PLASMA VOLUME, TOTAL CIRCULATING PROTEIN, AND "AVAILABLE FLUID" ABNORMALITIES IN PREECLAMPSIA AND ECLAMPSIA [1]

By EDWARD D. FREIS and JAMES F. KENNY

(From the Evans Memorial, Massachusetts Memorial Hospitals, the Medical and Obstetrical Services, Massachusetts Memorial Hospitals, and the Departments of Medicine and Obstetrics, Boston University School of Medicine, Boston)

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It has long been recognized that the red blood count may be abnormally high in eclampsia (1). Dieckmann (2) believed that the elevation of hematocrit was consequent upon a diminution in plasma volume, but this concept has not received general recognition.

In contrast to the elevation of hematocrit Strauss (3) and others (4, 5) stressed the low plasma albumin concentration which they believed to play a part in the oliguria, water retention and edema. If the plasma volume is indeed low, as claimed by Dieckmann, the combination of a low plasma volume and low plasma protein concentration would result in a marked deficiency of total circulating protein. Many of the clinical features of severe toxemia such as the edema, albuminuria and oliguria suggest that this may well be the case. With these considerations in mind we undertook to investigate the changes in plasma volume, total circulating protein and "available fluid" (thiocyanate space) associated with preeclampsia and eclampsia as compared to normal pregnancy.

MATERIALS AND METHODS

The patients with toxemia were studied under as nearly basal conditions as possible on the wards of the obstetrical service of the Massachusetts Memorial Hospitals. All of these patients were diagnosed clinically as having eclampsia or preeclampsia. In every case the pathological manifestations began in the last trimester of pregnancy. All cases diagnosed as having preeclampsia exhibited hypertension, edema and albuminuria. Cases of preeclampsia were called severe when in addition they exhibited oliguria, visual disturbances and/or epigastric pain.

Two control groups were used in this study. One was comprised of seven cases in the last trimester of normal pregnancy. Four of these patients manifested clinical edema of the face, hands and feet but were otherwise normal. The other control group consisted of six normal nonpregnant females (nurses and laboratory technicians). In all cases the subjects of both control groups were fasting at the time of the examination, and were resting in the supine position for at least one-half hour prior to the test.

Plasma volume and "available fluid" determinations were carried out with the dye T-1824 and a 5 per cent solution of sodium thiocyanate, respectively, as detailed in a previous communication (6). The "available fluid" volume as measured by this method includes all of the fluid spaces to which thiocyanate is distributed at equilibrium, including the plasma volume as well as the amount that enters the red blood cells. In the pregnant individual thiocyanate in all probability passes the placental membrane, but this fact does not nullify comparative studies between toxemic and normal pregnancy in the same stage of gestation. Total protein was determined from the plasma specific gravity by the method of Barbour and Hamilton (7), as modified by Weech (8).

RESULTS

"Available fluid"

The "available fluid" volume was highest in the severe preeclamptic and eclamptic group of patients, the mean being 321 ml. per kilo body weight and the range 291 to 355 ml. per kilo (Table I). The patients with normal pregnancy exhibited a mean "available fluid" volume of 282 ml. per kilo, range 235 to 315 ml. per kilo, while the nonpregnant normal females showed an average of 245 ml. per kilo body weight and a range of 210 to 267 ml. per kilo (Table II and III). Thus, in general, the greatest volumes of "available fluid" were encountered in the toxemic patients and the smallest volumes in the nonpregnant individuals, although there was considerable overlapping between the toxemic group and the group with normal pregnancy. The "available fluid" volume was well correlated with the degree of edema.

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TABLE I

Plasma volume, total circulating protein and "available fluid" volume in severe preeclampsia and eclampsia

Case	Time from delivery	Ht.	Wt.	Plasma volume		Hematocrit value	Total protein	Total circulating protein		"Available fluid"		Ratio
		cm.	*kilo*	*ml.*	*ml./kilo*		*gms. %*	*gms.*	*gms./kilo*	*ml.*	*ml./kilo*	*av. fl./P.V.*
Eclampsia	12 hrs. pre	170	93.2	3,440	37.0	39	5.3	182	2.0	27,100	291	7.9
	3 days post					37	5.4			22,800		
1—L. H.	14 days post		79	3,400	43.0	33	6.1	207	2.6	21,800	275	6.4
	2 days pre	165	72.2	3,560	49.3	38	6.2	220	3.0	24,200	335	6.8
	½ day pre (1,750 ml. plasma)*		73	5,320	72.9	30	5.9	314	4.3	26,400	361	5.0
2—M. S.	3 days post		66	3,360	49.4	29	5.5	185	2.8	22,400	339	6.8
	10 days post		59.4	2,270	38.2	38	6.5	147	2.5	15,200	254	6.7
Pre-eclampsia severe	1 day pre (500 ml. plasma)*	165	62.9	2,860	45.4	39	4.25	122	1.9	22,400	355	7.8
	½ day post		54	2,800	51.8	35						
3—E. H.	4 days post		49	2,760	56.3	33	5.3	146	3.0	15,450	315	5.4
	11 days post		46.4	2,480	53.4	34	5.5	136	2.9	13,900	299	5.6
	35 days post		48.1	2,500	51.9	38	5.5	137	2.8	15,200	315	5.6
	6 hrs. pre	169	68.6	3,440	50.1	37	4.7	162	2.3	21,300	310	6.2
4—V. P.	10 days post		59	2,420	41	39	6.3	152	2.6	16,100	273	6.6
5—E. G.	1 day pre	160	47.7	1,927	40.4	45	5.2	100	2.1	15,025	315	7.8
Mean					44.3				2.2		321	7.3

* Intravenous administration of citrated plasma between the first and second plasma volume determinations.

Plasma volume

The plasma volume determinations for the six normal nonpregnant females agreed well with those of other investigators for a similar group (9, 10), the range being 38.3 ml. to 54.3 ml. per kilo body weight with a mean of 44.8 ml. per kilo (Table II). The plasma volume levels for the normal pregnancy control group were much higher than the nonpregnant controls, the mean being 59.1 ml. per kilo and the range 47.0 to 70.5 ml. per

TABLE II

Plasma volume, total circulating protein and "available fluid" volume in normal nonpregnant females

Subject	Ht.	Wt.	Plasma volume		Hematocrit value	Total protein	Total circulation protein		"Available fluid"		Ratio
	cm.	*kilo*	*ml.*	*ml./kilo*		*gms. %*	*gms.*	*gms./kilo*	*ml.*	*ml./kilo*	*av. fl./P.V.*
M. F.	161	57.7	2,300	39.9	36	6.85	157	2.7	12,080	210	5.2
E. H.	167	46.8	2,540	54.3	38	6.6	168	3.5	12,450	267	4.9
C. B.	172	63.0	2,780	44.1	42	7.0	195	3.1	14,900	236	5.4
G. M.	165	62.1	2,375	38.3	42	6.4	152	2.4	14,000	226	5.9
V. N.	159	59.1	2,620	44.1	35	5.9	155	2.6	15,400	261	5.9
A. C.	172	60.0	2,910	48.5	38	5.5	160	2.7	15,800	263	5.4
Mean				44.8				2.8		245	5.5

TABLE III

Plasma volume, total circulating protein and "available fluid" volume in the third trimester of normal pregnancy

Patient	Ht.	Wt.	Edema	Plasma volume		Hematocrit value	Total protein	Total circulating protein		"Available fluid"		Ratio
	cm.	*kilo*		*ml.*	*ml./kilo*		*gms. %*	*gms.*	*gms./kilo*	*ml.*	*ml./kilo*	*av. fl./P.V.*
M. J.	160	63.5	+	4,180	64.2	34	6.8	284	4.4	19,700	310	4.7
C. G.	165	91.0	+	4,750	52.5	35	6.25	296	3.3	21,400	237	4.5
D. V.	167	69.0	+	4,860	70.5	32	6.4	311	4.5	21,700	315	4.5
M. K.	162	54.2	0	3,595	66.0	35	5.4	194	3.6	16,000	295	4.5
M. B.	171	81.5	+	3,890	47.8	36	6.1	237	2.9	21,100	259	5.4
M. L.	160	57.5	0	3,780	66.0	32	5.7	215	3.7	18,600	323	4.9
E. G.	166	105.0	0	4,950	47.0	40	6.1	305	2.9	24,800	235	5.2
Mean					59.1				3.6		282	4.8

kilo (Table III). In contrast, the five patients diagnosed clinically as having either severe preeclampsia or eclampsia exhibited a mean plasma volume of 44.3 ml. per kilo, range 37 to 50.1 ml. per kilo. Thus, in respect to plasma volume the patients with severe toxemias of late pregnancy more nearly resembled the nonpregnant controls than the pregnant controls.

Although the cases of severe toxemia in general exhibited lower plasma volumes in respect to body weight than patients with normal pregnancy there was some overlapping of individual cases (Figure 1). The plasma volume in respect to height or surface area still showed overlapping of the various groups.

However, when the plasma volume was considered in relation to the total extracellular fluid space as measured by thiocyanate, all patients with severe toxemia fell into a group distinct from the normal nonpregnant and the normal pregnant individuals (Figure 2). In normal pregnancy an increase in "available fluid" volume was balanced by a commensurate increase in plasma volume; the ratio of "available fluid" volume to plasma volume remained the same or was lower than the normal nonpregnant state. But in severe toxemia the relationship was no longer normal due to a failure of plasma volume to keep pace with the increasing extracellular fluid space. The distinguishing criteria of severe toxemia, therefore, lay in the ratio between the comparative volumes of the plasma and the total extracellular fluid, as measured by thiocyanate.

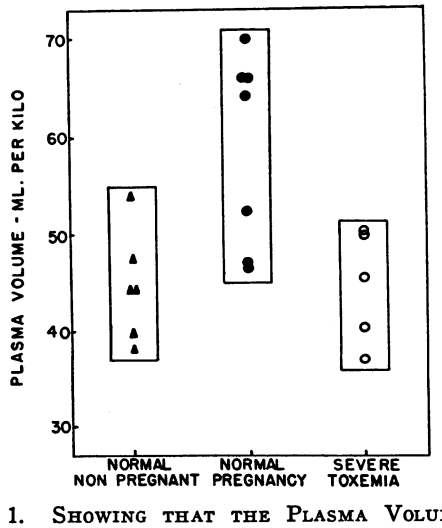

FIG. 1. SHOWING THAT THE PLASMA VOLUME IN RELATION TO BODY WEIGHT IS REDUCED IN SEVERE TOXEMIA AS COMPARED TO NORMAL PREGNANCY BUT THAT SOME OVERLAPPING OF INDIVIDUAL CASES OCCURS

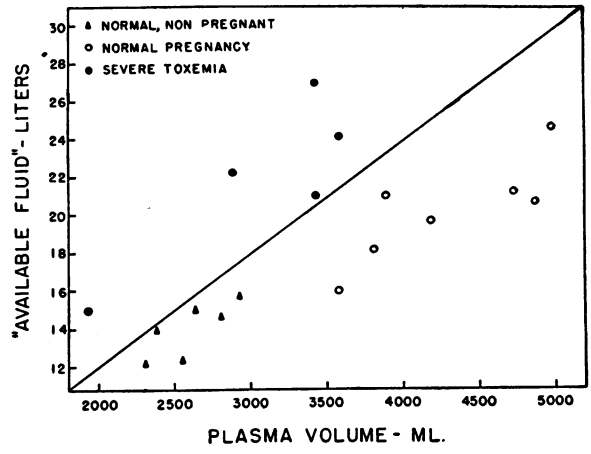

FIG. 2. SHOWING THAT THE RELATIONSHIP BETWEEN PLASMA VOLUME AND "AVAILABLE FLUID" RESULTS IN A CLEAR CUT DIFFERENTIATION BETWEEN THE SEVERE PREECLAMPTIC AND ECLAMPTIC PATIENTS AS COMPARED TO THE NORMAL NONPREGNANT AND THE NORMAL PREGNANT INDIVIDUALS

Additional evidence for a deficiency in plasma volume in the toxemias of late pregnancy was provided by Cases 1 and 3 of Table I. In normal pregnancy there is a marked increase in plasma volume during the period of gestation and a pronounced fall following delivery (11). Case 1 (Table I), an eclamptic, in contrast to patients with normal pregnancy, exhibited approximately the same plasma volume two weeks following delivery as she had prior to delivery. Similarly, the plasma volume of Case 3, who had severe preeclampsia, was determined 35 days following delivery. At this time she had experienced a normal menstrual period and was not nursing her child. Using this value as the nonpregnant basal level it was determined that the absolute plasma volume had increased only 13 per cent by the end of gestation, and that the plasma volume in terms of body weight had actually decreased by 13 per cent.

Total circulating protein

The total circulating protein was increased in normal pregnancy over that observed in the normal nonpregnant group. The mean for the nonpregnant control group was 2.8 gms. per kilo body weight, range 2.4 to 3.5, while in the group with normal pregnancy the mean was 3.6 gms. per kilo, range 2.9 to 4.5. This increase was due to an enlargement of plasma volume rather than to an increased plasma protein concentration. The

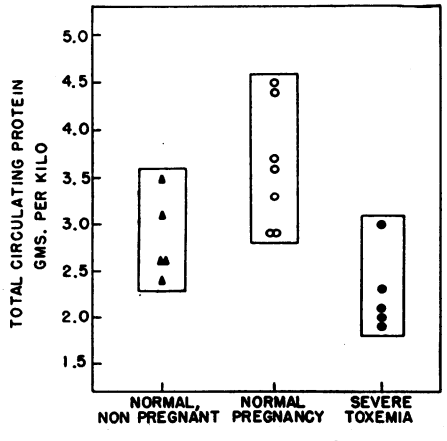

FIG. 3. SHOWING THAT THE TOTAL CIRCULATING PROTEIN IN RELATION TO BODY WEIGHT IS REDUCED IN SEVERE TOXEMIA AS COMPARED TO NORMAL PREGNANCY BUT THAT SOME OVERLAPPING OF INDIVIDUAL CASES OCCURS

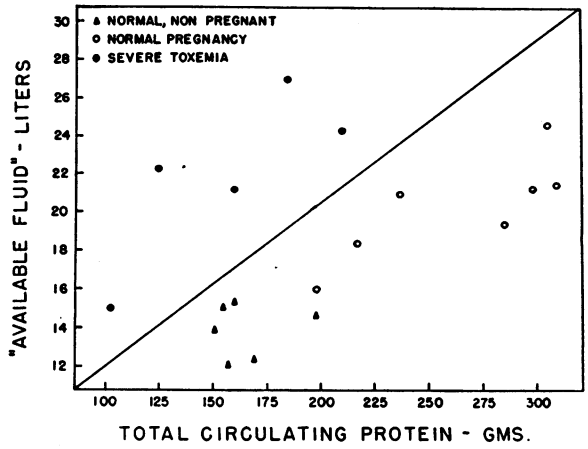

FIG. 4. SHOWING THAT THE RELATIONSHIP BETWEEN TOTAL CIRCULATING PROTEIN AND "AVAILABLE FLUID" RESULTS IN A CLEAR CUT DIFFERENTIATION BETWEEN THE SEVERE PREECLAMPTIC AND ECLAMPTIC PATIENTS AS COMPARED TO THE NORMAL NONPREGNANT AND THE NORMAL PREGNANT INDIVIDUALS

total circulating protein tended to be reduced in the cases of severe preeclampsia and eclampsia, the mean being 2.2 gms. per kilo body weight and the range 1.9 to 3.0. The reduction in total circulating protein was due in part to a reduction in plasma volume and in part to a reduced plasma protein concentration.

When the total circulating protein values were plotted in terms of body weight, as in the case of plasma volume, there was some overlapping of individual cases between the toxemic patients and the patients with normal pregnancy (Figure 3). However, as in the case of plasma volume, a clear distinction between the two groups became apparent in the relationship between total circulating protein and "thiocyanate space" (Figure 4).

Mild preeclampsia

The cases classified on clinical grounds as mild preeclampsia did not demonstrate the above-mentioned changes to such a striking degree (Table IV). These patients manifested edema, hypertension and albuminuria, but did not have the oliguria, headaches, visual scotomata or epigastric pain associated with the more severe forms. They belonged to the category designated as preeclampsia, grade I. The mean plasma volume for these four cases was 55.8 ml. per kilo, the average total circulating protein was 3.0 gms. per kilo and

TABLE IV

Plasma volume, total circulating protein and "available fluid" volume in mild preeclampsia

	Time from delivery	Ht.	Wt.	Plasma volume		Hematocrit value	Total protein	Total circulating protein		"Available fluid"		Ratio
		cm.	*kilo*	*ml.*	*ml./kilo*		*gms. %*	*gms.*	*gms./kilo*	*ml.*	*ml./kilo*	*av. fl./P.V.*
1—P. S.	7 days pre	155	103	4,750	46.0	39	5.7	271	2.6	27,030	262	5.7
	4 days pre		103	4,890	47.4	39	6.3	308	3.0	26,320	255	5.4
	1 day pre		98	4,330	46.3	39	5.7	247	2.5	25,640	274	5.9
	2 days post		91	3,600	40.0	39	6.1	220	2.4	23,800	261	6.5
	9 days post		90	3,500	38.8	40	6.8	238	2.6	22,200	246	6.3
2—V. F.	1 day pre	168	75.5	4,920	65.2	37	5.5	271	3.6			
	5 days post		59	2,408	40.8	42	5.9	142	2.4			
3—M. C.	1 day pre	165	71.4	4,320	60.5	31	5.1	220	3.1	22,050	307	5.1
	8 days post		64.5	3,230	50.0	25	5.9	191	2.9	19,600	304	6.0
4—E. L.	2 wks. pre	165	81.5	4,190	51.5	37	5.7	238	2.9	23,400	287	5.6
Mean					55.8				3.0		285	5.3

the ratio $\frac{\text{"available fluid"}}{\text{plasma volume}}$ was 5.3 in the three cases in which it was determined. It is to be noted that in respect to plasma volume and total circulating protein the first case of this mild group falls into the same category as the severe preeclampsias while the remaining cases fall into the normal group. It would appear that patients with the clinical diagnosis of mild preeclampsia belong to a heterogeneous group in which fluid volume relationships may be normal or slightly abnormal.

The hematocrit value tended to be higher than that usually seen in late pregnancy ranging between 37 and 45 in the group with severe toxemia. However, a close correlation between the degree of depression of plasma volume and the degree of elevation of the hematocrit value was not demonstrated.

DISCUSSION

The disturbed relationship observed between total circulating protein and plasma volume on the one hand and the "available fluid" volume on the other brings into consideration the forces that play a part in membrane equilibria. The following hypothesis is suggested.

In normal pregnancy when edema occurs interstitial fluid pressure rises. This rise upsets the balance between filtration and osmotic pressure so that water and crystalloids move into the plasma, and plasma dilution takes place. However, in normal pregnancy there is, apparently, a response on the part of the organism to add excess protein to the circulation. It will be noted in Figure 4 that those cases of normal pregnancy with the largest "available fluid" volumes also showed the greatest increases in total circulating protein. By the addition of this excess protein plasma oncotic pressure is maintained. As a result despite the edema the relationship of plasma to "available fluid" volume remains approximately the same as in the normal nonpregnant state. Figure 2 reveals such a straight line relationship between the normal nonpregnant individual and the normal pregnant individual.

In contrast to the edematous patient with normal pregnancy, the severely preeclamptic or eclamptic patient who develops edema is apparently unable to maintain the needed excess of circulating protein (Figure 4). Because of this failure, as plasma dilution occurs, plasma protein concentration, and hence, plasma oncotic pressure fall. Strauss has shown this fall in plasma oncotic pressure in preeclamptic and eclamptic patients by actual measurement (3). The result is a relative decrease in plasma volume and a deviation from the normal in the relationship between "available fluid" volume and plasma volume (Figure 2).

The observed abnormalities in fluid volume relationships in late toxemia are in all probability the result rather than the cause of the disease. Nevertheless, it is possible that these alterations may play an important role in certain of its more serious manifestations, such as the oliguria, the

cerebral edema (12, 13, 14) and the occasional termination in vascular collapse (15).

The results of this investigation have delineated two groups of preeclamptic patients: the severe cases who have headaches, visual scotomata, epigastric pain, oliguria, a diminution in plasma volume, total circulating protein, edema, and an elevation of the $\frac{\text{"available fluid"}}{\text{plasma volume}}$ ratio. Cases in the second group exhibit edema, albuminuria and hypertension, but have only mild symptoms referable to the central nervous system and do not tend to develop oliguria. Cases in this latter group may show normal or only slightly abnormal patterns of fluid distribution. These observations are in exact agreement with those of Dieckmann (2).

Additional evidence for the separation of preeclamptic patients into two groups is provided by Boyd (16). He observed that in some of these patients the blood lipid partition pattern was characteristic of eclampsia, while in others the distribution of blood lipids was similar to that observed in normal pregnancy. Boyd suggested that the cases of preeclampsia with an abnormal blood lipid partition are in reality eclampsia without convulsions, while the remaining cases with normal blood lipids are not literally preeclamptic at all. Our observations lend support to the hypothesis that severe preeclampsia and eclampsia are the same disease while many cases of mild preeclampsia belong in a different category. However, because of the relatively small number of cases we have studied and the difficulty in the clinical differentiation between mild and severe preeclampsia these results are to be regarded as suggestive rather than conclusive.

Although it is well recognized that eclampsia may occur in the well-nourished, it is of interest that all of the patients with severe preeclampsia and eclampsia gave histories of poor protein intake. This observation is in agreement with that of Strauss (3) and others (5, 17, 18). The importance of an adequate protein intake in the prophylaxis of the eclamptic toxemias of pregnancy would appear to merit further investigation.

SUMMARY AND CONCLUSIONS

1. Changes in plasma volume, total circulating protein and "available fluid" volume were followed in 4 cases of mild preeclampsia, 3 cases of severe preeclampsia and 2 cases of eclampsia; and were compared to the changes observed in 7 cases of normal pregnancy and 6 normal nonpregnant females.

2. The cases of severe preeclampsia and eclampsia revealed an abnormal reduction in plasma volume, and total circulating protein, in respect to "available fluid" volume.

3. Cases classified clinically as mild preeclampsia were made up of a heterogeneous group, some of which showed slight changes in fluid and protein distribution characteristic of eclampsia, others exhibiting changes typical of normal pregnancy.

4. It is suggested on the basis of the admittedly small series of cases that severe preeclampsia and eclampsia are characterized by an abnormal fluid distribution in which a deficiency of total circulating protein may play an important role.

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