

THE FILTRATION RATE, EFFECTIVE RENAL BLOOD FLOW, TUBULAR EXCRETORY MASS AND PHENOL RED CLEARANCE IN SPECIFIC TOXEMIA OF PREGNANCY¹

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The vascular and renal disorders of the last trimester of pregnancy are classified by the University Obstetrical Service in the following groups: specific toxemia, pre-existing essential hypertension, pre-existing glomerulonephritis and specific toxemia superimposed on pre-existing hypertension or nephritis (1).

Specific toxemia is clinically characterized by the rather abrupt appearance of hypertension, usually in the last trimester of a previously normal pregnancy. This rise in blood pressure is typically accompanied by edema and proteinuria. Hematuria and azotemia are not seen, but the convulsions of eclampsia may occur. The postpartum course of the disease likewise helps to identify it. Edema subsides soon after delivery. Proteinuria usually disappears in the puerperium, although traces of protein in the urine may be present for weeks. Blood pressure falls to a normal level in the majority soon after delivery, but it is a striking feature of such an attack that in many instances it is followed by permanent hypertension.

The present communication is an investigation of renal function in specific toxemia of pregnancy, based upon a study of inulin, phenol red and diodrast clearances and diodrast T_m . The inulin clearance is considered to be a measure of the rate of glomerular filtration, diodrast clearance a measure of effective renal blood flow and diodrast T_m a measure of tubular excretory mass (2, 3), within the definitions and limitations accorded to these terms by Smith (4).

Using these methods, Goldring *et al.* (5, 6, 7, 8) have demonstrated that renal ischemia of varying degree, associated with an increase in filtration fraction which is indicative of efferent arteriolar

hypertonus, is usually present in essential hypertension in men and non-pregnant women. Chesley *et al.* (9) have shown that the effective renal blood flow in toxemia of pregnancy, as determined by the diodrast clearance of twenty patients, is the same as that of normal pregnant and non-pregnant women. Corcoran and Page (10), using clearances of inulin and phenol red, found the filtration rate diminished, effective renal blood flow normal and the phenol red/inulin clearance ratio high during toxemia in seven subjects when compared to their postpartum values. In three of these subjects, in whom diodrast clearance was determined both antepartum and postpartum, they observed a fall in diodrast clearance and a rise in filtration fraction after delivery. They attribute the antepartum decrease in filtration fraction to swelling of the glomerular basement membrane. That the glomerular filtration rate and effective renal blood flow are unaffected in normal pregnancy was concluded in our previous report (11). This was based on inulin and phenol red clearances in twenty normal pregnant women, with diodrast clearance in eleven and diodrast T_m in eight.

MATERIAL AND METHODS

Thirteen patients, who had been seen early in pregnancy and found at that time to have no evidence of vascular or renal disease, have been studied in fourteen pregnancies complicated by specific toxemia. None gave a history of previous hypertension or kidney disease except for one patient who, though her blood pressure was normal between gestations, had developed a typical attack of specific toxemia in a previous pregnancy. In the last trimester, hypertension, proteinuria and edema appeared in all of these patients but, as may be seen in Tables I and II, proteinuria and edema had disappeared in some instances before the day of the antepartum tests. Two patients developed the typical antepartum convulsions of eclampsia and there were three intrauterine fetal deaths.

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These thirteen patients are divided into two groups depending upon the behavior of the blood pressure after delivery. One group is characterized by clinical cure, the other by residual hypertension. The classification of any patient was decided not at the time of the postpartum tests but in the follow-up toxemia clinic. The significance of this grouping with respect to renal function will be discussed.

RESULTS

The data on both groups appear in detail in Tables I and II. In eleven patients, inulin, phenol red and diodrast clearances, and diodrast T_m were determined, while in three, phenol red and inulin clearances only were done. The tests were performed as previously outlined (11). Each clearance figure represents the average of at least three urine collection periods; each diodrast T_m figure, an average of five periods. Urine

flow was maintained at high levels by methods already described and any test in which the urine flow was below 2 cc. per minute is not reported.

The average antepartum and postpartum values for each individual appear in Figures 1, 2 and 3. The antepartum figure is shown by a solid circle and the postpartum by an open circle, the arrow connecting them indicating the direction of change taking place after delivery. The data on toxemic patients are displayed against the statistical background obtained from normal women. In compiling these control data, nine normal non-pregnant women observed by Goldring, Chasis, Ranges and Smith (12), and eight normal pregnant women observed by us (11), have been treated as a single group. The mean and standard deviation from the mean of inulin and diodrast clearances

TABLE I
Specific toxemia of pregnancy with clinical cure postpartum

Subject	Ante-partum or post-partum	Sur-face area	Date	Duration of pregnancy in weeks by history	Time in weeks before or after delivery	Mean blood pressure during test	Protein-uria	Plasma clearances			Effective renal blood flow	Inulin/Phenol red	Filtration fraction	Phenol red/Diodrast	Dio-drast T_m	Effective renal blood flow/ T_{mD}	C_D/T_{mD}	C_{IN}/T_{mD}	
								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				
M.L.	A-P	1.44	September 18, 1938(b)	35	3	176/106	+++	148	517										
	P-P		September 26, 1938(b)	37	1	160/110	+++	86	288		28.6								
			October 6, 1938(b)			1	160/110	+++	118	369		32.0							
M.C.	A-P	1.88	October 4, 1938(b)	38	2	166/96	++	85	268										
	P-P		October 20, 1938(c)		1	184/120	++	91	313		31.7								
			December 13, 1938(a)		9	128/90	0	94	353		29.1								
M.A.	A-P	1.46	November 17, 1938(a)	30	6	140/110	+	85	266	458	790	32.0	18.6	58.1		21.9*	12.7*	2.36*	
	P-P		March 2, 1939(a)		9	120/74	0	133	308	538	846	43.2	24.7	57.2	37.1	22.8	14.5	3.59	
			July 25, 1939(c)		25	116/70	0	102	288	556	856	35.4	18.4	51.8	35.1	24.4	15.9	2.91	
M.S.	A-P	1.55	December 7, 1938(e)	35	4	154/110	++	101	406	842	1367	24.9	12.0	48.2		31.6*	19.5*	2.33*	
	P-P		December 15, 1938(a)	36	3	144/104	+++	82	403	792	1207	20.4	10.4	50.9		27.9*	18.3*	1.89*	
			December 21, 1938(a)	37	2	180/120	++++	77	392	750	1133	19.7	10.3	52.3		26.2*	17.3*	1.78*	
			January 10, 1939(a)		2	160/116	+	118	409	658	1024	28.9	17.9	62.2		23.6*	15.2*	2.72*	
			January 16, 1939(b)		3	158/116	0	98	372	537	835	26.3	18.3	69.3		18.4	11.8	2.15	
			March 6, 1939(d)		10	128/90	0	106	301	618	977	35.2	17.2	48.7		41.0	23.8	15.1	2.59
E.S.	A-P	1.7	March 15, 1939(a)	37	2	136/108	0	155	523	776	1257	29.6	20.0	67.4		68.2	18.4	11.4	2.27
	P-P		April 6, 1939(c)		2	122/86	Trace	123	388	517	872	31.7	23.8	75.1	67.3	13.0	7.68	1.83	
			July 6, 1939(d)		11	130/88	0	157	433	652	1042	36.3	24.1	66.4	62.0	16.8	10.5	2.53	
			November 25, 1940(c)	35	3	140/100	0	153	476	765	1290	32.2	20.0	62.2	61.0	21.0	12.4	2.49	
	P-P	1.7	December 23, 1940(c)		1	118/90	0	176	584	728	1175	33.0	23.9	72.4	70.0	16.8	10.5	2.52	
	F.P.	A-P	1.65	March 28, 1939(c)	31	9	148/100	+++	80	323	582	924	24.8	13.7	55.5		44.1	21.0	13.2
P-P			April 3, 1939(c)		32	160/110	+++	84	379	636	1043	22.2	13.2	59.6		45.4	23.0	14.0	1.85
			April 18, 1939(c)		34	160/114	++	101	437	651	1100	23.1	15.5	67.1		24.5†	14.5†	2.25†	
			June 8, 1939(d)		2	140/86	0	117	377	540	787	31.0	21.7	69.8		17.1	11.7	2.54	
			October 25, 1939(c)	39	2	138/98	+++	100	407	668	940	24.6	15.0	60.9		49.7	18.9	13.4	2.01
P-P	1.78	November 13, 1939(c)		2	124/84	0	92	337	468	770	27.3	19.7	72.1	55.1	14.0	8.48	1.87		

* Postpartum T_m .

† Antepartum T_m .

(a) Infusion with physiological saline.

(b) Infusion with physiological saline and sodium sulphate.

(c) Infusion with mannitol in distilled water.

(d) Infusion with sorbitol in distilled water.

(e) Infusion with 5 per cent glucose in distilled water.

TABLE II
Specific toxemia of pregnancy with residual hypertension postpartum

Subject	Antepartum or postpartum	Surface area	Date	Duration of pregnancy in weeks by history	Time in weeks before or after delivery	Mean blood pressure during test	Proteinuria	Plasma clearances			Effective renal blood flow	Inulin/Phenol red	Filtration fraction	Phenol red/Diodrast	Diodrast T_m	Effective renal blood flow/ T_m	C_D/T_{mD}	C_{IN}/T_{mD}
								Inulin	Phenol red	Diodrast								
G.C.	A-P P-P	1.68	November 15, 1938(a) November 28, 1938(a)	39	1 2	132/100 134/96	0 0	62 118	228 290		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		
M.C.	A-P P-P	1.8	January 19, 1939(e) January 24, 1939(e) February 10, 1939(d) February 21, 1939(d)	36 37 39	4 3 1 2	180/122 150/124 150/120 134/98	++ ++++ +++ 0	50 41 44 96	183 153 196 259	228 207 288 333	374 342 469 503	27.3 26.8 22.4 37.1	21.9 19.8 15.3 28.8	80.2 73.9 68.1 77.8	31.5 14.9 10.3	11.9* 10.9* 14.9 10.3	7.24* 6.57* 9.14 6.82	1.59* 1.3* 1.4 1.97
H.F.	A-P P-P	1.44	January 26, 1939(e) February 2, 1939(a) February 14, 1939(d) February 27, 1939(d) November 29, 1939(a)	31 32 34	4 3 1 2 41	160/120 158/112 190/136 192/134 150/106	0 + ++ 0 0	143 152 104 121 125	440 409 412 319 329	825 785 752 494 596	1290 1235 1360 856 983	32.5 37.2 25.2 37.9 38.0	17.3 19.4 13.8 24.5 21.0	53.4 52.1 54.8 64.6 55.2	36.7 48.4 42.6 36.3	30.3* 33.7 28.1 20.1 27.1	19.4* 21.4 15.5 11.6 16.4	3.36* 4.14 2.15 2.84 3.44
M.S.	A-P P-P	1.24	March 23, 1939(d) March 30, 1939(e) May 15, 1939(e)	35 36	2 1 6	160/110 162/110 130/90	++ + 0	89 85 92	279 278 237	535 481 384	854 690 652	31.9 30.6 38.8	16.6 17.7 24.0	52.2 57.8 61.7	36.5 35.8	23.4 19.3 18.0*	14.7 13.4 10.6*	2.44 2.37 2.54*
H.S.	A-P P-P	1.97	May 23, 1939(e) June 10, 1939(d) June 29, 1939(d)	35 37	4 2 2	144/104 130/90 130/98	+ ++ +++	106 122 119	331 376 299	583 574 448	908 855 666	32.0 32.5 39.8	18.2 21.3 26.6	56.8 65.5 66.7	42.4 40.0	21.4 14.3 16.2*	13.8 10.8*	2.5 3.05 2.89*
A.F.	A-P P-P	1.56	June 1, 1939(e) June 14, 1939(d)	42	1 2	134/90 162/94	+	105 115	391 318	743 431	1135 645	26.9 36.2	14.1 26.7	52.6 73.8	54.2 46.4	20.9 13.9	13.7 9.29	1.94 2.48

* Antepartum T_m .

- (a) Infusion with physiological saline.
- (b) Infusion with physiological saline and sodium sulphate.
- (c) Infusion with mannitol in distilled water.
- (d) Infusion with sorbitol in distilled water.
- (e) Infusion with 5 per cent glucose in distilled water.

and diodrast T_m for the series of seventeen normal women have been calculated, using each individual once.

Diodrast T_m . Tubular excretory function in toxemia is typically unaffected, for the values for diodrast T_m are distributed about equally above and below the normal mean. In only one instance (M. C., Table II) does the diodrast T_m fall below the lowest normal value, and in this patient it returns to normal after delivery.

Inulin clearance. The inulin clearance per unit of diodrast T_m appears in Figure 1, the heavy line representing the mean normal value, the light lines once and twice the standard deviation. The antepartum and postpartum observations are within normal limits with one exception.² There is, however, an increase in filtration rate after

delivery in all but three of these individuals, suggesting that during toxemia the filtration rate is reduced.

Diodrast clearance. The diodrast clearance per unit of diodrast T_m (Figure 2) is above the mean normal line antepartum in eight of eleven subjects. The antepartum observations, with the exception of M. C. mentioned above, show the effective renal blood flow in toxemia to be normal; in some instances it is distinctly above normal. The two points above the $+2\sigma$ line are the highest values of diodrast clearance, per unit of diodrast T_m , found in any of the women examined by Goldring *et al.* or by ourselves (11, 12).

In nine of eleven patients the diodrast clearance falls after delivery. This occurs in some cases even before the fall of blood pressure. This drop in diodrast clearance after delivery is evident both in the cured group and in the group with residual hypertension, but is greater in the latter.

Filtration fraction. In Figure 3 the filtration fraction is shown in relation to the diodrast clear-

² Inulin, phenol red and diodrast clearance and diodrast T_m in M. C. (Table II), and inulin and phenol red clearance in G. C. (Table II), all of which were well below normal antepartum, rose considerably after delivery. Corcoran and Page report a similar case (10).

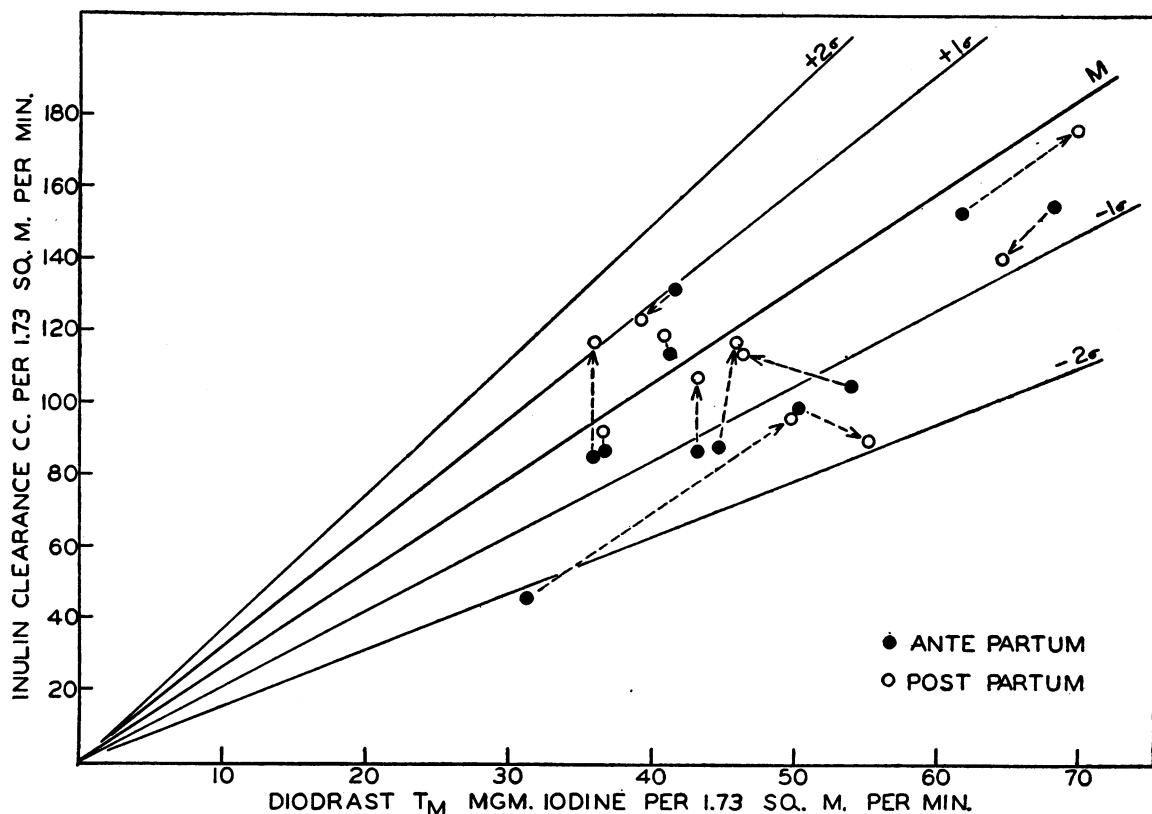


FIG. 1. COMPARISON OF ANTEPARTUM WITH POSTPARTUM INULIN CLEARANCES

ance per unit of diodrast T_m . The horizontal line at 0.20 represents the mean normal value for the filtration fraction. The vertical line at 13.2 is the mean normal value of diodrast clearance per unit of diodrast T_m . The central curved line is the course of the variables if the glomerular filtration rate maintains its mean normal value at varying rates of renal plasma flow. The parallel curved lines are $+2\sigma$ and -2σ .

The figures for filtration fraction before delivery are below the lowest normal value in only five of eleven subjects. Yet it can be seen that all of the antepartum filtration fractions are on or below the normal line and that all of the arrows point upwards, showing the increase in filtration fraction after delivery. The antepartum reduction in filtration fraction is dependent upon an increase in diodrast clearance, a reduction in inulin clearance, or both. After delivery it rises without exception, in part because of an increased inulin clearance and in part because of a decreased diodrast clearance, the postpartum rise being greater in the group with persistent hypertension.

Phenol red clearance. The clearance of phenol red (Tables I and II), like that of diodrast, suffers a reduction after delivery, but to a lesser extent. It can be seen also that the inulin/phenol red clearance ratio is somewhat reduced antepartum and increased after delivery, a phenomenon not observed in normal pregnancy (11). Although the variations from the normal in this ratio are small, they follow the changes in filtration fraction in direction and time and may be considered to have the same functional significance.

Although the phenol red/diodrast clearance ratio varies over a wide range in antepartum and postpartum observations, it rises consistently after delivery in all instances where the diodrast clearance falls. This increase in ratio accompanying a decrease in diodrast clearance is in agreement with the observation of Chasis *et al.* that the phenol red/diodrast clearance ratio varies inversely as the renal blood flow (13). Calculation of renal blood flow from phenol red clearance in subjects with toxemia of pregnancy, especially

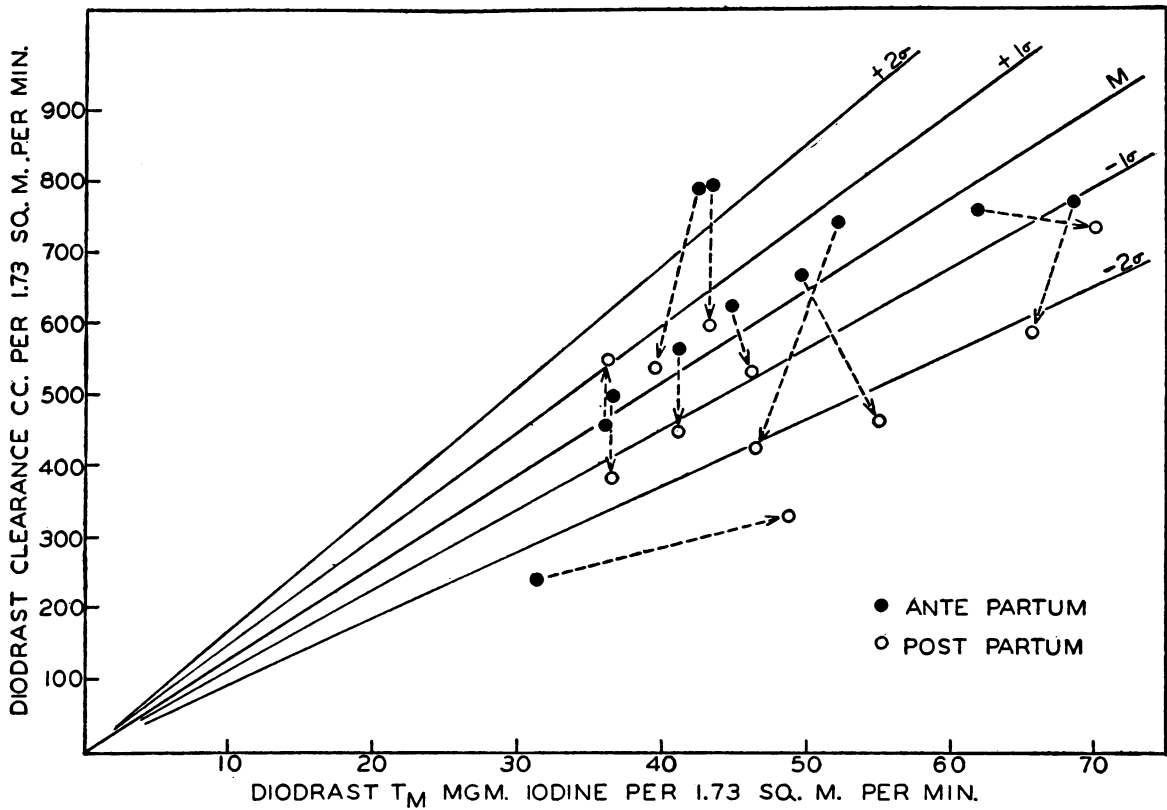


FIG. 2. COMPARISON OF ANTEPARTUM WITH POSTPARTUM DIODRAST CLEARANCES

for a comparison of antepartum with postpartum renal function, is evidently subject to greater error than is such calculation in normal subjects.

DISCUSSION

When renal function in fourteen pregnancies complicated by specific toxemia is compared to that of the control group, the clearances are found below the normal range in only two, while the filtration fraction is below normal in five. In other words, if judged from antepartum observations alone, one-half of this series of toxemic patients would appear to have normal kidney function. However, when these patients are considered as a group in comparison with the normals, as well as when antepartum figures are compared with postpartum figures, trends become evident which are not found in the pregnancy or puerperium of normal women. Before delivery there is a slight reduction in filtration rate and filtration fraction associated with a normal or slightly elevated effective renal blood flow. Fol-

lowing delivery the filtration fraction rises in every instance, in part because of a rise in filtration rate and in part because of a fall in effective renal blood flow. In the group with residual hypertension the increase in filtration fraction is more marked than in the group with clinical cure and reaches levels seen in essential hypertension (5, 6, 8).

The antepartum clearances and clearance ratios bear no consistent relation to the severity of the clinical manifestations or to the eventual outcome of the disease. The postpartum observations, however, fall readily into two groups and may offer some aid in prognosis. In the patients in whom hypertension was to persist, the diodrast clearance had fallen and the filtration fraction had risen considerably in the first test done postpartum, whereas in the cured group the inulin clearance had increased, the diodrast clearance had fallen slightly, and the filtration fraction had risen to normal in the first test done after delivery, regardless of whether the blood pressure had fallen to normal or not.

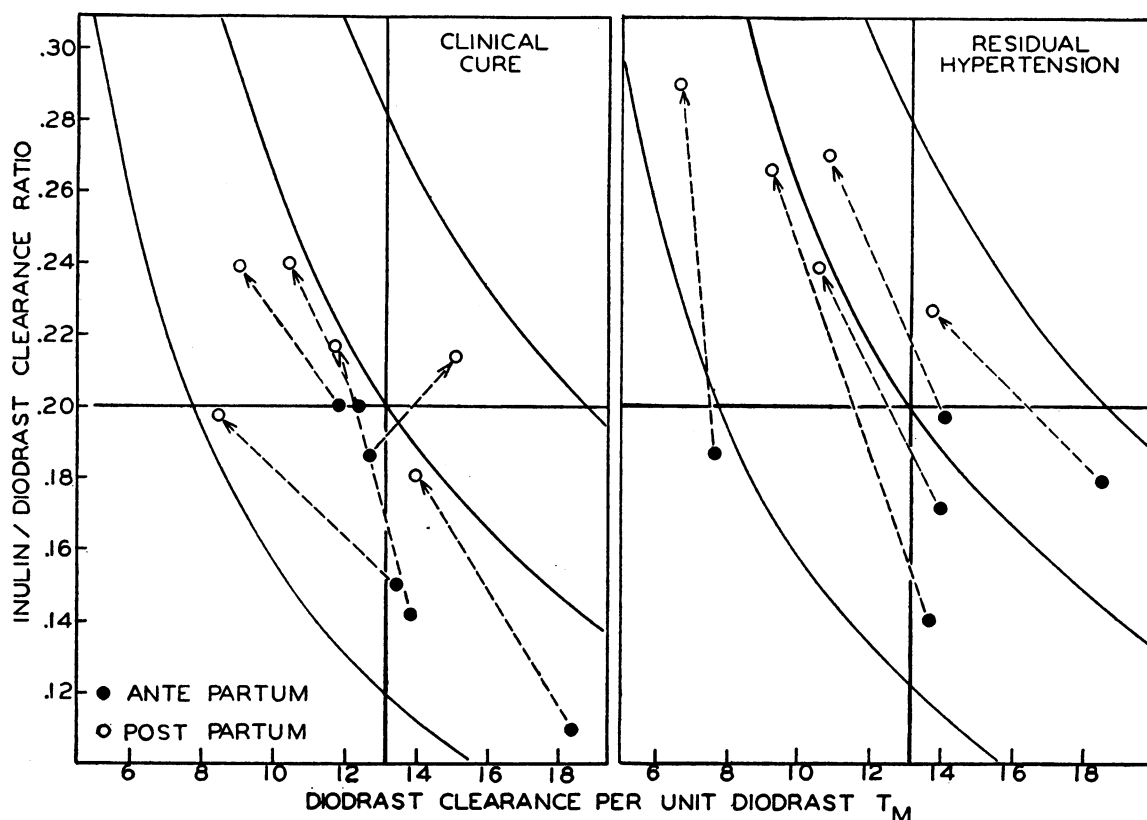


FIG. 3. COMPARISON OF ANTEPARTUM WITH POSTPARTUM FILTRATION FRACTIONS

The slight diminution in filtration rate antepartum could result from afferent arteriolar constriction, which would cause a fall in filtration pressure, from edema of the kidney with resultant increase in interstitial pressure or from thickening of the basement membrane of the glomerulus with an increase in resistance to filtration (14). Any one of these mechanisms could conceivably be operative antepartum and disappear within a few days after delivery.

That the inulin clearance remains a true measure of glomerular filtration rate in toxemia is open to possible question on the ground that the permeability of the supposedly thickened glomerular filtering bed to the large inulin molecule might be reduced. In five subjects, however, on whom clearances of sorbitol or mannitol were done (15), the clearances of these hexitols were found to be identical with the simultaneous clearance of inulin.⁸ If inulin is not filtered at the same rate as

these smaller molecules, the hexitol/inulin clearance ratio can otherwise be maintained at the observed value of 1.0 only through the unlikely circumstance that a fraction of the filtered hexitol, exactly equal to that of the unfiltered inulin, is reabsorbed by the tubules. Yet tubular function in these five subjects is within normal limits as measured by diodrast T_m .

The observed alterations in effective renal blood flow are apparently not solely dependent upon the arterial blood pressure, for in some instances the diodrast clearance falls before the blood pressure falls. This observation indicates that the relatively high effective renal blood flow before delivery, and its decrease promptly thereafter, must be related to alterations in the renal vessels. The changes in effective renal blood flow may be explained by variations in efferent arteriolar tone (14), namely, dilatation of slight degree ante-

⁸ Hexitol and inulin clearances both antepartum and postpartum on patients F. P. (Table I), and H. F. and

M. S. (Table II), and postpartum on E. S. (Table I) and M. C. (Table II), have already been published by Smith, Finkelstein and Smith (15).

partum followed after delivery by a return to normal tone in the cured group and by spasm in the hypertensive group.

The dramatic improvement in the toxemic patient after delivery or fetal death is well known. The changes observed in diodrast clearances and filtration fraction—namely, a reduction from the level of normal renal blood flow or actual renal hyperemia to a level of renal ischemia accompanied by evidence of efferent arteriolar spasm—are seen soon after delivery. Both of these phenomena are evidently associated with the emptying of the uterus or the cessation of placental circulation. In those pregnant patients in whom hypertension is to persist and in whom the efferent hypertonus characteristic of essential hypertension is to appear after delivery, it is possible that constriction of the efferent arteriole is prevented by some unknown factor effective so long as pregnancy continues. Such an hypothesis is supported by the fact that in a small series of women with essential hypertension (unpublished data) renal blood flow is higher antepartum than postpartum and in two individuals is higher during pregnancy than before pregnancy. The filtration rate in these women with essential hypertension is unaffected by pregnancy.

In respect to the genesis of hypertension in toxemia of pregnancy, both in patients whose blood pressure is to return to normal and in those in whom hypertension is to persist, there is no evidence that renal ischemia plays any part. Indeed, when the blood pressure is highest, there is neither the renal ischemia nor the efferent arteriolar hypertonus characteristic of essential hypertension. Yet those patients in whom hypertension persists show in their postpartum clearances renal disturbances which cannot be distinguished from those of essential hypertension. The failure to find a reduction in renal blood flow in toxemia of pregnancy in which hypertension is such a striking feature is an argument against the theory that renal ischemia is a primary causal factor of the hypertensive process.

CONCLUSIONS

1. In toxemia of pregnancy the tubular excretory mass (diodrast T_m) is normal; the effective renal blood flow (diodrast clearance) is normal

or above normal; the glomerular filtration rate (inulin clearance) is somewhat reduced when referred to postpartum values; the filtration fraction is normal or low.

2. Following delivery the filtration fraction increases, in part because of a fall in diodrast clearance and in part because of an increase in inulin clearance. In the group with clinical cure these changes leave the figures within the normal range. In the group with persistent hypertension the results of these functional tests are identical with those found in essential hypertension.

3. The view that renal ischemia is an essential factor in the production of hypertension is opposed by the evidence that in the presence of the hypertension of toxemia there is a normal or even an increased renal blood flow.

We are indebted to Dr. Homer W. Smith for having many analyses of diodrast iodine carried out in the Department of Physiology before the method was set up in this Laboratory. We wish further particularly to express our thanks to him for his interest and advice.

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