this is in agreement with previous studies. Similarly the pregnant patients who developed gestational diabetes had serum cystatin C levels within normal reference range of 0.58-1.1 mg/l (not included in the final analysis). Moreover serum cystatin C levels were not correlated with age, blood sugar, anemia and hemoglobin, infection or WBC. Progression of pregnancy and higher gestational age are associated with higher GFR and lower serum cystatin C levels in pregnant women.

Conclusions

The results of the present study show that serum cystatin C levels in pregnant women were slightly higher than those of the non pregnant counterparts at our center. Serum cystatin C levels are not affected by age, diabetes, anemia or infection.

Serum cystatin C levels were significantly correlated with serum creatinine and with GFR.

There was a linear relationship between serum cystatin C and GFR similar to serum creatinine. Serum cystatin C could detect changes in the GFR and was more sensitive than serum creatinine as cystatin C levels fell parallel, and much earlier than the change in GFR, with the progression of pregnancy than serum creatinine.

UTI or gestational diabetes had no significant effect on serum cystatin C levels; however, this needs further validation.

Serum cystatin C can be used during pregnancy as a reliable endogenous marker for kidney function and provides an earlier diagnosis of deterioration of GFR in all the three trimesters of pregnancy and during the postnatal period.

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