Mechanisms Regulating the Renal Excretion of Sodium during Pregnancy

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ABSTRACT Observations were made on the relation of the renin-angiotensin-aldosterone system and renal hemodynamic function to sodium balance in 43 pregnant dogs. Daily balance studies revealed that about 30–40% of ingested sodium was retained during the last half of pregnancy; during the same period, potassium balance was also positive but to a lesser extent. For groups of pregnant dogs, plasma renin activity ($n = 14$) and aldosterone secretion ($n = 19$) were significantly higher than normal; however, in some animals one or both functions were normal even though sodium retention was present. In contrast, plasma renin substrate concentration was consistently elevated during pregnancy in seven dogs. In a group of nine dogs in which both aldosterone secretion and plasma renin activity were measured, aldosterone secretion was elevated in the three dogs with the highest values for plasma renin activity; in two of the remaining six animals aldosterone secretion was elevated but plasma renin activity was normal or only slightly increased. The sequestration of sodium and water into the uterine contents was defined quantitatively in this study but evidence was lacking to support the idea that such changes led to renin release. The glomerular filtration rate (GFR) was significantly elevated throughout pregnancy but a significant decrease from the high level of mid-pregnancy occurred during the last half of pregnancy; this decrease in GFR probably contributed to the sodium retention. Administration of a large dose of deoxycorticosterone acetate (DOCA) to dogs in late pregnancy produced marked sodium retention but "escape" from the sodium-retaining steroid occurred. The data demonstrate that although increased activity of the renin-angiotensin-aldosterone system was frequently present during pregnancy, a normal rate of aldosterone secretion occurred. This finding and the observed "escape" from DOCA suggest the existence of sodium-retaining mechanisms other than the mechanism provided by a high plasma level of aldosterone.

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INTRODUCTION

This study was begun to help clarify the role of the renin-angiotensin-aldosterone system in sodium homeostasis during normal pregnancy. There is a paucity of electrolyte balance data from observations during pregnancy in women, and results from studies of plasma renin activity in pregnant women are conflicting. Some investigators (1–5) have reported that plasma renin activity is increased during normal pregnancy while others (6, 7) were unable to detect a difference in plasma renin activity in normal pregnant, as compared with nonpregnant, women. Also, in most series of measurements of plasma renin activity in pregnant women, a substantial number of normal values has been reported. On the other hand, aldosterone secretion was elevated in nearly all of a large series of pregnant women during the last trimester of pregnancy (8). Thus, the available data suggest that mechanisms other than increased activity of the renin-angiotensin system are responsible for hyperaldosteronism and sodium retention during pregnancy.

Observations were conducted in the dog so that more complete investigation could be made than is possible in pregnant women. Since daily sodium and potassium balances have not been measured throughout pregnancy in women, such observations were made during most of pregnancy in a large series of dogs. Plasma renin activity was measured and related to aldosterone secretion and sodium retention. The sequestration of sodium and water in the uterine contents was studied in an effort to determine how this phenomenon might relate to the increase in plasma renin activity. Renal hemodynamic function was determined throughout pregnancy and during the postpartum period to evaluate changes in relation

to sodium retention. Finally, the responsiveness of the renal tubules to large doses of deoxycorticosterone was investigated in late pregnancy to evaluate the role of the extra-adrenal sodium-retaining factor (9) in pregnancy.

METHODS

Experiments were conducted in 43 pregnant mongrel dogs and in 12 normal female mongrels weighing 16–25 kg. The animals used to study pregnancy were bred in the animal quarters and breeding dates recorded. The dogs were placed in metabolic balance cages and allowed 3–5 days to adjust to their new environment and diet. They were fed a diet of commercial canned dog food which contained 63–67 mEq/day of sodium and 55–58 mEq/day of potassium; water was allowed *ad libitum*. The dog food was prepared in batches and five to six cans of each batch were analyzed for sodium and potassium. There was a slight variation among batches and this is reflected in the range from 63–67 mEq/day for sodium and 55–58 mEq/day for potassium. Balance studies were begun during the 2nd or 3rd wk of pregnancy. Food was given in the afternoon and experimental procedures such as collection of urine, venipuncture, and renal clearances of creatinine (C_{Cr}) and para-aminohippurate (C_{PAH}) were done during the morning with the animals in the postabsorptive state. Three renal plasma clearance determinations were made each time renal function was studied; the infusion was given at a low rate (0.5 ml/min) to prevent hydration and the experimental procedure was identical with that used previously (10) in normal dogs. Blood samples were obtained from a peripheral vein at frequent intervals for measurement of plasma renin activity. The uterus and its contents were removed on approximately the 55th day of pregnancy and homogenized in a Waring Blendor. Pregnant dogs were given a large dose (15 mg/day) of deoxycorticosterone acetate (DOCA) intramuscularly for 5 days to examine the responsiveness of the renal tubules to mineralocorticoid excess; DOCA was injected during the 6th or 7th wk of pregnancy.

Plasma and urinary electrolytes and electrolytes from the homogenate of the uterine contents were measured with a flame photometer; from the homogenate, a filtrate was prepared by an acid extraction technique from 5 ml of nitric acid and 5 ml of sulfuric acid per 10 g of homogenate. Plasma renin activity was measured by a technique described by Schneider, Rostorfer, and Nash (11); a 3 hr incubation was done and values for plasma renin activity represent the angiotensin II formed per milliliter of plasma during this incubation period. Renin substrate was determined by a method described elsewhere (12). Creatinine and PAH were measured by routine colorimetric procedures.

Dogs that were near the end of pregnancy were anesthetized with pentobarbital sodium and the left adrenolumbar vein was cannulated for collection of adrenal vein blood. The concentrations of aldosterone and corticosterone were determined in adrenal vein plasma by the double isotope derivative assay technique of Kliman and Peterson (13).

RESULTS

Electrolyte balance studies. The average onset of sodium retention in 10 pregnant dogs occurred during the 4th wk of gestation (Fig. 1). The average rate of renal sodium excretion from the 11th to the 27th day of pregnancy was 55.7 ±3.0 SEM mEq/day on a sodium intake of 67 mEq/day; during the next 28 days of pregnancy renal sodium excretion was reduced to 38.3 ±3.1 mEq/day on essentially the same sodium intake ($P < 0.001$). Similarly, renal potassium excretion fell from 55.0 ±2.5 mEq/day for early pregnancy to 45.9 ±1.6 mEq/day for the last part of pregnancy ($P < 0.05$) (Fig. 1). In this group of dogs, pregnancy was usually terminated by removal of the uterus and its contents. Sodium balance gradually returned to the normal control level during the first 10–15 days of the postpartum

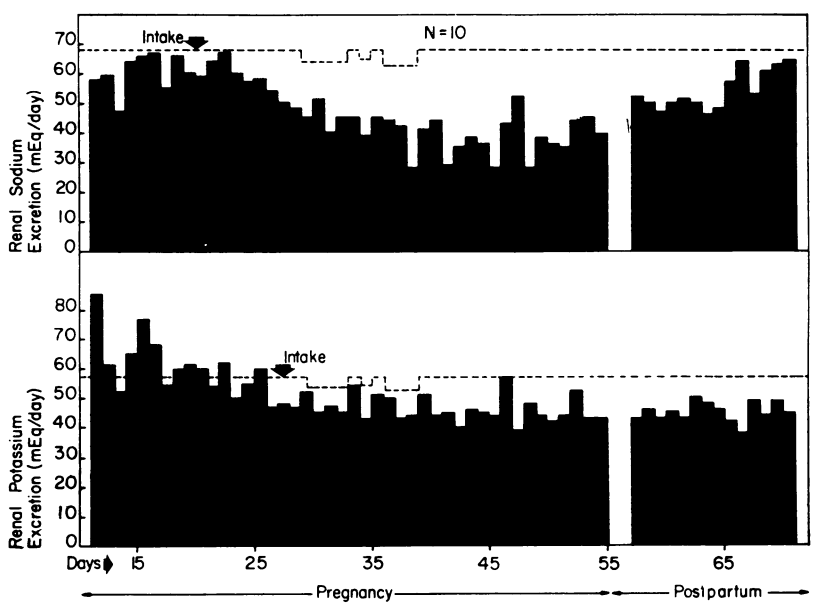

FIGURE 1 Renal sodium and potassium excretion in 10 pregnant dogs.

TABLE I

Electrolyte Content of the Pregnant Uterus with Its Contained Fetuses and Fluid

Dog No.	Initial body wt	Total Na content	Total K content	Wt of uterine contents	Na/kg of uterine contents	K/kg of uterine contents	Na retained during pregnancy	Uterine Na / Na retained × 100
	kg	*mEq*	*mEq*	*kg*	*mEq/kg*	*mEq/kg*	*mEq*	%
1	21.0	232	78	2.5	93	31	508	46
2	—	218	50	2.12	103	25	—	—
3	18.4	118	40	1.04	113	37	—	—
4	16.6	176	51	1.76	100	29	648	27
5	20.4	354	116	3.64	97	32	487	73
6	—	348	166	4.00	87	41	—	—
7	17.4	295	137	3.30	90	50	352	84
8	23.7	209	70	2.08	100	30	579	36
9	21.6	332	155	3.92	85	40	477	70
Mean	19.9	253.6	95.9	2.7	96.4	35.0	508.5	56
±SEM	0.4	9.2	5.4	0.1	1.0	0.9	16.7	3.8

period, but urinary potassium excretion remained low. In another group of pregnant dogs studied to relate plasma renin activity and sodium balance (Fig. 3), a similar decline in potassium excretion occurred; no postpartum observations were made for this group.

The relationship between the total quantity of sodium retained during pregnancy and the quantity sequestered by the uterus with its contained fluid and fetuses was determined (Table I). Sodium balance data were obtained on six of nine dogs in which uterine electrolyte studies were done. The sodium and potassium present in the uterus and the contents of the uterus were 96.4 ±1.0 and 35.0 ±0.9 mEq/kg of wet weight, respectively. The total sodium content of the uterus, fetuses, and amniotic fluid was 56 ±3.8% of the sodium retained by the kidney during pregnancy. Since this value seemed low, fecal electrolyte excretion was measured (Table II) in the second group of pregnant dogs (Fig. 3) and the data on fecal sodium excretion were included in a more definitive evaluation of sequestered sodium. There was no significant change in fecal sodium or potassium excretion during pregnancy and the values are not significantly different from the data reported for normal dogs (10). The average value of fecal sodium excretion of 6 mEq/day was used to make a more accurate calculation of the amount of sodium retained in the uterine contents during pregnancy. Thus, sodium retention was reduced from 508 to 334 mEq during pregnancy and uterine sodium was 79.6% of the sodium retained from external balance data.

TABLE II

Fecal Electrolyte Excretion in Pregnant Dogs during the 4th to 8th wk of Gestation

	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8
Sodium, *mEq/day*	5.7 ±2.0 (5)	6.7 ±1.7 (7)	6.5 ±1.6 (6)	6.1 ±0.3 (4)	5.6 ±1.2 (5)
Potassium, *mEq/day*	2.5 ±0.8 (5)	3.6 ±0.9 (7)	3.2 ±0.7 (6)	2.8 ±0.4 (4)	2.5 ±0.6 (5)

Plasma renin activity and renin substrate concentration. In another group of 14 pregnant dogs, plasma renin activity was elevated in comparison with that of a group of 12 normal dogs studied at the same time and under the same conditions (Fig. 2). This average value for the pregnant group is the mean of the average value recorded for each dog from several measurements at different intervals during pregnancy. Plasma renin substrate was also increased during pregnancy (Fig. 2); an analysis of individual values revealed that all values

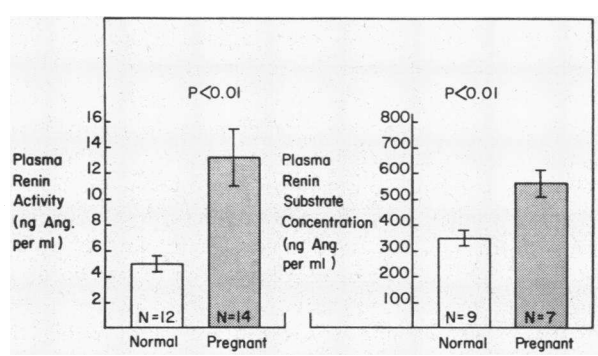

FIGURE 2 Plasma renin activity and plasma renin substrate concentration in normal and pregnant dogs. N represents No. of dogs.

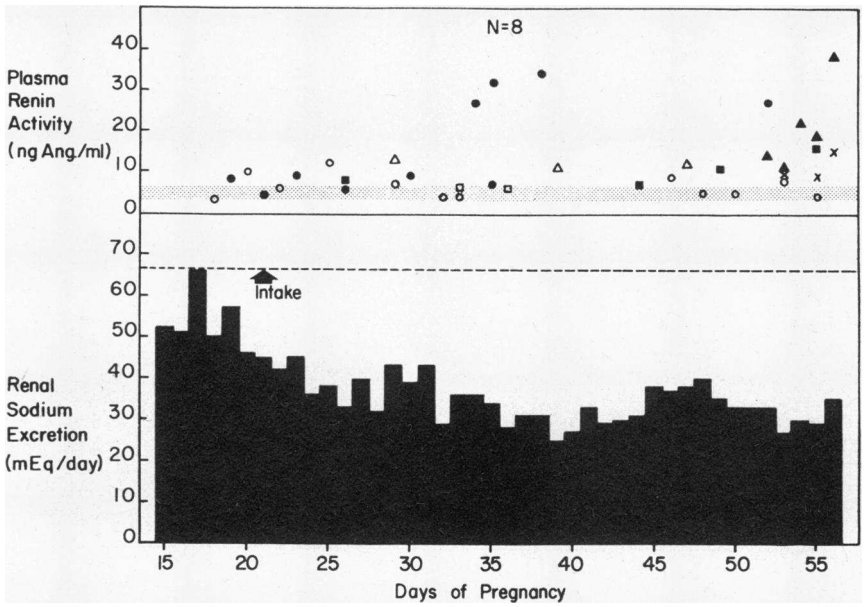

FIGURE 3 Relation of plasma renin activity to renal sodium excretion during pregnancy. The dotted band for plasma renin activity represents the mean ± the standard deviation for a group of normal dogs. Individual values are presented for plasma renin activity in eight different dogs for different times of pregnancy.

for plasma renin substrate concentration in pregnant dogs were above the highest normal value. The highest renin substrate values were not necessarily associated with the highest plasma renins, and elevated values for renin substrate occurred with normal values for plasma renin activity.

The relation of repeated measurements of plasma renin activity to renal sodium excretion at various times during pregnancy in 8 of these 14 dogs is presented in Fig. 3. Most of the elevated values for plasma renin activity were observed during the last half of pregnancy. More important perhaps is the finding that plasma renin activity was repeatedly normal in one of the eight dogs during the last trimester of pregnancy and was only slightly elevated in two other animals; these changes occurred in the presence of sodium retention.

Steroid secretion. The rates of aldosterone and corticosterone secretion were studied near the end of pregnancy (Table III). Duplicate samples were collected in 18 of the dogs and four samples were obtained in the remaining animal (dog 6). There is excellent agreement between the duplicate samples and among the four values in dog 6 for aldosterone secretion. For the group of 19 pregnant dogs, the average value for aldosterone secretion of 40.5 μg/min was significantly higher than the average normal value of 20 μg/min ($P < 0.02$). In 9 of the 19 dogs (Nos. 2, 4, 6, 9, 13, 14, 16, 17, and 19), aldosterone secretion was higher than the average control value for normal dogs by at least 4 times the SEM for the normal dogs; these normal animals were studied with the same sodium intake, at the same time, and under comparable conditions. However, aldosterone secretion in the remaining 10 pregnant dogs (Nos. 1, 3, 5, 7, 8, 10, 11, 12, 15, and 18) was not elevated. Neither corticosterone secretion nor adrenal blood flow was increased during pregnancy.

Relation of plasma renin activity to aldosterone secretion. In 9 of the 14 pregnant dogs in which plasma renin activity was measured, studies of aldosterone secretion were made (Table IV). The three highest values for plasma renin activity (dogs 4, 6, and 9) were associated with an elevation in aldosterone secretion. In the two remaining animals with a high rate of aldosterone secretion (dogs 3 and 7) plasma renin activity was 6 and 9 ng of angiotensin formed per ml of plasma and these values are within the normal range. For this group of nine pregnant animals both plasma renin activity and aldosterone secretion were significantly elevated above normal ($P < 0.01$ and $P < 0.05$ respectively).

Renal hemodynamic function. In 7 of the 10 pregnant dogs used in the first balance study (Fig. 1), glomerular filtration rate (GFR) decreased from the 4th to the 7th wk ($P < 0.01$) (Fig. 4). Similar directional changes in effective renal plasma flow (ERPF) were observed from the 4th to the 7th wk but the values were not statistically different ($P > 0.2$). The 2–3 wk postpartum

TABLE III

Steroid Secretion in Dogs

Dog No.	Aldosterone secretion	Corticosterone secretion	Adrenal blood flow
	μg/min	*μg/min*	*ml/min*
Dogs near termination of pregnancy			
1	18	5.93	7.50
	24	8.19	5.99
2	57	4.81	3.33
	42	7.45	3.75
3	26	7.16	3.00
	25	6.17	3.00
4	68	3.73	3.08
	80	3.90	4.00
5	15	5.30	8.00
	17	3.87	9.50
6	55	8.40	7.50
	48	8.45	6.67
	73	8.87	6.00
	55	8.80	5.00
7	18	5.88	4.60
	24	5.45	4.90
8	28	4.73	4.37
	28	4.91	4.27
9	35	4.73	4.50
	33	5.53	4.83
10	17	3.48	3.03
	18	3.39	3.10
11	29	3.98	12.00
	24	5.66	11.30
12	9	3.33	3.6
	13	3.29	3.5
13	42	7.20	8.2
	38	6.80	7.9
14	123	11.29	8.2
	111	10.39	7.3
15	19	3.17	4.40
	15	2.90	3.20
16	83	8.09	2.50
	68	6.71	2.40
17	78	6.65	12.60
	82	6.04	12.30
18	12	5.35	10.80
	11	5.58	10.20
19	47	3.33	2.40
	43	3.90	2.40
Mean	40.5	5.67	5.87
SEM	±6.6	±0.46	±0.73
Normal dogs (7)			
Mean	20	3.92	6.39
SEM	±3.0	±0.82	±0.94

TABLE IV

Plasma Renin Activity and Aldosterone Secretion

	Dog No.	Plasma renin activity ng angiotensin/ml	Aldosterone secretion *μg/min*
Pregnant dogs			
	1	8	27
	2	11	11
	3	6	40
	4	22	117
	5	9	17
	6	26	76
	7	9	80
	8	5	12
	9	16	45
Normal dogs			
	Mean	5.1	20
	SEM	0.5	3
	No. of dogs	12	7

value for GFR did not differ from the 7 wk value during pregnancy and it, too, was significantly lower than the 4 wk value. Postpartum ERPF was not significantly different from the 4th or 7th wk value (Fig. 4). Filtration fraction (FF) was 38.4% for the 4th wk of pregnancy and 36.5% for the 7th wk.

Renal "escape" phenomenon in pregnant dogs. It is well known that the renal tubules of patients and animals with secondary aldosteronism are unusually responsive to the sodium-retaining action of mineralocorticoid hormones (9). To examine the possibility that this mechanism is present in pregnancy and contributes to sodium retention, we gave 15 mg/day of DOCA to four dogs during the last part of pregnancy. The results are presented in Table V. During the control observations the rate of renal sodium excretion was similar to that observed for the pregnant dogs in Figs. 1 and 3. During DOCA administration, the degree of sodium retention was greater for the first 1–2 days but all four animals escaped from the sodium-retaining action of the steroid. The recovery period was characterized by loss of the excessively retained sodium so that a negative sodium balance resulted. Renal potassium excretion failed to increase with DOCA. Plasma potassium concentration was studied in three of the four dogs; a slight decrease occurred in two of the three dogs whereas no change was observed in the third animal. In one of the four dogs fecal potassium excretion was measured and it increased from 2.7 mEq/day during the control period to 13.7 mEq/day during DOCA injection. Consequently, the slight decrease in plasma potassium concentration

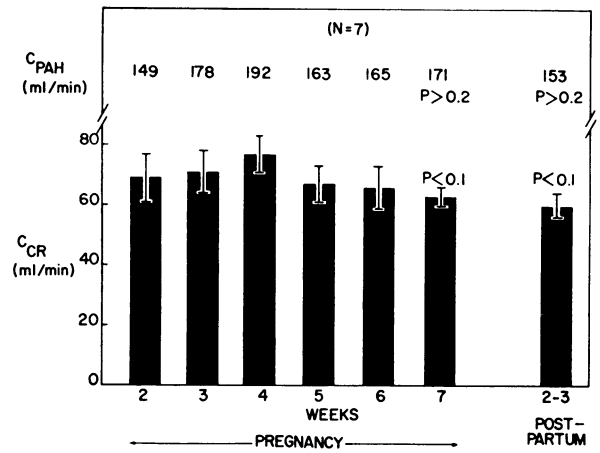

FIGURE 4 Renal hemodynamic function during pregnancy and the postpartum period in seven dogs. The *P* values are for comparison of data from the 4th wk of pregnancy with the values obtained during the 7th wk of pregnancy and the postpartum period.

probably reflects fecal loss of potassium. A marked increase in fecal potassium excretion has been a consistent finding in previous studies of the effect of DOCA in normal dogs (10).

DISCUSSION

There are reports (14, 15) of estimates of the degree of sodium retention in women especially during the last trimester of pregnancy but no quantitative sodium balance data are available to define the magnitude of the change. In the rat, Lichton (16) reported that sodium is retained throughout pregnancy but the only quantitative information provided was that 83 mEq of Na were retained per kg of weight gain. In the present study in pregnant dogs, electrolyte balance data were obtained and positive sodium and potassium balances were observed during the last half of pregnancy.

The question arises as to locus of sequestration of the retained salt and water. Is this limited to the uterus and its contents, or is there expansion of the maternal extracellular fluid and, possibly, the intracellular pool of sodium? Lichton (16) was able to account for all retained sodium in the uteri with their contained fetuses and fluid in pregnant rats. Also, measurements of sodium excretion in the postpartum period for these rats revealed further slight retention of sodium rather than sodium loss. The present data show that in the dog the average amount of sodium present in the uterus with its contents was 79.6% of that retained during pregnancy. This figure is undoubtedly low because balance errors are usually in the positive balance direction. In view of the error inherent in balance measurements, it is not possible to state that maternal sodium retention occurred; indeed, it is conceivable that all of the sodium retention was fetal. In pregnant women, of course, the occurrence of dependent edema is common. There is no evidence for intracellular accumulation of sodium in maternal tissues.

The present study was undertaken to investigate the mechanisms leading to sodium retention during pregnancy. Three possibilities have been evaluated, namely, (*a*) increased activity of the renin-angiotensin-aldosterone system, (*b*) a decrease in GFR and RPF, and

TABLE V

Effects of DOCA Administration on Renal Electrolyte Excretion in Pregnant Dogs

Dog No.	Control period			DOCA administration, 15 mg/day					Recovery period			
Renal sodium excretion in mEq/day*												
1	35	26	41	14	41	55	51	42	94	73	33	20
2	17	40	31	13	4	5	21	41	90	76	59	46
3	21	34	30	14	15	29	28	37	31	20	46	17
4	38	38	24	30	22	39	31	52	72	73	95	56
Mean	28	35	32	18	21	32	33	43	72	61	58	35
Renal potassium excretion in mEq/day*												
1	36	22	63	42	56	38	44	38	29	34	55	54
2	48	56	56	48	29	20	27	47	12	18	39	62
3	19	23	17	26	12	20	16	27	21	9	31	19
4	58	50	34	56	29	26	31	42	42	33	29	45
Mean	40	38	43	43	32	26	30	39	26	24	39	45

* Sodium and potassium intake was 63 and 55 mEq/day respectively.

(*c*) increased responsiveness of the renal tubules to the mineralocorticoid activity of aldosterone.

The renin-angiotensin system during pregnancy. In most of the reports of plasma renin activity in pregnant women (1–7), either the level of sodium intake was not stated or the women were on an unrestricted diet. In the series of 38 measurements by Brown, Davies, Doak, Lever, and Robertson (1), 18 of the 38 values for plasma renin were within the normal range. In the study of Gordon, Fishman, and Liddle (7), the range of values for plasma renin activity in normal women (360–1480 ng/100 ml) and in normal pregnant women (860–1515 ng/100 ml) did not differ appreciably and no statistics were reported to demonstrate that plasma renin activity was elevated during pregnancy. Maebashi et al. (6) found no difference in plasma renin activity in 11 normal pregnant women (0.82 ng/ml per 2 hr incubation ±0.43 SD) at 36–40 wk of gestation and in 18 normal nonpregnant women (0.97 ng/ml per 2 hr incubation ±0.54 SD). Geelhoed and Vander (5) reported a fall in plasma renin activity from the level observed before parturition to a postpartum level. Helmer and Judson (4) reported increased plasma renin activity during normal pregnancy; it was suggested that this change resulted primarily from increased plasma renin substrate concentration which was produced by increased estrogens. These variable results and the lack of adequate dietary control indicated the need for a reinvestigation during pregnancy.

The present data on plasma renin activity in pregnant dogs confirm those of Hodari, Bumpus, and Smeby (17), and Hodari and Hodgkinson (18). Plasma renin activity was frequently elevated and the increase for the group was statistically significant; it seems unlikely that the occasional normal value observed was related to the level of sodium intake since this was constant. Also, our earlier studies (12, 19) have been done at this level of sodium intake and there was no evidence that it depresses plasma renin activity. Consequently, the findings in dogs and the observations on women suggest that plasma renin activity varies from a normal level to an elevated one during pregnancy.

The mechanism of the increase in plasma renin activity during pregnancy has not been delineated. In the present study it was postulated that sequestration of ingested sodium and water to fill the uterine contents might stimulate renin release. It has been demonstrated (20) that adrenal zona glomerulosa hypertrophy and hypersecretion of aldosterone are associated with sequestration of sodium and water into the rapidly growing Walker sarcoma in rats. The present results provide quantitative data on the extent of sodium sequestration by the uterus, fetuses, and amniotic fluid. Since the data do not exclude some expansion of the extracellular fluid volume in the maternal tissues, evidence is lacking to support the idea that sequestration of salt and water by the uterus led to renin release.

The elevated plasma level of estrogens during pregnancy probably contributes to the increase in plasma renin activity. However, the certainty and extent to which estrogens increase plasma renin activity during pregnancy remain unknown. During oral contraceptive therapy to women, Newton, Sealey, Ledingham, and Laragh (21) found that plasma renin activity was elevated in only about half of the cases; and in the dog, 17 β-estradiol administered to normal animals produced only a slight increase in plasma renin activity that lasted only 1–2 days (personal observations). Newton and associataes (21) reported that an initial increase in plasma renin activity occurred, but within a few days plasma renin activity frequently returned toward or to normal; this was explained on the basis of a negative feedback mechanism. They postulated that the actual plasma renin level may have been depressed below normal but that normal or elevated plasma renin activity was maintained by an elevated renin substrate level. Newton and associates (21) suggested that the generation of increased amounts of angiotensin II by plasma from patients receiving estrogens was due to the increase in the renin substrate concentration in plasma. It is possible that similar changes occur during pregnancy and lead to generation of an increased amount of angiotensin II as reported by Newton et al. (21) during oral contraceptive therapy to women. However, the high values for plasma renin activity in pregnant dogs were not consistently associated with the highest values for renin substrate, and elevated plasma renin substrate was sometimes associated with normal values for plasma renin activity.

Aldosteronism during pregnancy. There have been several reports of increased aldosterone excretion in urine and of hypersecretion of aldosterone by normal pregnant women. Jones et al. (22) found an increase in the daily rate of aldosterone production in only three of the six pregnant women on a normal uncontrolled diet. In the most extensive study, Watanabe, Meeker, Gray, Sims, and Solomon (8), measured aldosterone secretion in 57 normal pregnant women 23–32 yr of age; dietary sodium intake was estimated to range from 80 to 190 mEq/day. The results revealed a high rate of aldosterone secretion during the 3rd trimester of pregnancy in nearly all the women. The rate of aldosterone metabolism has been reported (22) to be normal in pregnancy, so increased secretion of the hormone appears to be the only mechanism leading to hyperaldosteronemia in pregnancy.

In the present study, aldosterone secretion in pregnant dogs, was significantly elevated for the group of

19 animals. However, it is clear that the rate of aldosterone secretion was normal in 10 of the 19 pregnant animals. The duplicate values in individual dogs are in good agreement. For the group of 19 animals, corticosterone secretion and adrenal blood flow were normal.

The mechanism for the hyperaldosteronism of pregnancy is not completely understood. In pregnant women it has been suggested (1–4) that the renin-angiotensin system augments aldosterone secretion and the present data suggest that this is one of the mechanisms in the dog. In nine pregnant dogs in which both plasma renin activity and aldosterone secretion were measured, aldosterone production was elevated in the three dogs with a high plasma renin. However, results in the other two dogs with hyperaldosteronism and a normal plasma renin activity indicate that other mechanisms are also involved. Failure of a correlation of renin and aldosterone does not appear to be related to the effects of anesthesia and surgery; in the two pregnant dogs with normal plasma renin activity (Table IV), the values for aldosterone secretion were extremely high and outside the range for normal values obtained under the same conditions for collection of adrenal vein blood. As pointed out earlier, there is considerable evidence that the activity of the renin-angiotensin system is not consistently increased during the pregnancy in women. In a recent report (23) both estriol and estradiol increased aldosterone secretion in normal nonpregnant women. These considerations raise the question of the possible role of estrogens in increasing aldosterone secretion by a nonrenin mechanism. There is also the possibility of a decrease in renin metabolism by the liver (19) as a contributory mechanism to the high plasma renin activity, but no data are available on this point. There remains the question of whether the high plasma level of estrogens achieved during exogenous hormone administration is present during pregnancy. In other words, the steroid response to estrogens in humans could represent a pharmacological response, and estrogens might not be sufficiently elevated during pregnancy in women to contribute to the hyperaldosteronism.

A possible correlation has been sought (22) between elevated GFR and increased aldosterone secretion during pregnancy in women but the evidence is negative. The hypothesis arose from the idea that an increase in GFR could lead to salt loss and, thus, more aldosterone might be secreted and sodium balance partially achieved. There are, however, no data in pregnant women or dogs to show that sodium balance is negative even for short periods of time.

It has also been proposed that the increased plasma level of progesterone of pregnancy might increase aldosterone secretion (8). Administration of progesterone to normal human subjects produced a slight natriuresis (24, 25). However, it is not clear how progesterone could produce hyperaldosteronism if sodium balance is always positive rather than negative during pregnancy. Also, Landau, Plotz, and Lugibihl (26) failed to observe a natriuresis in pregnant women during exogenous progesterone administration. The initial natriuresis and associated increase in aldosterone secretion observed by Laidlaw, Ruse, and Gornall (27) during progesterone administration to normal human subjects are understandable but sodium retention then ensued while the high rate of aldosterone production continued. It appears, therefore, that during progesterone administration some other mechanism stimulates aldosterone secretion after the initial natriuresis.

Renal hemodynamic function during pregnancy. Another mechanism that might influence sodium excretion during pregnancy is a change in GFR with an influence on renal tubular reabsorption of sodium. Extensive studies of GFR and RPF in pregnant women by Sims and Krantz (28) revealed that GFR was increased 50% throughout pregnancy whereas RPF was only 25% above normal and declined to the control level during the last trimester of pregnancy. Filtration fraction was elevated throughout pregnancy and was 40% at term. These observations confirmed the earlier data of Bucht (29).

The present renal hemodynamic data in pregnant dogs were compared with the average values for normal female mongrel dogs of the same weight studied under almost identical conditions of sodium intake, postabsorptive state, and hydration (30). Pregnant animals had an elevated GFR throughout pregnancy and even during the postpartum period. Filtration fraction was consistently elevated throughout pregnancy in the dog but there was no evidence of a further increase during the last half of pregnancy when sodium retention occurred. This finding provides evidence against the idea that an increase in postglomerular plasma oncotic pressure is operative to promote sodium retention.

In the pregnant dogs used in this study, there was a progressive significant decline in GFR from the 4th to the 7th wk of pregnancy. Such a decline in GFR could have contributed to the decrease in sodium excretion observed during the last half of pregnancy. That factors other than the level of GFR are involved in the sodium retention of pregnancy is indicated by the finding of the same level of GFR in the postpartum period and in the 7th wk of pregnancy; sodium balance was normal during the postpartum period.

Extra-adrenal sodium-retaining mechanisms and the influence of estrogens. There are two groups of extra-adrenal mechanisms which could conceivably increase fractional renal tubular reabsorption of sodium during pregnancy and promote sodium retention. First, it is

possible that estrogens act directly on the renal tubules to influence sodium reabsorption. Second, there is the possibility of additional sodium-retaining factors (9) which act with aldosterone or with estrogens to promote sodium retention during pregnancy.

The second hypothesis was examined in the present study and the pregnant dogs escaped from the sodium-retaining action of DOCA. While the renal response of sodium excretion to DOCA was essentially normal, the usual renal loss of potassium which occurs in normal dogs given DOCA (10) was not observed. The explanation for the failure of kaluresis to occur is not clear. Maintenance of potassium balance and lack of hypokalemia during DOCA administration are frequently associated with marked sodium retention, and they presumably result from lack of delivery of sodium to the distal tubular exchange mechanism (9). This is not the explanation here since sodium excretion returned to the control level or above during DOCA injection.

During pregnancy, the retention of sodium occurred in some dogs in the presence of normal plasma renin activity and a normal rate of aldosterone secretion. The level of GFR was no lower in late pregnancy than during the postpartum period, and the response in renal sodium excretion to DOCA appeared to be normal. By exclusion, therefore, other sodium-retaining mechanisms seem to be involved in late pregnancy. A possible mechanism is the presence of a high plasma level of estrogens which could, as pointed out above, have a direct influence on the renal tubules. The mechanisms by which estrogens influence renal sodium excretion are unknown, and the precise role of estrogens in the sodium retention of pregnancy remains an unresolved problem.

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