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Research Article

SERIAL STUDIES OF RENAL FUNCTION DURING PREGNANCY AND THE PUERPERIUM IN NORMAL WOMEN [1, 2]

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Until recently there has been uncertainty as to whether kidney function in normal pregnancy differs significantly from that in the nonpregnant state. The earlier studies reviewed by Smith (1), Chesley (2) and Bucht (3) were for the most part limited to the immediate pre- and postpartum period when deviations from the nonpregnant state are less marked. On the other hand, the studies of Nice (4) demonstrated a marked increase of urea clearance in mid-pregnancy while those of Bonsnes and Lange (5) and Bucht (3) showed significant increases in both renal plasma flow and in glomerular filtration rate during mid-pregnancy which persisted to approximately the thirty-eighth week.

At the time the present study was begun, no serial studies of renal function during normal pregnancy and in the postpartum period had been reported and it was the purpose of this study to make such observations. Serial studies eliminate the element of apprehension encountered in single studies which, as emphasized by Miles and De-Wardener (6), may distort the results. Our findings confirm the increased renal function in pregnancy, and define the resultant lowering of the normal range of values for plasma urea and plasma creatinine during pregnancy. Previous observations are extended to include the puerperium and indicate that there is a decline of renal plasma flow to subnormal values during this period.

METHODS

Experimental and control subjects. The 12 pregnant subjects of this study ranged from 19 to 35 years of age, averaging 27 years. One subject (K) was studied during a second pregnancy. Their parity was from one to five children, with an average of two children. No patient exhibited any suggestion of toxemia during the study or during any previous pregnancy, nor was there any evidence of hypertension or urologic disease. One patient (E) was delivered by cesarean section at 38 weeks because of a placenta previa, and another (H) spontaneously delivered twins at 34 weeks. A group of nine nonpregnant women were control subjects. One of the control subjects (N) subsequently became pregnant. The average age was 25.7 years, with a range of 21 through 33 years and an average parity of 1.1.

Procedure. Renal clearances of para-aminohippurate (PAH) and of inulin were determined by the constant infusion technique of Goldring and Chasis (7). When creatinine clearances were measured, meat was eliminated from the diet, as recommended by Camara, Arn, Keimer and Newburgh (8). During the period of study, the patients were in a semi-supine position. For comparison, studies were also made on seven subjects in both supine and left lateral positions. A minimum of three collection periods of 15 to 30 minutes in length, depending on the urine flow, were employed. Each period was terminated by irrigation of the bladder with 100 to 200 ml. of physiological saline solution and 50 to 100 ml. of air, both of which were totally recovered before the next period was begun. In a subsequent series of clearance studies during pregnancy (9), the patients were asked to stand at the end of the collection period. In only one instance was more than a few additional ml. of urine obtained. These observations in conjunction with those of Chesley and co-workers (10), who found that during pregnancy no better results could be obtained by direct irrigation of the renal pelves, suggest that recovery of bladder urine is complete. The plasma concentrations of inulin and PAH were graphed for the period of each clearance study. The value at the midpoint of each collection period was interpolated from the graph for calculation of clearance. No allowance was made for time of delay, since the plasma concentrations of inulin and of PAH were maintained relatively constant. Concentrations of inulin ranged between 20 and 30 mg. per 100 ml. and of PAH between 1 and 2 mg. per 100 ml. The procedures were made essentially atraumatic by the use of indwelling needles, using Metacaine® as local anesthetic. In order to avoid conjugation of dextrose with PAH (11) and consequent lower apparent clearance rates, saline rather than dextrose was used in the preparation of the intra-

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[2] Presented in part at a meeting of the American Federation for Clinical Research, December, 1955.

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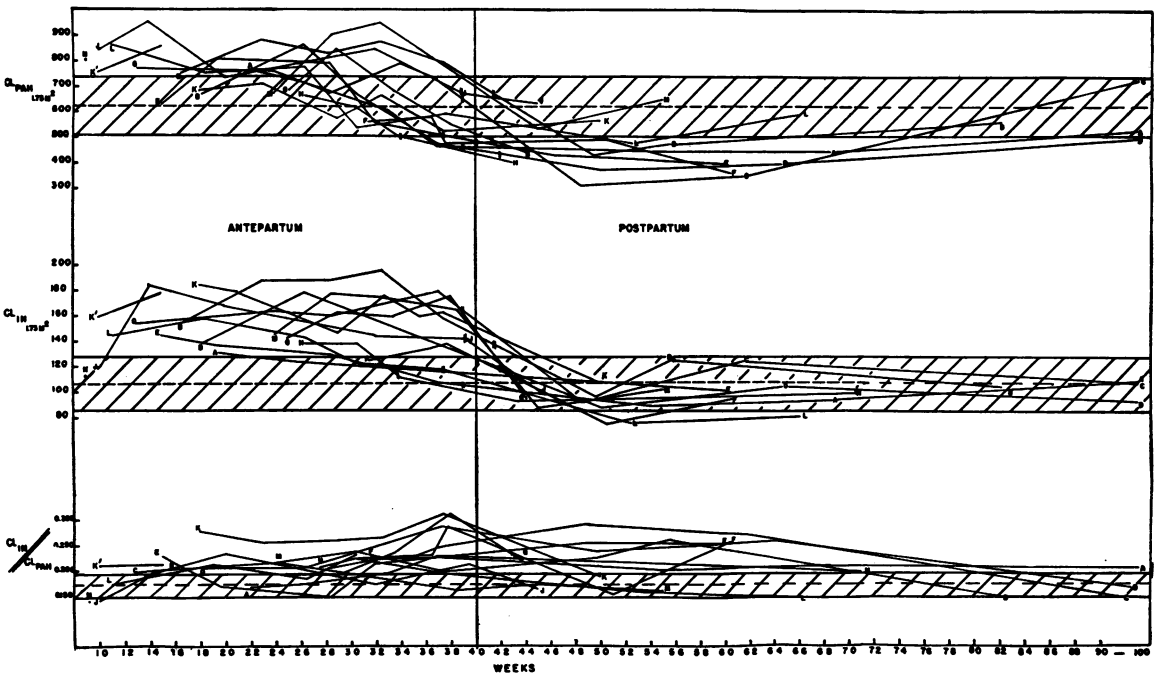

FIG. 1. GRAPHIC PORTRAYAL OF CLEARANCE DATA FROM TABLE I

The horizontal dashed lines represent the mean values for the group of normal nonpregnant subjects. The shaded areas represent two standard deviations from the mean. The paired vertical lines represent the actual times of delivery. Values are graphed for a subsequent pregnancy in one patient (K).

venous solutions. Inulin of uniform molecular weight, which was shown to contain negligible amounts of free fructose, was employed throughout the study.[4]

Blood pressure and pulse rate, except as noted, were taken at the beginning of each collection period. Body temperature was recorded at the beginning and end of the procedure.

Patients were shown to be free of infection by smears and cultures of urine taken at the beginning of each study. Heparin was used as an anticoagulant. Blood samples were centrifuged within an hour of drawing and analyzed the same day for PAH, or frozen and stored at $-20°$ C. until analyzed at a later time.

Analytical procedures. All determinations were carried out in duplicate.

Inulin was determined by the method of Roe as modified by Schreiner (12) and three standard solutions were run with each set of analyses. Plasma proteins were precipitated by the Somogyi method using zinc sulfate and sodium hydroxide (13). Correction was made for the inulinoid blank of plasma, but in samples of urine from the fasting subjects, a negligible blank value was found. Nine analyses at random of frozen aliquots of a known preparation of urine containing 200 mg. per 100 ml. of inulin had a mean and standard deviation of 202 ± 7.2 mg.

Para-aminohippurate was determined by the method of Brun (14) employing 3 ml. aliquots of the protein-free filtrate used for inulin determinations. Recoveries of PAH added to urine and plasma were found to be within 5 per cent. The Metacaine® used for local anesthesia did not interfere with this determination.

Creatinine was determined by the method of Borsook, as modified by Hare (15). When analyzing plasma, in order to obtain satisfactory ranges of optical density using the Coleman model 6 spectrophotometer, 6 instead of 2 ml. of protein-free filtrate was employed in the procedure.

Urea was determined by a modification of the method of Gentzkow (16), adding iodine after nesslerization to avoid turbidity (17). Analyses of a series of control aliquots of plasma containing 14.6 mg. per 100 ml. gave a standard deviation of ± 0.37 mg.

Calculations. All values for clearances were corrected to a standard body surface area of 1.73 M.^{2}. The effective renal plasma flow (ERPF) has been taken as the actual clearance of PAH uncorrected for the extraction ratio. The filtration fraction was calculated from the ratio C_{IN}/C_{PAH}.

RESULTS

In Table I the significant data on the subjects including the individual clearance values are re-

[4] Inulin from the Warner-Chilcott Company was provided without charge for the initial studies of the series. PAH was obtained from the Sharp and Dohme Company.

TABLE I

Renal clearance studies in 12 patients during pregnancy and the puerperium

Subject Age Parity	Time of clearance	Body surface area	Hematocrit	Blood pressure	Pulse	Clearance of para-amino-hippurate (PAH)	Clearance of inulin	Clearance of creatinine	Plasma creatinine	Plasma urea nitrogen
	weeks	*M.²*	%	*mm. Hg*		*ml./min.*	*ml./min.*	*ml./min.*	*mg./100 ml.*	*mg./100 ml.*
E. M.	13	1.65				772	154	200	0.40	
34	24	1.71	40	115/58	62	759	164	199	0.46	10.1
3	31	1.74	40	110/57	58	676	159	169	0.45	6.7
	34	1.77	40	121/58	59	790	153	181	0.40	
"C"*	37	1.79	38	114/57	61	732	179	192	0.40	7.5
	49	1.67	45	129/66	44	316	92	113	0.64	14.3
	62	1.63	45	120/62	51	456	124			11.5
	94	1.62	48	105/59	64	726	107	134	0.56	8.0
A. M.	17	1.70	34	98/50		756	155	153	0.47	
28	23	1.73	35	107/50	76	887	188	181	0.50	11.7
2	28	1.74	35	99/73	76	829	172	178	0.48	8.1
	33	1.76	33	105/57	78	875	196	186	0.44	9.5
"B"	38	1.76	36	105/54	78	796	158	175	0.50	8.4
	50	1.69	43	115/66	64	433	97			16.1
	56	1.69	37	106/69	62	480	126			14.5
	122	1.67	39	99/57	67	600	89	126	0.67	15.4
R. S.	18	1.51		115/65	80	673	139	167	0.42	8.7
19	26	1.60	37	98/60	84	868	159	205	0.38	7.9
0	37	1.63	37	117/80	76	479	137	114	0.53	8.5
	50	1.55	40	104/68	60	373	88	84	0.64	11.0
"D"	65	1.53	39	119/74	52	399	104	52		8.9
	97	1.55	40	106/72	55	492	82	103	0.67	14.3
G. H.	8	1.62	47	108/62	77	843	119			10.8
27	12	1.64	40	111/62	80	952	185	170	0.45	10.3
1	18	1.67	40	98/68	80	739	169	165	0.46	8.9
	32	1.73	40	110/60	80	847	146	152	0.47	9.1
"J"	40	1.75	40	119/67	70	671	143	124	0.52	10.9
	45	1.63	51	109/65	65	640	105	87	0.58	15.1
N. W.	24	1.76	37	94/58		676	146	106	0.51	12.5
32	29	1.77	35	90/60	75	902	179	144	0.52	11.8
4	33	1.78	35	90/60	75	950	176	172	0.51	9.7
	39	1.78	32	86/60			165	142	0.54	9.7
"M"	45	1.54	43	101/67	60	535	92			13.4
	55	1.61	42	89/57	54	650	103	136	0.67	16.6
D. B.	18	1.78	37	97/59	62	678	189	183	0.45	8.0
32	23	1.81	40			708	181		0.41	7.4
2	29	1.84	35			568	148	158	0.43	6.9
	33	1.85	36	102/64	71	663	176	181	0.40	8.6
"K"	36	1.87	34	102/68	67	445	160	116	0.46	7.3
	38	1.89	34	108/72	72	523	163	165	0.41	7.9
	50	1.68	43	102/70	60	564	107	116	0.56	10.8
D. B.	10	1.77	35	102/62	60	757	159	158	0.43	8.5
33	15	1.81	40	100/58	74	860	178	195	0.41	10.5
3										
M. M.	19	1.53					131	150	0.63	
31	22	1.54	33	100/80	75	768	128	169	0.50	8.7
2	26	1.56	33	100/70	75	716	125	148	0.51	9.5
	33	1.60	35	100/60	80	609	119	130	0.62	7.6
"A"	37	1.62	35	98/60	66	467	107	94	0.66	9.9
	55	1.50	46	98/75	72	443	89	115	0.71	9.6
	69	1.47	45	102/70	68	449	94			10.0
	99	1.47	45	103/70	64	528	108	76	0.72	10.8
P. F.	32	1.65	35	110/60	76	565	125	149	0.46	8.5
23	37	1.67	40			583	135	164	0.48	8.5
1	38	1.67	39	111/60	60	480	137	139	0.54	8.0
	51	1.58	42	97/53	68	498	76	94	0.59	13.4
"F"	61	1.56	42			369	95	88	0.67	15.6

* The letters in quotation marks are those used in the graph of Figure 1.

TABLE I—*Continued*

Subject Age Parity	Time of clearance	Body surface area	Hematocrit	Blood pressure	Pulse	Clearance of para-aminohippurate (PAH)	Clearance of inulin	Clearance of creatinine	Plasma creatinine	Plasma urea nitrogen
	weeks	*M.²*	%	*mm. Hg*		*ml./min.*	*ml./min.*	*ml./min.*	*mg./100 ml.*	*mg./100 ml.*
I. B.	15	1.65				631	145	187	0.42	10.3
27	19	1.66	37	100/50	75	809	137	198	0.37	11.3
0	28	1.69	39	112/55	80	790	130	168	0.41	8.0
	32	1.70	39	107/58	81	560	119	138	0.35	8.4
"E"	49	1.61	44	100/60	60	433	110	100	0.67	12.9
	100	1.60	40	109/63	64	400	101	94	0.61	10.2
G. S.	25	1.58	39	105/58	80	686	143	160	0.53	8.3
31	29	1.58	40	98/58	76	848	162	173	0.43	8.9
2	34	1.61	37	97/58	76	681	160	152	0.46	6.7
	38	1.65	39	98/60	68	558	165	132	0.59	6.1
"G"	44	1.53	47	115/68	56	444	97	99	0.64	12.6
A. Ma.	27	1.89				667	139	150	0.58	10.9
20	31	1.92				624	158	247	0.44	8.2
1	43	1.80				407	92	122	0.67	16.0
"H"	71	1.78	47	100/60		507	100	82	0.71	17.2
G. L.	11	1.37	38	92/50	75	856	147	185	0.43	7.9
27	19	1.40	39			742	159	134	0.562	7.0
3	27	1.44	35	98/48	78	780	144	117	0.550	7.0
	31	1.44	32	93/53	78	534	124	132	0.500	7.4
"L"	38	1.47	35	110/72	75	598	116	125	0.500	7.6
	53	1.35	40	83/53	80	476	76	79	0.775	11.0
	66	1.33	44	95/61	80	591	84	107	0.800	11.3

corded. Figure 1 graphically portrays the clearance data from Table I. Several interesting observations regarding the individual serial studies can be made: *1*) Though the pregnant subjects deviate from the nonpregnant normal range, all individuals do not deviate in a similar manner; and *2*) regardless of when the initial studies were done during pregnancy, there is a tendency for the initial values to be relatively but not significantly depressed. This was particularly true in the individual subjects who were poorly relaxed during their initial study. Since serial studies on these subjects were to be compared with single observations on nonpregnant control subjects, repeat studies on the controls were done to determine whether there might be a significant difference when the subject became accustomed to the procedure. The mean values with their standard deviations and the standard deviations of the differences of the means in clearance of inulin and PAH and the difference in the standard deviation of the means between the two sets as shown in Table II were not significant. For statistical purposes the values from both sets were averaged to afford data as nearly comparable as possible to that recorded from the experimental subjects.

A difficulty in making comparison with nonpregnant normals might be the possible relationship of the menstrual cycle to the measurements. However, no correlation could be found between the results obtained in 18 clearance studies in the nine normal subjects and the stage of the menstrual cycle.

In Figure 2 is shown graphically the mean values at various stages of pregnancy and the puerperium for the clearances of inulin and of PAH, as well as the filtration fractions with their relation to the normal, nonpregnant means. In order to have adequate points for statistical analysis, the points

TABLE II

Comparison of initial and repeated renal clearance studies in nine normal nonpregnant subjects

	Clearance of inulin			Clearance of para-aminohippurate		
	Mean (*ml./min.*)	S.D.*	S.E.†	Mean (*ml./min.*)	S.D.*	S.E.†
Initial study	100	11.8		576	99.4	
Repeat study	108	10.5	3.9	623	57.8	27.4
Average	103.4	9.75		600	70	

* Standard deviation.

† Standard error, based on comparison of paired observations.

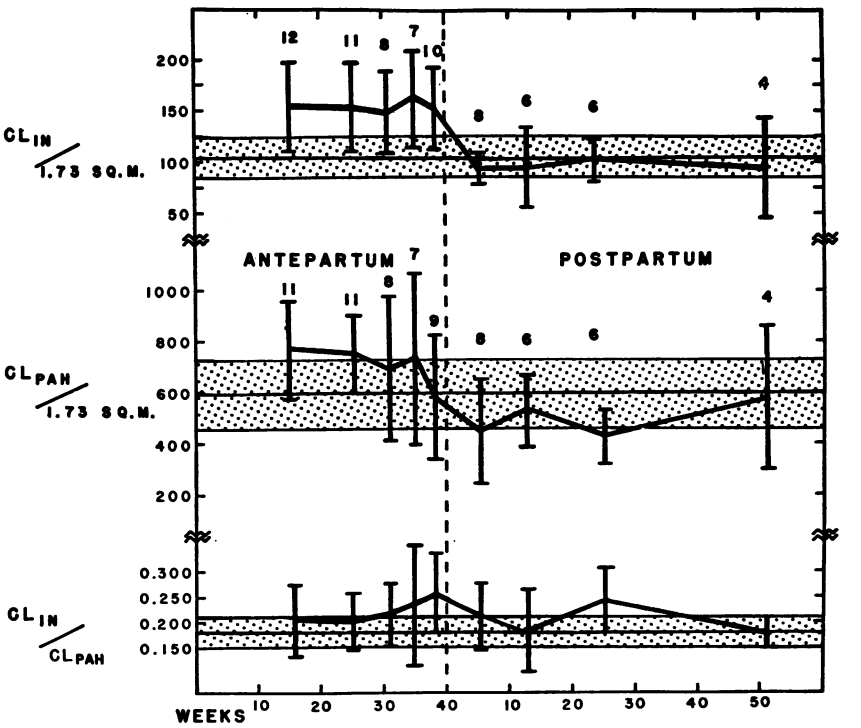

FIG. 2. DIAGRAM SHOWING THE MEAN AND TWO STANDARD DEVIATIONS OF SERIAL CLEARANCE VALUES IN NORMAL PREGNANCY IN RELATION TO NONPREGNANT CONTROLS

Numbers above the bars represent the number of observations averaged at each stage of pregnancy. See text for details of construction.

within periods of 11 and 8 weeks were employed through the twenty-eighth week of gestation and of 4 weeks from the twenty-eighth through the fortieth week. During the postpartum period, intervals of 8 weeks were employed during the first 18 weeks and of 18 weeks from the eighteenth through the thirty-sixth week. Since the data were not accumulated at the same time intervals for each patient, the mean of the time intervals for all studies falling within designated periods are plotted as the ordinate. This treatment of the data avoids employing values from straight lines connecting widely separated points. In this and subsequent graphs the heavy horizontal line represents the mean of our series of observations on normal subjects with the stippled area demonstrating the range of two standard deviations above and below the mean.

Effective renal plasma flow

The effective renal plasma flow (ERPF) was found to be significantly elevated ($p < 0.01$) to 770 ml. per minute by the fifteenth week of pregnancy and remained elevated through the twenty-fourth week. However, during the weeks immediately ante partum the ERPF progressively returned to normal range. During the postpartum period, the values were observed to be significantly below normal for a variable number of weeks and as long as 25 weeks in five subjects. In all except three subjects (E, F and H) in whom late follow-up studies could not be obtained, it was found that the values eventually returned to the normal range. In this small series no correlation could be found between the depression of renal plasma flow and the presence or absence of lactation. If renal blood flow is calculated from the renal plasma flow in the usual manner from the hematocrit, a significant increase over the nonpregnant state is still found during the periods from the fifteenth through the thirty-sixth weeks of pregnancy, but not thereafter. Thus the increased plasma flow apparently represents a true increase in total blood flow and not merely a reflection of the hemodilu-

tion of the latter months of pregnancy. Accordingly the postpartum depression of plasma flow is reflected in a similarly significant depression of renal blood flow.

One patient, designated as N in Figure 1, had previously served as a normal control and was later studied in the ninth week of pregnancy. The renal plasma flow was increased from 557 to 805 ml. per minute, but the glomerular filtration rate (GFR) was essentially unchanged (105 and 113 ml. per minute) giving a decrease in filtration fraction from 0.19 to 0.14.

Glomerular filtration rate

In contrast to the renal plasma flow, the glomerular filtration rate, as indicated by the inulin clearance, remained significantly elevated ($p < 0.01$) from the fifteenth to thirty-eighth week of pregnancy and fell to the range of normal as early as measured in the postpartum period. Once again, individual subjects (A, D, H and L) deviated from this pattern.

Filtration fraction

The filtration fraction (GFR/ERPF) was significantly elevated throughout the entire course of pregnancy and did not return to normal range until the postpartum period. Because the increased glomerular filtration rate was maintained in spite of the return to normal of the plasma flow, the filtration fraction became more markedly elevated as term was approached. Patients who initially had low values for plasma flow, nevertheless consistently developed an increase in filtration fraction.

Endogenous creatinine clearance and serum creatinine concentration

Figure 3 shows the variations in endogenous creatinine clearance. The changes for the most part closely parallel those of the inulin clearance. However, there is wide individual variation in the ratio of creatinine to inulin clearance. As noted originally by Bucht (3), the ratio drops toward unity as term is approached, though in this series the change was not statistically significant. During the latter part of pregnancy there is less deviation in the values of this ratio. As a result a more reliable approximation of the true filtration rate is obtained. Consistent with the increase in filtration rate, the plasma creatinine concentrations during pregnancy (Figure 4) are sharply reduced from 0.67 ± 0.14 to 0.46 ± 0.13 mg. per 100 ml. ($p < 0.01$). There is very little overlap with the range found in nonpregnant women. Since the method employed in which creatinine is adsorbed on Lloyd's reagent is more specific, these values for plasma creatinine are lower than if they had been determined by the more commonly used unmodified Folin method.

Plasma urea nitrogen concentrations

In the control subjects the usual wide range of normal concentrations of plasma urea nitrogen was found: a mean of 13.1 with a standard deviation of ± 3.0. In the pregnant subjects, as shown in Figure 5, from the fifteenth week to term the mean was 8.7 mg. with a standard deviation of ± 1.5 mg. These returned to the nonpregnant range early in the postpartum period.

Effect of parity and age

Parity ranged from zero to five previous pregnancies. Age ranged from 19 through 35. In

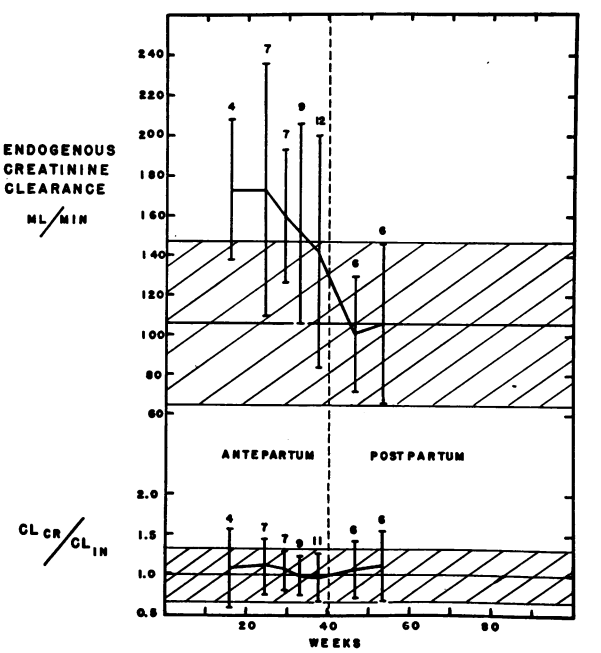

FIG. 3. ENDOGENOUS CREATININE CLEARANCE (HARE METHOD) DURING PREGNANCY AND THE PUERPERIUM
For method of construction of the graph, see Figure 2.

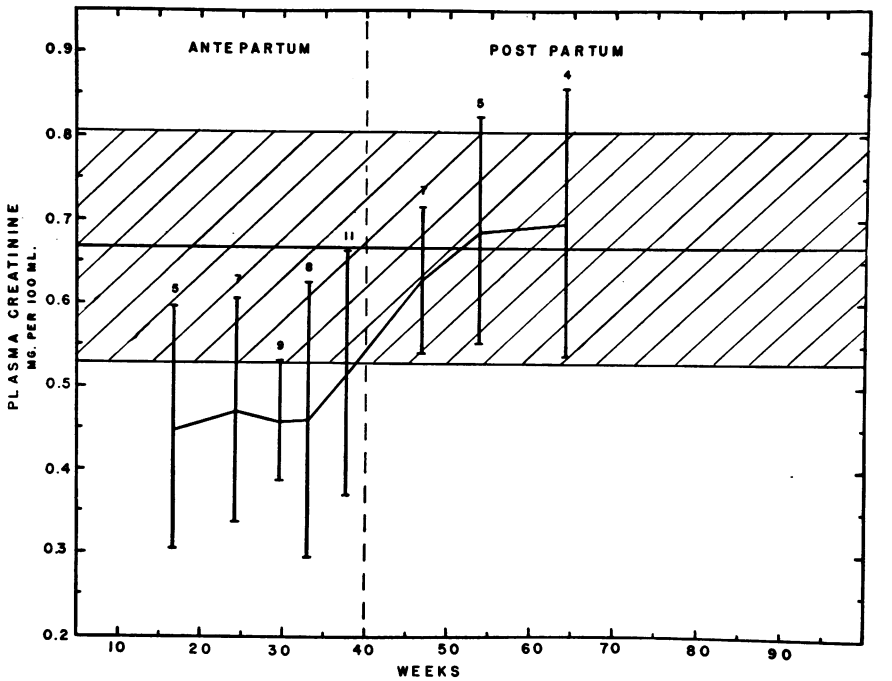

FIG. 4. PLASMA CREATININE (HARE METHOD) DURING PREGNANCY AND THE PUERPERIUM IN RELATION TO NONPREGNANT STATE

For details of construction, see Figure 2.

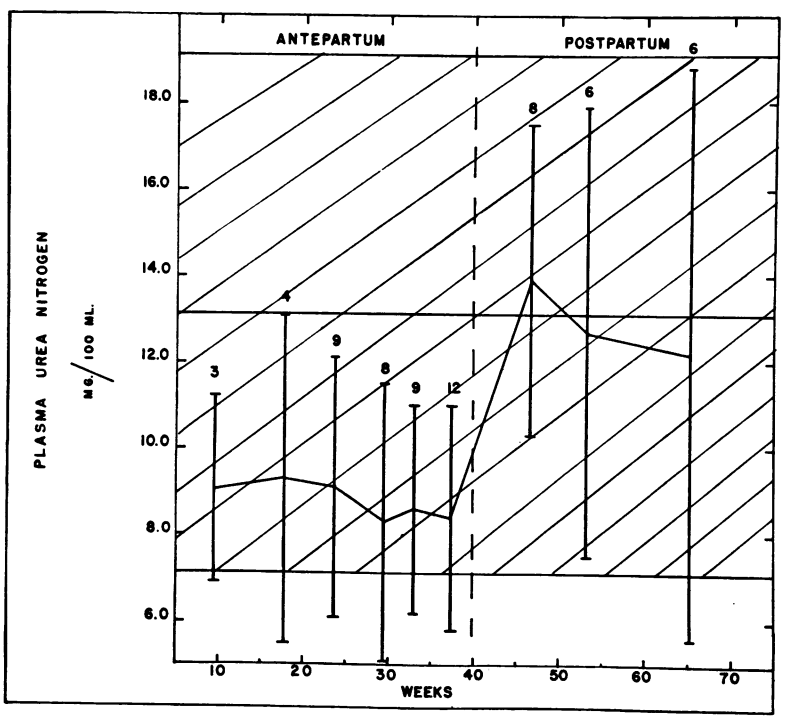

FIG. 5. PLASMA UREA NITROGEN DURING PREGNANCY AND THE PUERPERIUM

For the method of construction of the graph, see Figure 2.

this series no correlation of these factors with renal function during pregnancy was apparent.

Posture

The effect of posture on renal function in the late stages of pregnancy was studied. Duplicate clearance determinations were carried out on subjects alternately in the supine and in the left lateral position. Two sets of duplicate collection periods of 20 to 30 minutes were performed in one position and compared with one set in the other position. No significant differences were evident. The weighted average of the glomerular filtration rates in the supine position in seven subjects was 147 ml. per minute, while that in the left lateral position was 139 ml. per minute. In order to investigate the possibility that endogenous clearances during the daytime might be lower due to erect posture, endogenous creatinine clearance measurements were made during day and night periods. In six patients so studied there were no significant differences between the two periods; in seven the night clearances were higher; and in eight they were lower. Similar comparisons were made in four institutionalized patients at intervals of two weeks throughout pregnancy. Again, no consistent pattern was noted.

DISCUSSION

The data from the above serial studies essentially confirm the finding of Bucht (3) that there is an increase in renal clearance of inulin and of para-aminohippurate during pregnancy. They also confirm his finding that in late pregnancy an elevated filtration rate is maintained in the face of a declining renal plasma flow, producing an elevated filtration fraction. Our findings are similar to those of Bonsnes and Lange, who in their preliminary report (5) noted a rise of glomerular filtration in mid-pregnancy, and PAH clearances which followed the inulin clearances in direction but not in magnitude. The mean filtration rate and plasma flow found in the present study during the middle trimester is somewhat lower than those of Sohar, Scadron and Levitt (190 ml. and 800 ml. per minute, respectively) (18), but again agree in indicating an elevation of filtration fraction as term is approached. By extending the serial measurements throughout the puerperium until the values returned to the normal range it is demonstrated that for an extended period after delivery renal plasma flow may be significantly depressed.

No attempt has been made to calculate total renal resistances since in pregnancy both the mean arterial pressure and the renal venous pressure are uncertain. Likewise fractional renal resistances have not been estimated, since the evidence provided by Pappenheimer and Kinter (19) has raised considerable doubt as to the mechanism of production and localization of such resistances.

In this study the conventional correction of clearance values to a body surface area of 1.73 $M.^2$ has been made, which tends to minimize the increase in these values in relation to lean body mass, since as pregnancy advances there is a disproportionate gain in total body water (20).

There are a number of consequences of the increase in filtration rate during pregnancy. The generally accepted normal ranges of plasma concentration of urea and of creatinine, which are cleared predominantly by glomerular filtration, must be revised downward for pregnant subjects. Likewise any substance which is cleared predominantly by filtration and which is normally reabsorbed by the renal tubules will be excreted in increased quantities during pregnancy, unless there is a concomitant increase in the capacity of the renal tubules to reabsorb that substance. Page, Glendening, Dignam and Harper (21), in the course of studies on the mechanism of histidinuria in pregnancy, noted the increase in glomerular filtration rate during pregnancy and found that this increase in the quantity filtered accounted for about half of the excess histidine excreted. Studies in this laboratory indicate that a similar mechanism accounts for certain instances of benign glycosuria of pregnancy (9).

Simultaneous endogenous creatinine clearances parallel the increase in inulin clearance during pregnancy. Active tubular secretion of creatinine is suggested by a ratio of creatinine to inulin clearance greater than unity. Like Bucht (3) we have noted that the ratio approaches unity as pregnancy nears term, though in our series the observation was not of statistical significance.

The increase in renal function during pregnancy raises the question as to whether true anatomical hypertrophy of the kidney may develop. Available

evidence suggests that this is not so. In guinea pigs the kidneys increase in weight only during the puerperium (22). We have found (23) in our laboratory that there is no absolute increase in weight of the kidneys during pregnancy in the rat, but that there is an actual decrease in the weight of the kidney per unit of rat weight. We have also found that there is no change in the number of active glomeruli, when these are demonstrated by the technique of Moses and Schlegel (24) employing the fluorescent dye, thioflavin-S.

Coincident with the increase in renal function during pregnancy, there is an increase both in total body water (20) and in plasma volume. The latter, as shown by Berlin, Goetsch, Hyde and Parsons (25), reaches 125 per cent of normal by the sixteenth week and increases to 155 per cent of normal by the thirty-sixth week. By the time that plasma volume reaches its peak, however, renal plasma flow has already declined well toward the nonpregnant range. Hence it seems unlikely that the increase in renal plasma flow is merely a passive reflection of some correlate of hypervolemia. There is a closer correlation between renal plasma flow and resting cardiac output during the course of pregnancy. This has recently been shown by Bader, Bader, Rose and Braunwald (26) to be elevated to 4.1 L. per minute from the fourteenth to the twenty-fourth weeks, and to decline toward the nonpregnant normal after the twenty-fifth week. While a major portion of the increment in cardiac output in mid-pregnancy is accounted for by the demands of the placenta (27), approximately 300 ml. per minute of the increment can be accounted for by the increase in renal blood flow.

A number of observations suggest that the increase in renal function in pregnancy is mediated by endocrine factors. The secretion of a number of hormones of both adrenal and placental origin is markedly increased during gestation. Certain hormones, notably thyroid, adrenal cortical, and somatotropic, have the capacity to cause an increase in renal function and therefore may actively contribute to the increased renal function of pregnancy, and their partial withdrawal during the postpartum period may in part explain the regression of renal function during the puerperium. Thyroid hormone produces renal hypertrophy in rats (28) and an increase in filtration rate and Tm_D in normal dogs (29). The concentration of precipitable iodine rises early in pregnancy (30), but in contrast to the effect of this agent in animals there is apparently no histological hypertrophy of the kidney, and Tm_{PAH} (and hence presumably Tm_D) is not increased (18). In addition, in subsequent studies in this laboratory no difference was found in the concentration of protein-bound iodine between a group of six pregnant patients with low filtration rates as opposed to six comparable patients with high filtration rates. Thus the contribution of the thyroid remains to be defined. Relative to the adrenal steroids, Garrod, Davies and Cahill (31) have shown in the dog that desoxycorticosterone increased GFR only when causing excessive retention of sodium and water; on the other hand, cortisone exerts an immediate increase in the filtration rate. The excretion of aldosterone has been found by chemical determination to be increased to 10 times normal values during late pregnancy (32) and to return to the nonpregnant rate of excretion immediately postpartum. Ingbar and co-workers (33) found in man that inulin clearance was increased by adrenocorticotropic hormone (ACTH) and by cortisone. The excretion of glucocorticoids is increased during pregnancy (34) and the serum concentration of 17-hydroxycorticoids increases early in pregnancy, reaching nearly seven times the normal nonpregnant value (35), so it is reasonable to assume that cortical steroids may contribute significantly. Finally, striking augmentation of renal function has been produced experimentally by anterior pituitary hormone. In the dog, White, Heinbecker and Rolf (36) have demonstrated doubling of the clearance of PAH and of inulin after 9 to 12 days of administration of growth hormone. In man, Heller, Smith and Lubin (37) described in five male patients with acromegaly augmented clearance of PAH and a proportionally greater increase in filtration rate, similar to that seen in the latter months of pregnancy. However, in contrast to the findings in pregnancy there is abnormally high tubular excretory capacity for PAH as well. There are no data to indicate whether there is increased secretion of somatotropin in human pregnancy. However, Contopoulos and Simpson (38) recently demonstrated that there is a threefold increase in growth-promoting activity of plasma from pregnant rats at the sixteenth to

twentieth days of gestation as measured by bio-assay on hypophysectomized rats. This increased activity was not decreased by hypophysectomy of the mother at the twelfth day of pregnancy, which suggests a fetal or placental origin of the growth-promoting factor.

Thus it appears likely on the basis of the indirect evidence cited above, although not proven, that augmented endocrine secretions, notably somatotropin, adrenal cortical and possibly thyroid, account for the increase in renal function in pregnancy.

SUMMARY

Serial renal function studies by standard techniques have been carried out on 9 control subjects and 12 pregnant subjects from the fifteenth through the fortieth weeks of pregnancy and at intervals during the puerperium, with the following results:

1. The estimated renal plasma flow and renal blood flow were approximately 25 per cent higher than control values throughout early and mid-pregnancy, declined to control values during the last trimester, and then decreased to values significantly below the control values for many months during the puerperium.

2. The glomerular filtration rate was increased approximately 50 per cent throughout pregnancy, returning to the range of nonpregnant subjects early in the puerperium.

3. The filtration fraction was significantly elevated throughout pregnancy, rising to approximately 40 per cent above control values as term was approached, and remaining inconstantly elevated during the puerperium.

4. As a result of the increase in filtration rate the concentrations of urea and creatinine in the plasma were reduced to approximately one-half and two-thirds, respectively, of the concentrations in nonpregnant subjects.

The possible mechanisms producing these changes are discussed.

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