KIDNEY FUNCTION DURING NORMAL PREGNANCY

I. THE INCREASED UREA CLEARANCE OF NORMAL PREGNANCY [1,]

By MARGARET NICE

(From the Laboratory of Maternity Hospital and the Department of Biochemistry, School of Medicine, Western Reserve University, Cleveland)

(Received for publication May 23, 1935)

With the advent of urea and creatinine clearance tests as measures of kidney function, the possibility of more closely associating the etiology of the toxemias of pregnancy with renal pathology was reopened. Thus, Stander, Ashton and Cadden (1) undertook an investigation of renal function in the toxemias of pregnancy and determined the urea and creatinine clearance rates, in conjunction with a number of other tests of kidney function, on 65 women in various stages of pregnancy. They found no important variations in normal pregnancy or in the low reserve kidney of pregnancy. However, both clearances were subnormal, at from 55 to 80 per cent, in nephritic toxemias (Stander's classification (2)). Cadden and McLane (3) extended these studies on 343 pathological pregnancies, using urea and creatinine clearance and the phenolsulphonephthalein tests of kidney function, and concluded that only urea clearance was sufficiently sensitive to differentiate chronic nephritis from the other toxemias of pregnancy. Their antepartum averages were: for 9 cases of normal pregnancy, 122.7 per cent; for 90 of low reserve kidney, 101.7; for 87 of nephritis, 75.3; for 17 of preeclampsia, 84.4; and for 4 cases of eclampsia, 54.7 per cent. Hurwitz and Ohler (4), in 103 tests performed in the ninth month of pregnancy, found urea clearance values from 90 to 140 per cent, averaging 127 per cent, in normal pregnancy, and from 26 to 84 per cent in eclampsia, chronic nephritis and the late toxemias of pregnancy. There were a few high values in the last two groups. Cantarow and Ricchiuti (5) determined 44 urea clearance rates on 39 cases of normal pregnancy. Seven were in the third, fourth and fifth months, 4 in the sixth, 5 in the seventh, 3 in the eighth, and 25 in the ninth month of pregnancy. Their clearance values varied from 28 to 184 per cent and appeared to fall from an average of 111 per cent in the third month to 59 per cent in the ninth month. In some recent work Dieckmann (6) found urea clearance decreased to averages below 50 per cent in patients with toxemia, hypertension or nephritis during the latter half of pregnancy. For normal pregnancy it averaged 102.3 per cent in 27 tests before delivery and 124.5 per cent in 10 tests immediately following delivery.

From these investigations it is apparent that the functioning level of the kidney during normal pregnancy must be more definitely established before its measurement during the toxemias can be of real value. A greater number of measurements should be repeated in series throughout normal pregnancies. The urea or the more difficult creatinine clearance test offers the most suitable method of accomplishing this end. Since Hayman, Halsted and Seyler (7) have found the results of the two tests completely comparable, the urea clearance appears to be the most practical test of kidney function available. Accordingly, the present work was undertaken to establish the changes of urea clearance rate through as long periods of normal pregnancy as possible.

METHODS

A series of urea clearance tests, determined by the method of Möller, McIntosh and Van Slyke (8), was run on each of 13 normal pregnant women at intervals of two or three weeks. Several tests were obtained as early as the third and fourth months of gestation and as late as the eighth month postpartum. The tests were carried

[1] An abstract of this paper appears in the April, 1935, Proceedings of the American Society of Biological Chemists, J. Biol. Chem., 1935, **109**, p. xlix.

[2] The data presented in this paper are taken in part from the thesis submitted by Margaret Nice to the Graduate School of Western Reserve University, June, 1934, in partial fulfillment of the requirements for the degree of Master of Science.

out in the morning after a light breakfast, the latter being considered by Hayman (9) to have no effect upon urea excretion. No coffee or medication was permitted. The patients were kept in a sitting posture and given enough water to insure maximum clearance. Two one-hour urine specimens were collected by voiding, and one blood sample was drawn at the end of the first hour.

The blood and urine urea nitrogen determinations were made by the urease-aeration-titration method of Van Slyke and Cullen (10), using 4 cc. of blood or 0.5 cc. of urine. The urine ammonia nitrogen was similarly measured on one or 2 cc. of urine and subtracted from the urine urea nitrogen. From these results the standard or maximum clearance was calculated with corrections for body size as suggested by McIntosh, Möller and Van Slyke (11). The clearances were calculated in per cent of the normal values given by Möller, McIntosh and Van Slyke (8), the average of each pair being reported. No high results were recorded unless the two tests from which they were averaged checked within 10 per cent of their average.

Since the blood urea is lower in pregnancy than in the nonpregnant normal, the urea clearance was estimated before and after feeding urea in order to determine whether there was a change in the clearance values when the blood urea was brought to normal or above. Thus 10 or 20 grams of urea were given to each of 7 pregnant women after a blood and urine specimen had been taken for a preliminary one hour test. Following a one half hour interval the second test was started. Blood samples were taken at the beginning and the end of this hour, and a one hour urine specimen collected. The urea contents of the last two blood samples were usually within 10 per cent of each other, and were averaged for the calculation of the second clearance.

RESULTS

The results are collected and summarized in Table I. The antepartum urea clearance rates range from 80 to 286 per cent, the postpartum

TABLE I

Urea clearance rates during normal pregnancy and puerperium

Case number	Para	Age	Months of pregnancy											Months of puerperium				Non-pregnant
			3	4	5	5½	6	6½	7	7½	8	8½	9	2	4	6	8	
		years	*per cent of Van Slyke's nonpregnant normal*											*per cent*				*per cent*
1	III	23							97	113*		184	116					96
2	I	19	80	198		117	89	140		92	127	200		83	86*			120
3	IV	31					168		150	188	123	254	117		126*	95	112	83
4	III	25					164	136		247		144						117
															80			
5	I	22				97		95		122	162*	148	140		113*	103		108
												107						
6	I	26			204	118		181	179	155	110	102	111	108	90	103		97
7	I	19			227	206				153	130	163		97				120
8	I	21					136*		130*	162*		286	134*			69*		109
9	I	25									126		91			101*		95
10	IV	32		130		139			158	158	155	111*	125	66	77			91
11	I	18				152	123	106	185	118		111	182	127	86*			101
12	I	18						137	140	151*	185*	160		118	61			117
													203				99	
13	I	20									154		108				97*	
Means (trimester)					145.5						154.0							
Mean									153.0						95.5			105.0
Standard deviation									45.0						18.0			12.0
Probable error of the mean									3.5						2.6			2.5
Difference													57.5†				9.5†	
Probable error of the difference													4.3				3.6	

* Standard clearances.

† If the difference is over 4 times the probable error of the difference, it is significant, Dunn (12).

from 61 to 120 per cent, and the nonpregnant normals from 82 to 120 per cent. A statistical analysis, according to the procedures outlined by Dunn (12), shows that the variations of urea clearance from month to month during pregnancy are not significant; nor is the slight increase of 8.5 per cent from the second to the third trimester. The antepartum mean of 153 per cent, however, is significantly higher than the postpartum mean of 95.5 per cent or the nonpregnant mean of 105.0 per cent. The last two values are not significantly different and closely approximate Van Slyke's normal of 100 per cent. This establishes a definitely increased urea clearance rate during normal pregnancy, which is independent of the progress of pregnancy.

The standard deviation of 45 for the antepartum values is much larger than that of 18 for the postpartum results, or of 12 for the nonpregnant normals. This wide variation occurs also in the rates for each individual.

The antepartum blood urea nitrogen values were low, averaging 7.7 mgm. per 100 cc., and showed a definite tendency to increase from an average of 6.2 mgm. in the third month to one of 8.3 mgm. in the ninth. The postpartum average was normal at 12.0 mgm. The relationship of the low antepartum blood urea to the high clearance is observed by plotting maximum clearance rates against their respective blood urea nitrogen values, as was done in Figure 1. The curve of the means of the clearances at successive blood urea levels indicates a rough inverse proportionality between the two.

When the blood urea nitrogen was raised by feeding urea, the same increased clearance rates were found in the second hour tests with the high blood urea nitrogen as in the first hour tests where it was low (Table II).

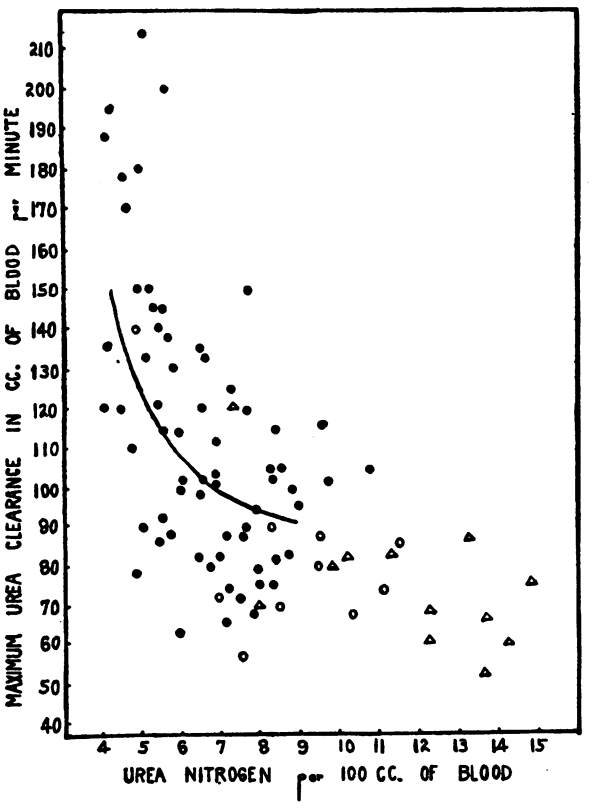

FIG. 1. THE RELATIONSHIP BETWEEN THE MAXIMUM UREA CLEARANCE RATES AND THE BLOOD UREA NITROGEN VALUES OF PREGNANCY.

● Antepartum ○ Nonpregnant
△ Postpartum — Mean urea clearance

TABLE II

Urea clearance rates before and after feeding urea

Case number	Month of pregnancy	Blood urea nitrogen		Urea clearance rates	
		Before feeding urea*	After feeding urea* (Average of 2 determinations)	Before feeding urea*	After feeding urea*
		mgm. per 100 cc.	*mgm. per 100 cc.*	*per cent*	*per cent*
21	8	10.2	18.2	167	161
22	8	5.6	16.8	140	136
23	4	9.6	19.8	110	148
24	9	9.6	18.8	119	152
25	9	9.2	20.6	104	60
26	7	7.5	28.5	196	186
27	9	7.8	29.1	135	107
N-1	Nonpregnant	12.7	21.8	101	134
N-2	Nonpregnant	9.2	17.7	125	115

* Patients 21 to 25, inclusive, and N-1 and N-2 received 10 grams of urea before the second test; 26 and 27 received 20 grams.

DISCUSSION

With the exception of the reports of Cantarow and Ricchiuti (5) and of Dieckmann (6), these results are in agreement with similar work of other investigators. The high urea clearance rate of pregnancy has been indicated by both Cadden and McLane (3) and by Hurwitz and Ohler (4).

The urea feeding experiments uphold the conclusions of Van Slyke et al. (13) and of Taylor, Drury and Addis (14), that urea clearance is unaffected by the blood urea level.

The low antepartum blood urea nitrogen values have been found previously by other workers (4, 15) and could be considered as the result of an increased excretion of urea. This interpretation is emphasized by the concurrence of the high antepartum urea clearance values with the low blood urea.

The standard deviation of 45 for the urea clearance rates of pregnancy appears to be an exaggeration of the normal nonpregnant clearance variation, which was first pointed out by Bruger and Mosenthal (16). This exaggeration parallels the increase in the clearance rate for pregnancy.

Conclusions cannot be adequately drawn from the present work until the daily variation of kidney function during pregnancy has also been established. Work along these lines is now in progress, and further discussion is reserved until a later paper.

SUMMARY

The urea clearance test was run 93 times on 13 normal pregnant women from the fifth month of pregnancy to the eighth month postpartum; 10 times on 4 normal nonpregnant women; and also before and after feeding urea to 7 pregnant women.

The mean antepartum urea clearance found is 153 per cent of normal. This is significantly higher than the postpartum mean of 95.5 per cent, or than the mean of 105 per cent for the nonpregnant normals. The standard deviations for the three groups are 45, 18 and 12, respectively.

The rough proportionality between the low blood urea and the high urea clearance of pregnancy is of considerable interest and suggests the dependence of the former upon the latter.

Raising the low blood urea by feeding urea did not alter the high urea clearance.

I am indebted to Dr. Edward Muntwyler for advice and criticism throughout this work.

BIBLIOGRAPHY

1. Stander, H. J., Ashton, P., and Cadden, J. F., The value of the various kidney function tests in the differentiation of the toxemias of pregnancy. Am. J. Obst. and Gynec., 1932, **23**, 461.
2. Stander, H. J., Medicine Monographs, 15. The Toxemias of Pregnancy. Bailliére, Tindall and Cox, London, 1929.
3. Cadden, J. F., and McLane, C. M., A study of the various kidney function tests in relation to the toxemias of pregnancy. Surg., Gynec. and Obst., 1934, **59**, 177.
4. Hurwitz, D., and Ohler, W. R., The urea clearance test in toxemias of pregnancy. (A preliminary report.) J. Clin. Invest., 1932, **11**, 1119.
5. Cantarow, A., and Ricchiuti, G., Urea clearance test in pregnancy. Arch. Int. Med., 1933, **52**, 637.
6. Dieckmann, W. J., Renal function in the toxemias of pregnancy. Am. J. Obst. and Gynec., 1935, **29**, 472.
7. Hayman, J. M., Jr., Halsted, J. A., and Seyler, L. E., A comparison of the creatinine and urea clearance tests of kidney function. J. Clin. Invest., 1933, **12**, 861.
8. Möller, E., McIntosh, J. F., and Van Slyke, D. D., Studies of urea excretion. II. Relationship between urine volume and the rate of urea excretion by normal adults. J. Clin. Invest., 1928, **6**, 427.
9. Hayman, J. M., Jr. Unpublished. Private Communication.
10. Van Slyke, D. D., and Cullen, G. E., The determination of urea by the urease method. J. Biol. Chem., 1916, **24**, 117.
11. McIntosh, J. F., Möller, E., and Van Slyke, D. D., Studies in urea excretion. III. The influence of body size on urea output. J. Clin. Invest., 1928, **6**, 467.
12. Dunn, H. L., Application of statistical methods in physiology. Physiol. Rev., 1929, **9**, 275.
13. Van Slyke, D. D., Rhoads, C. P., Hiller, A., and Alving, A. S., The relationship between urea excretion, renal blood flow, renal oxygen consumption, and diuresis. The mechanisms of urea excretion. Am. J. Physiol., 1934, **109**, 336.
14. Taylor, F. B., Drury, D. R., and Addis, T., The regulation of renal activity. VIII. The relation between the rate of urea excretion and the size of the kidneys. Am. J. Physiol., 1923, **65**, 55.
15. Killian, J. A., and Sherwin, C. P., Some chemical studies in normal and abnormal pregnancies. I. Significant chemical changes in the blood in the toxemias of pregnancy. Am. J. Obst. and Gynec., 1921, **2**, 6.
16. Bruger, M., and Mosenthal, H. O., Urea clearance test as an index of renal function. I. Studies of normal subjects. II. The effect of ingestion of carbohydrate (dextrose). Arch. Int. Med., 1932, **50**, 351 and 358.