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Research Article

THE FILTRATION RATE, EFFECTIVE RENAL BLOOD FLOW, TUBULAR EXCRETORY MASS AND PHENOL RED CLEARANCE IN NORMAL PREGNANCY [1]

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Alterations in kidney physiology have long been sought to explain certain phenomena of normal pregnancy. Most suggestive of a renal disturbance was the well known tendency of pregnant women to retain salt and water, clinical evidence of which is found in the edema of late pregnancy and in the diuresis of the first few days postpartum. There was also the apparent readiness with which pregnant women developed specific toxemia with its proteinuria. It had indeed been suggested that certain types of toxemia were caused by the alleged strain of pregnancy imposed on the "low reserve" kidney (1).

Additional interest has been given this subject by recent observations that the steroid hormones of the testis and the ovary cause an increased retention of salt and water (2, 3, 4, 5) and when injected into rats and mice lead to a considerable increase in the size of the kidney (6, 7, 8). Two of these substances, estrogen and progesterone, are produced by the placenta and are present in great concentration in the body fluids of all pregnant women. Good reasons therefore exist for considering the possibility of change in kidney physiology, although no consistent abnormality in renal function has yet been demonstrated in normal pregnancy (9, 10, 11).

The present report concerns the measurements of glomerular filtration, effective renal blood flow and the total functioning tubular tissue in normal pregnant women. Tests were carried out during pregnancy and were repeated after delivery, so that the effects of delivery on the kidney function of a single individual can be studied.

The rate of filtration at the glomerulus is determined by the inulin clearance, the rate of effective renal blood flow by the diodrast clearance, and the maximum tubular excretory function or tubular excretory mass by diodrast T_m. The physiological basis for these measurements has been reviewed by Smith and his associates (12, 13, 14, 15). Smith has also recently discussed the functional significance and limitations of renal clearances (16).

MATERIAL

For the tests patients were selected from the prenatal clinic or the ward. Fifteen women were studied in the last lunar month, three in the ninth month, and three in early pregnancy. Nine of these twenty-one were again tested after delivery. None had hypertension, proteinuria, edema, or a history of kidney disease, hypertension or specific toxemia of pregnancy.

METHOD

The patient was given a liter of water to drink the evening before the test. The next morning between 7:30 and 8:30 she was given another liter. No breakfast was allowed.

Inulin, phenol red and diodrast were given by continuous intravenous infusion at a controlled rate. When this work was begun in May, 1938, physiological saline was used in the infusion fluid. At the same time, tests were started on patients with specific toxemia of pregnancy in whom it was soon found that an adequate urine flow could not be obtained by this method. A two per cent solution of sodium sulphate (anhydrous) in saline was tried next, and later an eight per cent solution of sorbitol or mannitol in distilled water was used.[2] From July, 1939 to the present time eight per cent mannitol in distilled water has been employed routinely. With this infusion fluid, the urine flows have ranged from two to ten cc. per minute, usually being about five cc. per minute. The error in clearance values resulting from pos-

[1] This study was made with the aid of a grant from the Commonwealth Fund.

[2] We are indebted to the Winthrop Chemical Company for the diodrast and to the Abbott Laboratories for the mannitol used in this investigation. The inulin used was prepared by the U. S. Standard Products Company, the phenol red by Messrs. Hynson, Westcott and Dunning, and the Sterisol saline and distilled water by Schering and Glatz, Inc.

sible incomplete emptying of the bladder was minimized by maintaining a high urine flow. Any test in which this was below two cc. per minute was discarded.

Urine specimens were collected by a six-holed rubber catheter left in the bladder throughout the test. At the end of each urine collection period the bladder was washed out with physiological saline followed immediately by insufflation with air. Care in this step is particularly necessary in studying patients in late pregnancy, because the fetal head makes impossible the suprapubic pressure usually employed to insure complete emptying.

Two or three venous blood samples were taken during the clearance periods, and three during the diodrast T_m periods. Plasma levels of diodrast, phenol red and inulin were interpolated to the midpoint of each urine collection period.

Blood pressures, pulse rates, and mouth temperatures were taken at frequent intervals throughout the test. Hematocrits were determined on the sample of blood taken just before the infusion was begun. The first urine sample was examined routinely for protein and formed elements.

Iodine was analyzed by the Kendall method (17). Inulin was analyzed by the method of Folin (18, 19) in the earlier experiments and by that of Alving, Rubin and Miller (20) in the more recent ones. Certain modifications of these methods were introduced according to published directions by Smith *et al.* and Goldring *et al.* (14, 21).

RESULTS

Inulin and phenol red clearances were done on twenty normal pregnant women, with diodrast clearance in eleven and diodrast T_m in eight. After delivery inulin and phenol red clearances were done on ten women, with diodrast clearance and diodrast T_m in six.

The values for the three clearances, the diodrast T_m and the significant ratios are given in Table I. Each clearance figure is the average of three or more urine collection periods, each diodrast T_m the average of five. The inulin clearances average 124 cc. per minute antepartum and 116 cc. per minute postpartum; the phenol red clearances average 371 cc. per minute antepartum and 362 cc. per minute postpartum; diodrast clearances average 631 cc. per minute antepartum and 525 cc. per minute postpartum. The effective renal blood flow appears in the table only in the cases in which diodrast clearances were done. Before delivery the average value is 970 cc. per minute and after delivery it is 858 cc. per minute.

The filtration fraction, or inulin/diodrast clearance ratio, which measures the proportion of the effective plasma flow filtered at the glomerulus, is nearly identical antepartum and postpartum. The inulin/phenol red clearance ratio is used to indicate changes in filtration fraction in those instances where diodrast clearances were not done, on the assumption that any change in inulin/phenol red clearance ratio reflects a similar change in filtration fraction of the same functional significance, if not of identical degree. The figures for this ratio antepartum and postpartum are likewise nearly identical. The phenol red/diodrast clearance ratio, although varying widely in different individuals, shows no consistent change between antepartum and postpartum observations in the same individuals.

The diodrast T_m averages 45.6 mgm. of iodine per minute antepartum and 46.6 mgm. of iodine per minute in postpartum observations. In the last three columns the effective renal blood flow, diodrast clearance, and inulin clearance have been related to the diodrast T_m. This is a convenient way in which to compare figures in different individuals because kidney function as measured by the respective clearances is related to standard amounts of renal tissue and variations due to kidney size are thereby eliminated.

Review of the data in Table I shows that no significant changes occur in inulin clearance, phenol red clearance, diodrast clearance or diodrast T_m in pregnancy when renal function is compared to the postpartum observations as a standard of reference.

Comparison of the average figures from the smaller groups made up only from those individuals on whom both antepartum and postpartum observations were made (Table II) again shows no significant differences. Diodrast clearance and diodrast T_m were determined in only three subjects both antepartum and postpartum. While this is a small group to average, the figures again indicate no change in renal function.

Comparison of our results in pregnancy and the puerperium with those in normal non-pregnant women, as observed by Goldring, Chasis, Ranges and Smith (21), and normal non-pregnant and pregnant women, as observed by Chesley and Chesley (10, 11) appears in Table III. Our clearances, ratios and clearances per unit T_m in pregnancy are almost identical with those in non-pregnant women, as reported by Goldring *et al.*

TABLE I

Results of kidney function tests in normal pregnancy and in the puerperium

Subject	Infusion fluid	Surface area	Antepartum: Date	Duration of pregnancy in weeks by history	Time in weeks before delivery	Mean blood pressure during test	Plasma clearances: Inulin	Plasma clearances: Phenol red	Plasma clearances: Diodrast	Effective renal blood flow	Inulin/Phenol red	Filtration fraction Inulin/Diodrast	Phenol red/Diodrast	Diodrast *Tm*	Effective renal blood flow/Tm_D	C_D/Tm_D	C_{IN}/Tm_D
		sq.m.					*cc. per 1.73 sq.m. per minute*			*cc. per 1.73 sq.m. per minute*	*per cent*	*per cent*	*per cent*	*mgm. iodine per minute*			
1. D. R.	(a)	1.51	May 26, 1938	41	1	128/70	140	404			34.7						
2. L. P.	(b)	1.58	July 7, 1938	40	0	124/50	93	290			32.1						
3. C. B.	(b)	1.50	August 11, 1938	40	1	128/88	94	276			34.1						
4. S. M.	(b)	1.65	August 18, 1938	41	2	120/80	169	471			35.9						
5. H. D.	(b)	1.50	September 22, 1938	41	1	122/80	128	382			33.5						2.49*
6. H. Q.	(b)	1.38	October 13, 1938	38	1	120/80	135	403			33.5						
7. R. S.	(b)	1.57	October 19, 1938	39	2	110/80	138	430			32.1						
8. W. O.	(a)	1.58	November 9, 1938	40	1	120/80	86	293			29.4						
9. B. D.	(a)	1.48	January 5, 1939	40	1	110/70	114	284			40.1						
10. E. S.	(c)	1.83	October 28, 1940	40	2	110/70	116	297			39.1						2.13*
11. V. M.	(c)	1.58	October 18, 1940	40	1	112/72		321	462	712			69.5		18.1*	11.8*	
12. G. R.	(c)	1.65	September 12, 1940	40	1	110/68	134	437	797	1220	30.7	16.8	54.9				
13. M. B.	(c)	1.55	December 16, 1940	38	4	118/70	123	378	662	983	32.6	18.6	57.1				
14. M. E.	(c)	1.66	May 3, 1939	32	8	120/76	99	360	545	845	27.5	18.2	66.1	48.9	17.3	11.1	2.02
15. A. B.	(c)	1.60	May 11, 1939	34	4	116/78	125	370	586	833	33.8	21.3	63.1	41.4	20.1	14.2	3.02
16. L. D.	(c)	1.37	June 22, 1939	14	24	120/76	162	428	774	1242	37.9	20.9	55.3	48.9	25.4	15.8	3.32
17. H. H.	(c)	1.50	December 6, 1939	12	?	134/80	123	378	800	1241	32.6	15.4	47.3	48.1	25.8	16.6	2.56
18. L. B.	(c)	1.75	January 18, 1940	40	0	108/78	134	400	548	844	33.5	24.5	73.0	53.8	15.7	10.2‡	2.49
19. M. A.	(c)	†1.55	November 27, 1939	13	27	105/66	139	402	665	1040	34.6	20.9	60.5	46.0	22.7	14.5	3.02
			February 27, 1940	26	14												
20. I. J.	(c)	1.68	April 24, 1940	34	3	124/80	138	474	646	954	29.1	21.4	73.4	40.2	23.7	16.1	3.43
21. M. B. O.	(c)	1.53	May 1, 1940	40	1	124/80	85	260	457	760	32.7	18.6	56.9	37.7	20.2	12.1	2.26
22. R. D.	(b)																
Averages							124	371	631	970	33.4	19.6	61.6	45.6	20.9	13.7	2.67

Subject	Infusion fluid	Surface area	Postpartum: Date	Time in weeks after delivery	Mean blood pressure during test	Plasma clearances: Inulin	Plasma clearances: Phenol red	Plasma clearances: Diodrast	Effective renal blood flow	Inulin/Phenol red	Filtration fraction Inulin/Diodrast	Phenol red/Diodrast	Diodrast *Tm*	Effective renal blood flow/Tm_D	C_D/Tm_D	C_{IN}/Tm_D
		sq.m.				*cc. per 1.73 sq.m. per minute*			*cc. per 1.73 sq.m. per minute*	*per cent*	*per cent*	*per cent*	*mgm. iodine per minute*			
1. D. R.	(a)	1.51	(a) June 9, 1938	2	104/72	139	475			29.3						
2. L. P.	(b)	1.58														
3. C. B.	(b)	1.50														
4. S. M.	(b)	1.65														
5. H. D.	(b)	1.50	(c) February 1, 1940	70	116/74	107	363	599	922	29.5	17.9	60.6	51.4	17.9	11.7	2.08
6. H. Q.	(b)	1.38	(b) October 26, 1938	1	120/80	128	401			31.9						
7. R. S.	(b)	1.57														
8. W. O.	(a)	1.58	(b) November 29, 1938	2	116/84	109	353			30.9						
9. B. D.	(a)	1.48	(a) January 23, 1939	2	124/84	103	317			32.5						
10. E. S.	(c)	1.83	(c) November 18, 1940	2	110/70	123	341	569	955	36.1	21.6	59.9	54.4	17.5	10.46	2.26
11. V. M.	(c)	1.58	(c) October 26, 1940	1	120/80		444	525	876			84.5	39.3	22.3	13.4	
12. G. R.	(c)	1.65														
13. M. B.	(c)	1.55														
14. M. E.	(c)	1.66														
15. A. B.	(c)	1.60														
16. L. D.	(c)	1.37														
17. H. H.	(c)	1.50														
18. L. B.	(c)	1.75	(c) January 29, 1940	2	104/70	102	356	435	707	28.7	23.5	81.9	53.4	13.25	8.16‡	1.91
19. M. A.	(c)	†1.55														
20. I. J.	(c)	1.68	(c) May 24, 1940	2	120/74	144	443	642	1080	32.5	22.5	69.0	49.4	21.9	13.8	3.08
21. M. B. O.	(c)	1.53	(c) June 19, 1940	3	112/78	68	193	381	609	35.2	17.8	50.7	31.9	19.1	12.0	2.13
22. R. D.	(b)		(b) September 9, 1938	3	120/80	140	376			37.3						
Averages						116	362	525	858	32.0	20.8	68.9	46.6	18.65	13.25	2.28

(a) Infusion in saline. (b) Infusion in saline and sodium sulphate. (c) Infusion in mannitol and distilled water. * Postpartum *Tm* used. † Average of two tests. ‡ In this patient, 18 L. B., C_D/Tm_D is abnormally low. There is, however, no clinical evidence or history of hypertension or kidney disease to warrant her exclusion from the group.

TABLE II

Averages of antepartum and postpartum observations in same patients

Number and type of case	Plasma clearances			Effective renal blood flow	Inulin/ Phenol red	Inulin/ Diodrast	Phenol red/ Diodrast	Diodrast T_m	Effective renal blood flow/ T_{m_D}	C_D/T_{m_D}	C_{IN}/T_{m_D}
	Inulin	Phenol red	Diodrast								
	cc. per 1.73 sq. m. per minute			*cc. per 1.73 sq. m. per minute*	*per cent*	*per cent*	*per cent*	*mgm. iodine per minute*			
9 antepartum	120	355			33.8						
9 postpartum	114	360			31.7						
3 antepartum	119	378	550	852	31.5	21.6	68.7	43.9	19.4	12.5	2.71
3 postpartum	105	331	486	800	31.7	21.6	68.1	44.9	17.8	10.8	2.34

TABLE III

Averages of normal pregnant women compared with normal non-pregnant women and normal men

Number and type of case	Plasma clearances			Effective renal blood flow	Inulin/ Phenol red	Filtration fraction	Phenol red/ Diodrast	Diodrast T_m	Effective renal blood flow/ T_{m_D}	C_D/T_{m_D}	C_{IN}/T_{m_D}
	Inulin	Phenol red	Diodrast			Inulin/ Diodrast					
	cc. per 1.73 sq. m. per minute			*cc. per 1.73 sq. m. per minute*	*per cent*	*per cent*	*per cent*	*mgm. iodine per minute*			
9 normal non-pregnant women*	119		600	996		19.8		46.7	21.3	12.8	2.54
30 normal men*					32.2						
15 normal non-pregnant women†			545	844							
15 normal pregnant women†			591	856							
20 normal pregnant women	124	371			33.4						
8 normal pregnant women	126	384	628	970	32.9	20.1	61.2	45.6	21.3	13.7	2.77

* Goldring, Chasis, Ranges and Smith.

† Chesley and Chesley.

The diodrast clearances are also essentially the same as those reported by Chesley and Chesley.[8]

Renal function as revealed by these tests is unaltered by normal pregnancy and undergoes no change in the days immediately following delivery. One cannot therefore explain the slight salt and water retention of normal pregnancy on the basis of a decreased filtration rate. There is no evidence of any hormonal effect on kidney function which might accompany the morphological change known to follow the injection of similar substances into small laboratory animals.

[8] Chesley's infusions contained only glucose and diodrast; infusions used by Goldring, Chasis, Ranges and Smith contained inulin and diodrast in saline; our infusions were made up of inulin, phenol red, diodrast and, in various instances, saline, sodium sulphate or sorbitol or mannitol. The close comparison of diodrast clearance figures found in these three groups seems to rule out Chesley's suggestion (10) that infusions of inulin and phenol red may cause a renal hyperemia.

CONCLUSION

The filtration rate (inulin clearance), effective renal blood flow (diodrast clearance), tubular ex-

cretory mass (diodrast T_m) and phenol red clearances are not altered in pregnancy or in the puerperium of normal women.

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