ENDOGENOUS CREATININE AND BLOOD UREA NITROGEN CLEARANCES IN NORMAL PREGNANCY

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SUMMARY: Endogenous creatinine and BUN clearances were determined during the first trimester (n=11), second trimester (n=17) and the third trimester (n=27) of healthy pregnant women. Both of the clearances increased significantly during the first trimester and sustained a high level till term, relatively decreasing below the first trimester values towards the end pregnancy. The increments observed in the corrected creatinine and corrected BUN clearances were determined to be higher. Being an expected result of these findings, plasma creatinine and BUN levels in pregnant women decreased significantly from their nonpregnant controls.

Key Words: Pregnancy, creatinine clearance, blood urea nitrogen clearance.

INTRODUCTION

When the literature is reviewed, the results of renal clearance studies in normal pregnancy differ from each other. These differences may result either from specific anatomic and functional changes of pregnancy or from different methods used in analysis. The results are also affected by the posture of pregnant women (8).

In the first serial study performed by Sims and Krantz, it was reported that GFR level is 50% higher than normal during normal gestation, and though it decreased relatively, it was observed at high levels till term (14). While the data of Sims and Krantz concerning the 1st trimester are still accepted, Davison and Dunlop determined that creatinine clearance C_{cr} decreases during the 3rd trimester and declines to the value of nonpregnants near term (2,3,6,7).

The reason of getting different results from clearance studies in pregnancy is the significant mechanical effect of the gravid uterus on renal hemodynamics. C_{cr} values increase in lateral recumbent position, while they decrease in supin and upright positions. Furthermore clearance values obtained by infusion techniques were found to be very high because of the increased intravascular volume during pregnancy (1,9,10,12).

As a result of increased GFR in pregnancy, BUN and plasma creatinine values decrease below those of normal nonpregnant cases (3,8,13,14).

In this study, we aimed to determine the Cr and BUN clearances in normal pregnancy, by considering the anatomic and functional changes and methodological differences which lead to different results.

MATERIALS AND METHODS

Subjects

The subjects were selected from normal pregnant women who applied to the Gynecology and Obstetrices Clinic of Cukurova University Medical School, for being controlled periodically or for normal labour. The ones who had a systemic disease, preeclampsia or obstetric complications were excluded from this study. The number of the subjects were 11 in the 1st trimester, 17 in the 2nd trimester and 25 in the 3rd trimester. The total number of the subjects was 55.

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The nonpregnants were selected from the women who applied to the Gynecology and Obstetrics Clinic of the same center, due to some gynecological complaints and infertility problems or for being performed tubal ligation. The ones having systemic disorders were not included in this study. The nonpregnant group included 27 women.

All the subjects who had toxemia, hypertension, cardiac disorders, renal or/and urinary tract disturbances diabetes mellitus, and the ones having systolic blood pressure above 140 and diastolic above 80 mmHg were also excluded. Clinical details and the mean blood pressure values of the pregnant and nonpregnant subjects are demonstrated in Table 1.

All of the subjects were evaluated for fasting blood glucose, and plasma uric acid, sodium, potassium, calcium, and inorganic phosphate levels; the ones with abnormal values were also not included in this study.

Materials and Methods

Renal clearances were determined by applying the standard method (11,16). Urine was collected twice; the first one in the morning (1st period) and the second in the afternoon (2nd period). Each Urine collection period lasted two hours.

During the tests, all of the subjects were held in their normal daily activities, and were not kept in a specific posture.

After a light breakfast in the morning, urine collection for the first period was begun at 09.00 am. After emptying the bladder, each subject had a glass of water (150-200ml) at 09.00 am. At 10.00 am, the first blood samples were taken. At 11.00 am urine collection for the first period was terminated.

After a light lunch, urine collection for the 2nd period was begun at 1.00 pm. After emptying the bladder, each subject had a glass of water at 1.00 pm. At 2.00pm, the second blood samples were taken. At 3.00 pm, urine collection for the second period was terminated.

We aimed to evaluate the endogenous creatinine and blood urea nitrogen clearances, with the corrected creatinine and corrected BUN clearances for the 1st and the 2nd periods.

Because of the marked increment in intravascular volume during pregnancy, inulin and PAH clearance tests, which require infusion techniques were not applied in this study. Because simultaneous inulin and endogenous creatinine clearance values were determined to change parallely, creatinine clearance was preferred to be measured instead of C_{in} (8, 14).

All chemical analysis were performed spectrophotometrically, creatinine values by standard picric acid method (Jaffe reaction) (15), and urea nitrogen values by standard urease-nesslerization (11) method.

Creatinine clearances in the 1st and the 2nd periods were calculated using the standard formula (U_x, V/P_x). Urea nitrogen clearances were calculated as 'maximum clearances ($U_x.V/P_x$)' in the subjects with urine volumes more than 2 ml per minute, and as 'standard clearances ($U_x./V/P_x$)' in those with urine volumes equal to or less than 2 ml/min (11,16).

Creatinine and BUN clearance values were corrected to a standard of 1.73 m^2 (C_x 1.73/A), in order to obtain the corrected creatinine clearance (C_{ccr}) and corrected BUN clearance (C_{cBUN}) levels.

Table 1: Clinical details of the pregnant and nonpregnant groups (Mean ± SE)

						*BP (mm Hg)	
Group	Age (year)	Parity	Weight (Kg)	Height (cm)	*BSA (m_2)	Syst.	Diast.
I. Trim n = 11	28.36 ± 1.13	1.91 ± 0.61	68.27 ± 4.50	160.27 ± 1.13	1.7 ± 0.05	112.27 ± 4.17	72.73 ± 3.26
II. Trim n = 17	25.47 ± 1.18	2.0 ± 0.69	63.56 ± 2.66	158.24 ± 1.56	1.64 ± 0.04	109.41 ± 2.31	69.71 ± 1.63
III. Trim n = 27	28.48 ± 1.0	1.52 ± 0.33	70.63 ± 1.72	159.93 ± 0.80	1.72 ± 0.02	113.33 ± 2.6	70.37 ± 1.73
Nonpregn. n= 27	29.41 ± 0.87	3.19 ± 0.58	62.78 ± 1.63	161.48 ± 1.19	1.65 ± 0.02	116.67 ± 2.07	71.11 ± 1.63
Total n= 82	28.15 ± 0.54	2.22 ± 0.28	66.26 ± 1.17	160.13 ± 0.60	1.68 ± 0.01	113.48 ± 1.33	70.79 ± 0.94
Min. Value Max. Value	16 36	0 12	46 99	147 175	1.42 2.00	90 140	50 80

*BSA : Body surface area.

* BP : Blood pressure

Table 2: Creatinine Clearences and Urine Volume Values (*V/min) of the Pregnant and Nonpregnant Groups (Mean ± SE)

Group	V/min (ml)	C_{cr1} (ml/min)	C_{cr2} (ml/min)	$C_{cr.av}$ (ml/min)
I. Trim n = 11	1.27 ± 0.20	110.55 ± 8.46	138.98 ± 18.75	125.29 ± 10.42
II. Trim n = 17	1.24 ± 0.1	121.53 ± 15.92	123.21 ± 12.94	122.39 ± 10.02
III. Trim n = 27	1.19 ± 0.09	124.79 ± 8.50	112.78 ± 8.38	118.80 ± 6.64
Nonpregn. n= 27	1.25 ± 0.12	97.72 ± 8.21	98.34 ± 7.06	98.05 ± 4.56
Total n= 82	1.23 ± 0.06	113.29 ± 5.29	113.83 ± 5.26	113.58 ± 3.78
	F=0.09 p=0.97 (> 0.05)	F=1.69 p= 0.18 (>0.05	F=2.40 p=0.08 (>0.05)	F=3.084 p= 0.03 (<0.05)

*V / Min: Mean value of the urine volumes collected during the I. and II. clearance periods.

The mean clearance values were obtained from the clearances of the 1st and the 2nd periods.

In statistical analysis of the results student-t test, correlation-regression and variance analysis methods (Statistical Graphics Co., 1988 StSC, Version 3.0) were used.

RESULTS

Creatinine Clearance (C_{cr})

Creatinine clearance values are demonstrated in Table 2.

Compared with nonpregnant values, the mean C_{cr1}, C_{cr2} and $C_{cr.av}$ levels were found to be higher in all trimesters. While the difference was nonsignificant in the values of urinary volume/minute; C_{cr1}, C_{cr2} and $C_{cr.av}$ values differed significantly between the pregnant and nonpregnant groups (Table 2; p<0.05). ("1","2" and "av" in the abbreviated symbols of clearances express the "1st period", the "2nd period" and the "average=mean" clearances, respectively).

The mean $C_{cr.av}$ value of pregnant women at term (40 weeks) was found to be lower than that of the other 3rd trimester pregnants (28-39 weeks), but this difference was not significant (p>0.05).

In our study, we determined no correlation between parity and $C_{cr.av}$ values (r=0.095).

Corrected Creatinine Clearance (C_{ccr})

Compared with nonpregnant values, the mean C_{ccr1}, C_{ccr2} and $C_{ccr.av}$ levels were determined to be higher in all trimesters. According to variance analysis results, these differences were found to be nonsignificant (p>0.05). In all groups, the mean corrected creatinine clearance values were found to be higher than those of C_{cr}, obtained without being corrected to the body surface area.

Blood Urea Nitrogen Clearance (C_{BUN})

BUN clearance values are demonstrated in Table 3.

Compared with nonpregnant values, the mean C_{BUN1}, C_{BUN2} and $C_{BUN.av}$ levels were found to be higher in all trimesters, the difference being very significant (Table 3; p<0.01).

Corrected BUN Clearance (C_{cBUN})

Compared with nonpregnant levels, the mean C_{cBUN} values were found to be higher in all trimesters, and this difference was very significant (p<0.01). Corrected BUN clearance values in all groups were determined to be higher than those of C_{BUN} obtained without being corrected to the body surface area.

Plasma Creatinine (pcr) and BUN values

The mean pcr and BUN values of the pregnant group were lower than those of nonpregnants, and this difference was statistically significant (p<0.05 and p<0.01, respectively).

DISCUSSION

Creatinine Clearance

Compared with nonpregnant levels, creatinine clearance values in the first and the second periods, and the mean C_{cr} values were determined to be higher in all of the pregnant groups. The differences between the groups were not statistically significant for the C_{cr1} and C_{cr2} values (p>0.05), but it was very significant for the mean

Table 3: BUN Clearence Values of the Pregnant and Nonpregnant Groups (Mean ± SE)

Group	C_{BUN1} (ml/min)	C_{BUN2} (ml/min)	$C_{BUN.av}$ (ml/min)
I. Trim n = 11	133.24 ± 27.39	143.12 ± 35.7	138.19 ± 30.37
II. Trim n = 17	73.84 ± 13.19	75.92 ± 11.59	74.9 ± 11.57
III. Trim n = 27	96.01 ± 12.12	81.4 ± 8.35	88.73 ± 9.64
Nonpregnant n= 27	63.38 ± 7.29	60.68 ± 7.83	62.03 ± 6.82
Total n= 82	85.66 ± 6.87	81.72 ± 6.97	83.71 ± 6.53
	F= 4.19 p= 0.0008 < 0.01	F= 5.22 p= 0.003 < 0.01	F= 5.21 p= 0.003 < 0.01

C_{cr} levels (Table 2; 0.01 <p<0.05) While the mean C_{cr1} values increased gradually from the 1st trimester to term, the mean C_{cr2} and $C_{cr.av}$ values decreased relatively approaching to term. This trend seen in C_{cr2} and $C_{cr.av}$ values were attributed to the effect of posture.

The mean $C_{cr.av}$ values of the 1st, 2nd and the 3rd trimester pregnant groups and the nonpregnant group were determined to be (±SE) 125.29 ± 10.42, 122.39 ± 10.02, 118.80 ± 6.64 and 98.05 ± 4.56 ml/min, respectively (Table 2). It was demonstrated that this difference between the groups was not due to the urinary volume changes seen in pregnancy (8) (Table 2. The mean urinary volume values do not differ in the pregnant and nonpregnant groups, p>0.05).

These findings are the expected results of the markedly increased intravascular volume and decreased periferic resistance seen in normal pregnancy. Because of the increment in total fluid volume during the 12.-32. weeks and the marked increment in cardiac output in the 20th week of pregnancy, the mean creatinine clearances in the 1st and the 2nd trimesters were found to be higher. Because of relative decrements in extra cellular fluid volume and cardiac output, and also due to the postural effects, the mean C_{cr} was determined to be relatively decreased in the 3rd trimester (8,10,13).

In this study, the mean $C_{cr.av}$ values in the 28th-39th weeks of pregnancy and during term (40th week) were found to be (±SE) 123.08 ± 14.36 and 117.01 ± 7.50 ml/min, respectively, the difference between the groups being nonsignificant (p>0.05). This finding was attributed to the relative decrements in total fluid volume and cardiac output near term, and also to the mechanical effect of markedly enlarged gravid uterus (10,12,13). Although creatinine clearance decreased relatively in the 40th week, it was still higher compared with the nonpregnant level.

In our study, creatinine clearance values varied in great ranges, which was also determined by some other investigators (2, 3).

Our results are similar to those of Sims and Krantz, who determined the endogenous creatinine clearance value to be 50% higher than normal during the 15th-38th gestational weeks (14). Davison also investigated that the mean creatinine clearance value was 45% higher than normal during the 1st trimester (3).

In the study of De Alvarez (4), 24 hour creatinine clearance value was 50% higher than normal in the 1st trimester, which was determined to be slightly lower than the nonpregnant values during the 2nd and the 3rd trimesters. These results are in contrast with ours, the reason of which may be the marked effect of posture on GFR during the 2nd and especially the 3rd trimesters, due to the long clearance test applied in this study (1, 8, 12).

In a study of Dignam (5), GFR measured by inulin clearance increased during pregnancy, reaching its highest levels in the 3rd trimester. While being similar to our mean C_{cr1} values, these results differ from our C_{cr2} and $C_{cr.av}$ levels. This difference may be due to the application of different methods. In Diagnam's study, infusion technique was applied and the pregnants were held in lateral recumbent position; they were also permitted to drink water throughout the test period, in order to cause maximum diuresis. It is known that the clearance values increase in lateral recumbency, especially during the 2nd and 3rd trimesters (8, 9).

Results of creatinine clearance tests applied close to term also differ from each other. In some studies, the increment in GFR values persists till term, while in some others, GFR decreases relatively towards the 40th week, as it is also determined in our study in terms of C_{cr2} and $C_{cr.av}$ values (2, 6).

According to Dunlop and Davison (7), 24-hour creatinine clearance increases 45% of normal value in the mid of the 2nd trimester, which decreases significantly in the 3rd trimester, declining to the nonpregnant values near term. These results contrast with ours. In our study, creatinine clearance decreased relatively in the last week of pregnancy, but was still determined to be higher compared with nonpregnant values.

These differences observed near term are possibly due to the methodological pitfalls and postural effects. Urine collection errors become prominent during pregnancy due to the increment in residual urinary volume and to the mechanical effect of the enlarged gravid uterus, especially during the 3rd trimester. These facts lead to obtain different results from the clearance tests applied during pregnancy (8,12,13).

Creatinine clearance or GFR persists in high levels till delivery when clearance measurements are made in proper conditions and methods (6, 8).

Being similar with the results of Sims and Krantz (14), we could not find any significant correlation between the creatinine clearance and parity (r=0.095).

In our study, corrected creatinine clearances in the 1st and the 2nd periods and the mean C_{ccr} levels in all pregnant groups were higher compared with nonpregnant values, the difference being nonsignificant (p>0.05).

In all groups, the mean C_{ccr} values were determined to be slightly higher than those of C_{cr}. Because the body surface area increases as the pregnancy progresses, C_{ccr} values measured during pregnancy show great variations. Due to this reason, some investigators claim that clearance values must not be corrected to the body surface area during pregnancy (6).

Blood Urea Nitrogen Clearance

Compared with nonpregnant levels, the mean C_{BUN1}, C_{BUN2} and $C_{BUN.av}$ values were determined to be higher in all trimesters. The mean BUN clearances, which were found to be maximum in the 1st trimester, declined to their lowest levels in the second trimester and then, increased relatively during the 3rd trimester. The values of the 1st trimester pregnant group were almost 100% higher than those of nonpregnants. The differences in the BUN clearance values were determined to be extremely significant (Table 3; p<0.01).

Corrected C_{BUN} levels were determined to be slightly higher than C_{BUN} values calculated without being corrected to the body surface area. Compared with nonpregnant values, the increments in C_{cBUN} levels of the pregnant groups were found to be very significant (p<0.01).

The increased levels of C_{BUN} and C_{cBUN} determined in pregnant groups may be the result of increased extracellular fluid and cardiac output (8,10), but it is hard to explain the relative decrease in the 2nd trimester and the following increase in the 3rd trimester. While expecting an increase in C_{BUN} values in the 2nd trimester due to the markedly increased ECF during the 12.-32. gestational weeks, and expecting a decrease in C_{BUN} levels in the III. trimester due to the relatively decreased cardiac output after the 28th week, the results of our study contradict these facts. The relative decrease during the 2nd trimester can be explained by postural effect. Such an explanation can not be made for the increase observed in the 3rd trimester, since the extremely enlarged uterus must decrease the clearance values by manifesting the postural effect during this period (8,12). Thus an alteration in the renal handling of urea during the III. trimester could also contribute to the observed changes and this possibility requires further investigation.

In our study, the two important tests which represent GFR, the endogeneous creatinine and BUN clearances, were determined to be significantly increased in the 1st trimester. Though they relatively decreased in the 2nd and the 3rd trimesters, they were still observed to be higher compared with nonpregnant values. In many studies, it was investigated that GFR measured by creatinine or urea clearances during the 2nd and the 3rd trimesters was significantly affected by postural changes, and our results also support these findings (8,9,12). The controversial results of clearance tests applied during pregnancy may result either from postural effects or methodological differences. Unfortunately in some studies, inadequate explanation was given about the methods used to measure GFR (8).

Plasma Creatinine (pcr) and BUN values

The mean pcr concentrations in pregnant and nonpregnant groups were determined to be (±SE) 0.85 ± 0.01 and 0.94 ± 0.04 mg/dl, respectively, the difference between the groups being very significant (p<0.05).

The mean BUN values of the pregnant and nonpregnant groups were found to be (±SE) 10.26 ± 0.24 and 11.94 ± 0.64 mg/dl, respectively. This difference was also very significant (p<0.01).

These findings are the expected results of the increased creatinine and BUN clearances during pregnancy. BUN and pcr values were found to decline during gestation, which was also demonstrated by Sims and Krantz (14), and Dunlop (7). These results have clinical importance; the values accepted to be normal in nonpregnant women, may be a sign of glomerular dysfunction during pregnancy (7,8,14).

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