Plasma progesterone and aldosterone in pregnancy

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Summary: Plasma progesterone, aldosterone and renin activity were measured simultaneously in seven women during normal pregnancy. Beginning at the 2nd trimester and until approximately 4 weeks before delivery there was a constant increase in plasma progesterone concentration. There was a significant correlation between weight gain and duration of pregnancy and between weight gain and plasma progesterone concentration. There was also an increase in plasma aldosterone concentration although this was less consistent than that of progesterone. And there was a significant correlation between plasma progesterone and aldosterone concentrations and between the progesterone/aldosterone ratio and duration of pregnancy and weight gain.

Résumé: Les déterminations simultanées du taux plasmatique de la progestérone et de l'aldostérone ainsi que de l'activité de la rénine plasmatique ont été effectuées chez sept femmes avec une grossesse normale. Une augmentation constante du taux de la progestérone a été mise en évidence à partir du 2e trimestre et jusqu'à environ 4 semaines avant l'accouchement. Une corrélation significative entre la prise de poids et la durée de la grossesse et entre le taux de progestérone plasmatique et la prise de poids a été observée. Nous avons aussi observé une augmentation du taux de l'aldostérone plasmatique, moins importante cependant que celle de la progestérone. Nous avons pu mettre en évidence des corrélations significatives entre les taux plasmatiques de progestérone et d'aldostérone et entre le rapport progestérone/aldostérone, la durée de la grossesse ainsi que la prise de poids.

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Various endocrine changes take place at different stages of normal human pregnancy. There is general agreement that plasma renin activity (PRA) and concentration are frequently, but not invariably, increased in pregnancy and that the concentration of plasma renin substrate (PRS) is consistently elevated above the normal nonpregnant range.[1,2] This pattern is similar to that of plasma estradiol in pregnancy. Estradiol and other estrogens stimulate the hepatic synthesis of PRS.

Pregnancy is also associated with increased production of aldosterone,[3,4] which is derived mostly from the maternal adrenal glands, with a minimal contribution from the fetus.[5]

The stimulation of the renin-angiotensin-aldosterone axis in early pregnancy is possibly a consequence of maternal sodium depletion resulting from an increase in glomerular filtration rate, which in turn is a result of increased renal blood flow. This blood flow decreases progressively during most of the 3rd trimester, with the filtration rate decreasing only in the last month.[1] Other findings indicate a dramatic decrease in plasma progesterone and increase in estradiol concentrations during the last 5 weeks of human pregnancy.[6]

Evidence suggests that part of the increase in aldosterone secretion is secondary to sodium loss induced by the increased progesterone secretion, which antagonizes aldosterone action at the renal tubular level.[7] This part of the increase in aldosterone secretion may appear, therefore, as a homeostatic adjustment, at least during the 2nd and the beginning of the 3rd trimester of pregnancy, to the increase in progesterone production, in order to maintain normal sodium balance.

Another factor that must be taken into account is the sodium-retaining property of estrogens and the possibility that estrogens stimulate directly renal production of renin.[8]

The present study was designed to measure simultaneously plasma aldosterone, progesterone and renin activity in order to understand their relationship during the course of normal pregnancy.

Subjects and methods

Seven normal pregnant women without edema, history of toxemia, hypertension, proteinuria or excessive obesity were studied by means of simultaneous measurements of plasma progesterone, aldosterone and renin activity on three occasions during pregnancy: (a) between the 12th and 25th weeks of pregnancy, (b) between the 25th and 34th weeks

and (c) between the 34th and 40th weeks. A fourth sample was taken 2 to 5 days post partum. The time of gestation was calculated from the last menstrual period. All deliveries were normal and at term and no babies presented any abnormality. The diet was a liberal one, although the subjects were asked to avoid excessive intake of food and salt. It has been shown that plasma aldosterone concentration is similar in normal subjects on random or controlled diet.[9,10]

Blood samples were taken with the subjects in the recumbent position between 10:30 am and 11:30 am in an outpatient obstetric clinic.

Plasma progesterone was measured by protein-binding assay[11] after purification by a procedure developed in our laboratory. After addition of an internal standard, aliquots of 0.3 ml (during pregnancy) or 2 ml (post partum) of heparinized plasma were extracted with 30 or 40 ml, respectively, of dichloromethane. The organic phase was washed successively with sodium hydroxide, acetic acid and distilled water. Purification of the extract was achieved by Sephadex LH-20 chromatography in a system consisting of isooctane:benzene:methanol in a ratio of 80:10:5. The fraction corresponding to the mobility of the orange band of Sudan-3 dye was collected and used for protein-binding assay. Mean recovery measured in duplicate was 51% (n = 56), with a percentage of variation of 9.5 (n = 12) and 5.7 (n = 6) for interassay and intra-assay, respectively. Included in each series of determinations were two control samples of steroid-free plasma (steroids having been removed by a charcoal adsorption technique) to which 3 and 6 ng, respectively, of progesterone had been added. Mean values (± SD) obtained (n = 14) were 3.17 ± 0.5 ng and 5.9 ± 0.5 ng, respectively. Blank was not distinguishable from 0.

Plasma aldosterone was measured by a radioimmunoassay technique developed in our laboratory[9] and PRA by the method of Boucher *et al.*[12]

Results

Details concerning each patient and the results of the measurements of plasma progesterone, aldosterone and renin activity are shown in Table I. The plasma progesterone value increased consistently throughout pregnancy, especially in the 3rd trimester, with a significant correlation with the duration of pregnancy ($r = 0.884$, $P < 0.001$) (Fig. 1). The value decreased abruptly just after delivery. There was a significant correlation between weight gain and duration of pregnancy ($r = 0.772$, $P < 0.001$) and between weight gain and progesterone values ($r = 0.674$, $P < 0.005$) (Fig. 2).

The mean plasma aldosterone value (Fig. 1) at the 3rd month of pregnancy was significantly higher (18.6 ± 4.2 ng/dl) than the values after delivery (7 ± 1.2 ng/dl) or in normal controls.[9,10] There was a progressive and definite increase in plasma values of aldosterone until delivery, although this was less consistent than for progesterone (Fig. 1). No correlation could be established between plasma aldosterone values and weight gain, although there was a significant degree of correlation between plasma aldosterone and duration of pregnancy ($r = 0.559$, $P < 0.02$) (Fig. 1). After delivery, plasma aldosterone values decreased rapidly towards those of healthy, nonpregnant women.

Beginning at the 2nd trimester and until approximately 4 weeks before delivery there was a significant correlation between plasma progesterone and aldosterone values (Fig. 3) ($r = 0.509$, $P < 0.02$) and between the progesterone/aldosterone ratio and the duration of pregnancy ($r = 0.446$, $P < 0.05$) and weight gain ($r = 0.594$, $P < 0.005$) (Fig. 4). PRA was also increased during pregnancy, confirming pre-

Table I—Clinical data and plasma values of progesterone, aldosterone and renin activity

Patient no.	Age (yr)	Para	Study period A. Pregnancy (wk) B. Post partum(d)	Weight (kg) Initial	Weight (kg) Change	Progesterone (μg/dl)	Aldosterone (ng/dl)	P (ng/dl)/ A (ng/dl)*	PRA (ng/ml·h)
1	18	1	A. 13	68.2	+ 1.4	3.24	24.5	132	—
			21		0	6.48	46.3	140	3.0
			34		+ 9	13.0	64.5	201	3.7
			B. 2⅓			0.52	8.0	65	1.8
2	19	0	A. 25	79.6	—	5.33	32.7	163	2.7
			34		—	13.25	93.5	142	2.5
			40		—	22.13	79.0	280	6.5
3	21	0	A. 19	59.1	− 0.5	4.48	22.7	197	2.5
			28		+ 5.5	8.50	28.0	303	1.9
			37		+12.7	9.33	42.6	219	6.0
			B. 3			0.09	5.2	18	1.3
4	38	3	A. 19	59.1	0	4.58	21.3	215	4.6
			27		+ 1.8	12.55	23.8	527	8.3
			36		+ 8.4	20.90	26.0	804	1.7
			B. 2			0.26	12.8	28	2.8
5	18	0	A. 16	50.0	− 2.3	4.78	46.3	103	2.0
			25		+ 2.3	7.18	46.1	156	6.6
			36		+ 3.6	15.87	70.3	226	1.5
			B. 4½			0.06	6.5	8	0.4
6	33	3	A. 13	63.6	0	3.54	21.0	168	0.3
			22		+ 0.4	4.85	11.6	418	2.0
			36		+ 4.1	14.37	28.8	499	2.4
			B. 2			0.26	5.0	51	0.5
7	34	0	A. 22	48.6	+ 7.3	8.0	28.0	286	8.3
			31		+10.9	13.40	43.2	310	16.6
			36		+11.6	18.50	42.7	433	26.6
			B. 3			0.12	5.0	24	9.3

*progesterone/aldosterone ratio

vious observations from this laboratory.[13] No correlation could be established between PRA and plasma aldosterone values during pregnancy.

Discussion

Our findings in these seven women with a normal pregnancy establish clearly a progressive increase in plasma concentration of progesterone and aldosterone from the 12th week of pregnancy until the 36th week, with an abrupt decrease to normal values in the first days post partum. They show a significant relation between the increase in plasma progesterone concentration and weight gain and between plasma progesterone and aldosterone concentrations. The positive correlation between plasma progesterone concentration and weight gain is in disagreement with another study in which the urinary excretion of pregnatriol was used as an indicator of progesterone,[14] but it does not necessarily reflect progesterone production. Our findings of increased plasma aldosterone values during pregnancy are in accordance with those of Weir *et al.*[15] This increase is due to the progressive increase in the secretion rate,[16] for the metabolic clearance rate does not change during pregnancy.[17,18] The positive correlation between plasma progesterone and aldosterone values confirms the observations of Jones *et al.*[16]

The progesterone/aldosterone ratio deserves several comments. First, the progesterone plasma value increases about 1000 times by the end of pregnancy, whereas the aldosterone value increases about 10 times. In fact, this 100:1 ratio is relative and its significance depends greatly on the protein-binding of progesterone and aldosterone during pregnancy and the availability of the free hormone at the receptor levels. Increased plasma concentrations of steroid-binding proteins, transcortin, albumin and the aldosterone-binding fraction of plasma[19,20] may also account for the elevation of plasma values of progesterone and aldosterone.

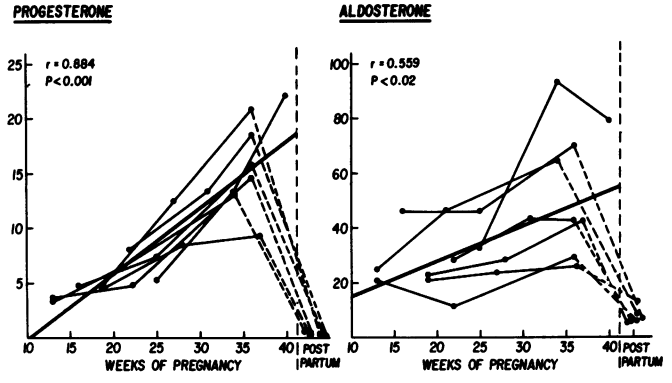

FIG. 1—Plasma progesterone (μg/dl) and aldosterone (ng/dl) concentrations during pregnancy in seven women with at least three determinations of each steroid. Straight solid line indicates mean values. Broken line indicates mean duration of pregnancy.

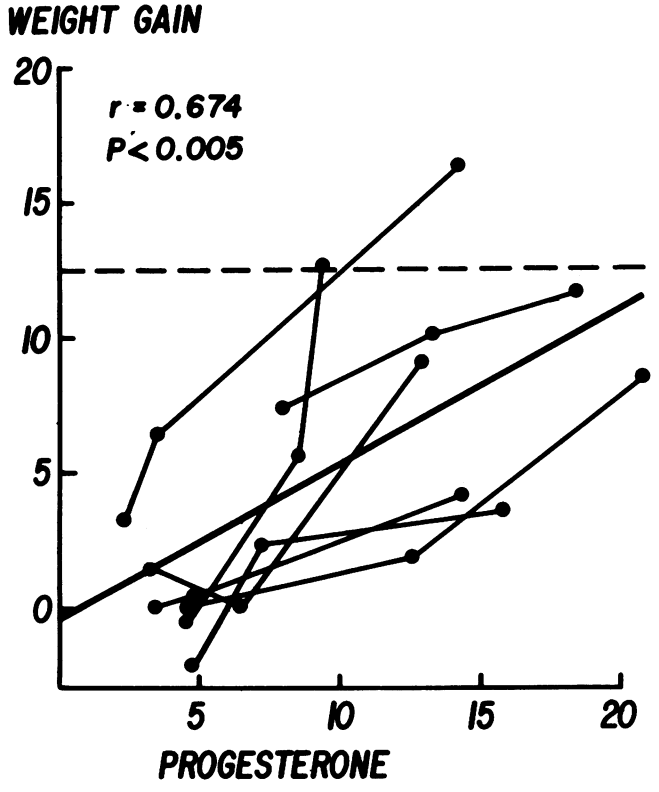

FIG. 2—Relation between weight gain (kg) and plasma progesterone concentration (μg/dl) in seven women with a normal pregnancy. Broken rule indicates mean values of weight gain in normal pregnancy.

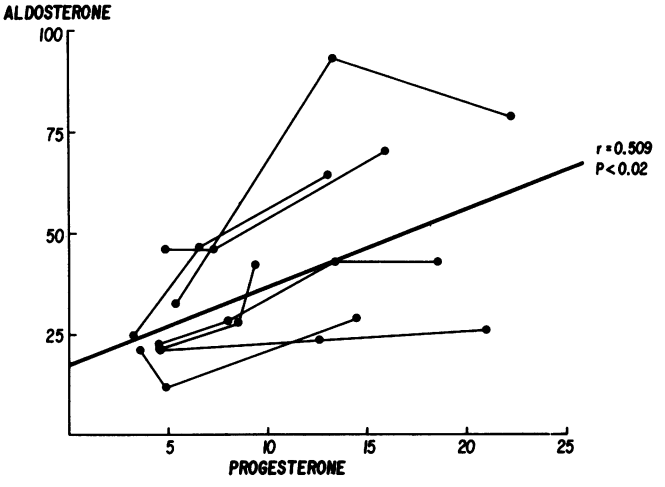

FIG. 3—Relation between plasma values of aldosterone (ng/dl) and progesterone (μg/dl) in seven women with normal pregnancies who each had at least three simultaneous determinations.

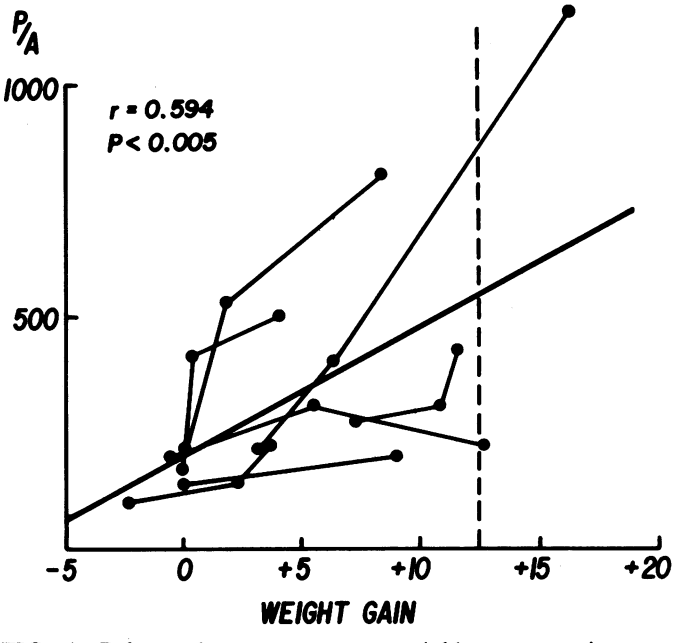

FIG. 4—Relation between progesterone/aldosterone ratio and duration of pregnancy and weight gain (kg). Broken line indicates mean values of weight gain in normal pregnancy.

A second point concerns the significant correlation of the progesterone/aldosterone ratio and weight gain. Our preliminary data appear to indicate that the aldosterone plasma concentration does not increase when the weight remains relatively stable, in contrast to the situation in patients with a weight gain of 8 to 10 kg during pregnancy.

One patient not included in this series had idiopathic cyclic edema before her pregnancy and severe edema of the lower extremities with morning facial edema at the 24th and 30th weeks of pregnancy. Plasma aldosterone values were 200 ng/dl at the 24th week, 160 ng/dl at the 30th week and 221 ng/dl at the 37th week, with simultaneous plasma progesterone values of 9.8, 13.3 and 20.9 μg/dl. This resulted in low progesterone/aldosterone ratios of 49, 80 and 90, which indicated a relative hyperaldosteronism, which was responsible for the severe edema. PRA values were 6, 3 and 2.3 ng/ml·h for the same respective periods.

A significant positive correlation has been demonstrated by others between plasma aldosterone and concurrent PRA and plasma renin substrate (PRS) values[2] but not between aldosterone and PRA values. In this study we have confirmed a lack of correlation between plasma aldosterone and PRA values. Increased PRS or PRA values suggest but do not necessarily indicate an increased capacity to generate angiotensin II.

Elevated plasma concentration of the aldosterone-binding fraction of plasma protein[19,20] could account for part of the elevation of the plasma concentration of aldosterone in pregnancy, although an elevation of free plasma aldosterone concentration is also present.[19] This provides another possible explanation for the salt retention and blood pressure increase[21] noted in late pregnancy when plasma progesterone concentration decreases greatly.[6] The majority of patients with mild essential hypertension tolerate pregnancy without great difficulty, and often pregnancy ameliorates the symptoms of hypertension because many women have a transient decrease in blood pressure during the 2nd trimester of pregnancy.[22] This may be due in part to the antihypertensive properties of progesterone, the concentration of which sharply increases at this time;[23,24] it may be related to direct antialdosterone activity and also the ability of progesterone to increase renal blood flow.[25] In addition, progesterone administration[26] resulting in plasma concentrations in a similar order of magnitude as in the luteal phase of the normal menstrual cycle[20,26] or in essential hypertension[10,11] causes natriuresis, an increase in PRA and aldosterone excretion.

Because of the importance of the renin-angiotensin-aldosterone axis in the regulation of blood pressure–volume homeostasis in normal subjects, in pregnant women and in patients with essential hypertension, and because of the many similarities in changes in the metabolism of aldosterone in pregnancy and in hypertension, the interrelationship between endocrine changes peculiar to pregnancy and the renin-angiotensin-aldosterone system deserves some comments.

Our group has demonstrated important disturbances in aldosterone metabolism and regulation in patients with early benign essential hypertension: about one third of such patients have increased plasma values[10,20,27] and often a concomitant increase in plasma progesterone values.[10,11]

Pregnant subjects excrete proportionally more 18-oxo-conjugate and less tetrahydroglucuronide of aldosterone than nonpregnant subjects, presumably because of a decrease in splanchnic clearance and an increase in the extrasplanchnic clearance of aldosterone[16-18] in the presence of an unchanged overall clearance rate.[17,18] A similar shift in both urinary metabolites of aldosterone exists in essential hypertension[10,28,29] in the presence of a greatly reduced rate of metabolic clearance of aldosterone[10,29] and a slightly reduced hepatic blood flow.[30] Hepatic blood flow was found to be the same in pregnant as in nonpregnant subjects.[31]

In addition, Luetscher and his group[32] have provided strong evidence of a relative state of hyperaldosteronism in patients with essential hypertension maintained on salt loads at or above 300 meq per day. Although such salt loads depress aldosterone secretion, excretion and plasma concentration in healthy subjects, these indices are suppressed to a lesser extent in patients with essential hypertension, the values being about three times those observed in healthy subjects similarly treated. The absence of hypokalemia in patients with benign essential hypertension is difficult to explain and has been used as a major argument against any state of relative hyperaldosteronism in such patients. A possible explanation may be provided by the threefold increase in mean plasma progesterone values in patients with benign essential hypertension. Hypokalemia is also absent in women with a normal pregnancy.

Many similarities in the modifications of steroid metabolism between pregnancy and essential hypertension are of particular interest in view of the evidence that in most instances so-called specific hypertensive disease of pregnancy or pre-eclamptic toxemia merely represents the first expression of recognition of hypertension in a genetically predisposed woman.[33,34] It is possible, therefore, that certain quantitative rather than qualitative differences in some of the parameters discussed above, brought out by pregnancy, are responsible for the development of hypertension.

The high progesterone/aldosterone ratio may be the explanation for the absence of hypertension, edema, hypernatremia and hypokalemia during normal pregnancy despite the hyperaldosteronism, which appears to be a normal physiologic mechanism of homeostatic adjustment to the greatly increased production of progesterone.

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Retrospect

The treatment of the pernicious vomiting of pregnancy

I have been using the suggestive method of treatment for all cases of vomiting of pregnancy, including the pernicious type, both in hospital and private practice, for the last four years and have found it most satisfactory. Nor have I experienced a failure yet, though I say this in all humility, realizing that no cure is infallible.

What is this suggestive treatment? In my practice it is a very simple matter, necessitating merely a certain elementary knowledge of psychology and some moral courage. First of all I get the patient, public or private, into hospital, if I can; for these cases do not respond as satisfactorily when treated at home. One can usually assure the patient that she will only need to stay in hospital a week. If I can't get her into hospital I get her into a room by herself and exclude from this room all old women. If a patient can afford a nurse so much the better; and the nurse must be impressed with the efficacy of the treatment.

Having got the patient into hospital — or its best substitute — the vomit bowl is kept away from her. If she wants to vomit she is told to vomit into the bed and when she does vomit the nurse is instructed not to be in too great a hurry to change her. If she is greatly dehydrated she is given rectal injections of 5 per cent glucose solution, either in quantity or by the Murphy drip. If she has any idea that an abortion — which she may desire — is to be done she is firmly disabused of that idea. She is told that under no circumstances will an abortion be done. If, on the contrary, she does not want to lose her baby the other tack is taken.

I do not make a practice of explaining things to the patient herself, but instead give my orders to the nurse in the patient's hearing; and I find that a certain curtness of manner works to advantage. Ordinary food is brought to the patient by the nurse at the regular meal hours and put before her as though we were quite convinced that the patient could keep such food down. She is never asked if she thinks she can keep some nourishment down; the nourishment is placed before her; she is told to eat it and assured that she will keep it down. It is better to give solids than liquids. No visitors are allowed near the patient; no fuss is made over her; and the nurse is instructed to leave her to herself as much as possible. — Atlee HB: The treatment of the pernicious vomiting of pregnancy. Can Med Assoc J *15: 388, 1925*