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Sodium and mineralocorticoids in normal pregnancy

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For many years clinicians have speculated that abnormal sodium metabolism plays an important role in the pathogenesis of hypertension. This consideration probably has been most evident in obstetrical practices directed toward preventing hypertensive disorders of pregnancy. It was commonly assumed that normal gestation was associated with sodium-retaining tendencies, which were thought to be causally related to the development of preeclampsia. Accordingly, pregnant women customarily were treated as though threatened by excessive sodium retention; dietary salt restriction and diuretics were prescribed routinely as precautionary measures.

In view of this concern, it is quite understandable that the discovery of aldosterone and the recognition of its causal relationship to hypertension in Conn's syndrome quickly led early investigators to study the possible pathogenic role of this potent mineralocorticoid in the hypertensive disorders of pregnancy. Initial reports suggesting that aldosterone levels were higher in preeclamptic than in nonpregnant women generated considerable excitement, which quickly was tempered by the observation that aldosterone secretion was increased to an even greater extent in normal gravidas [1]. Since then, results of numerous studies have provided confirmation that aldosterone levels are markedly elevated in normal gravidas compared with nonpregnant women on similar salt intakes [2, 3]. More recently, it has been shown that secretion of another potent mineralocorticoid, desoxycorticosterone, also is increased substantially during normal pregnancy [4, 5]. Nonetheless, normal gravidas do not demonstrate clinical evidence of mineralocorticoid excess, and the blood pressure falls below pregnancy values during the first two trimesters.

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Although the regulation of aldosterone secretion in pregnancy has been studied extensively, the physiologic significance of the markedly increased secretion of aldosterone remains controversial. There is considerable evidence that normal pregnancy results in a tendency towards a reduced *effective blood volume*, despite the high levels not only of aldosterone and desoxycorticosterone, but also of estrogens, which have sodium-retaining effects in man. Thus, some propose that the enhanced secretion of aldosterone is a compensatory response required to maintain normal volume homeostasis [6]. Others argue that the augmented extracellular and intravascular fluid volumes measured in normal pregnancy, as well as the accompanying rise in cardiac output and in the GFR, are inconsistent with functional hypovolemia, and suggest that these changes more likely reflect sodium retention induced by aldosterone hypersecretion [7].

Questions regarding the role of increased aldosterone in pregnancy, whether it is associated with a tendency to lose or to retain sodium, not only have a bearing upon routine management of pregnant women, but are also of fundamental importance to our understanding of the pathophysiology of the gestational hypertensive disorders. In attempting to resolve these issues, it would seem appropriate to review studies that might help to define the role of increased mineralocorticoids in normal pregnancy.

Aldosterone in pregnancy

Aldosterone in pregnancy starts to rise above the normal range almost as soon as pregnancy is established and continues to increase steadily throughout the course of gestation, as shown in Figs. 1 and 2 [2, 3, 5]. Early in the third trimester, a striking further increment occurs that results at term in a tenfold to twentyfold elevation of plasma aldosterone over levels measured in the nonpregnant state. Aldosterone is not tightly bound to plasma proteins,

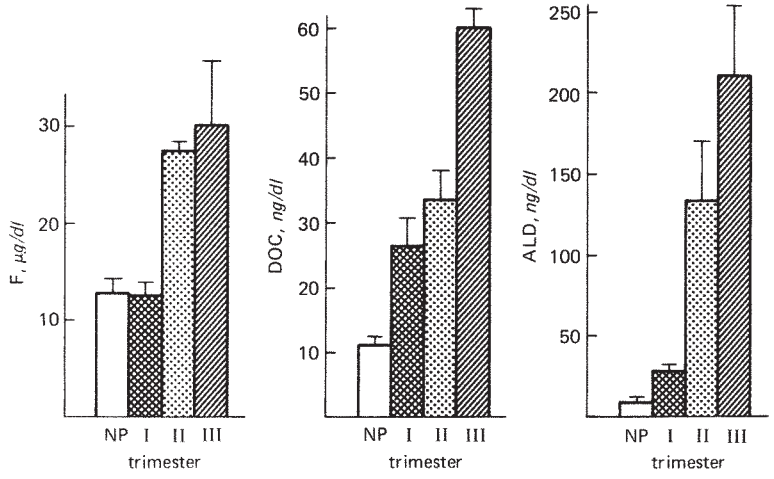

Fig. 1. *Mean plasma concentrations of cortisol (F), desoxycorticosterone (DOC), and aldosterone (ALD) measured sequentially at 0800 hours during pregnancy and 3 months postpartum.* NP denotes not pregnant. (Reprinted with permission from The C. V. Mosby Company [5])

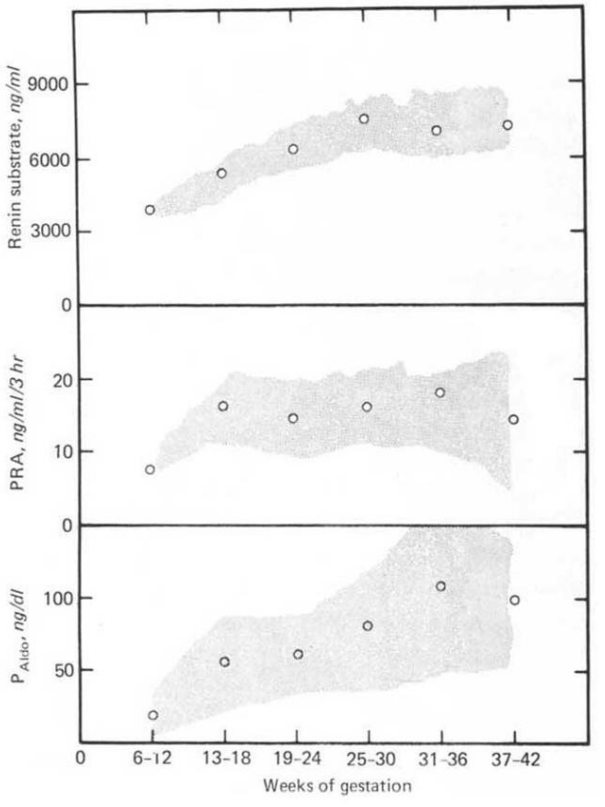

Fig. 2. *Sequential changes in renin substrate concentration, plasma renin activity, and plasma aldosterone in normotensive pregnancy measured in 6-week intervals.* (Reprinted with permission of John Wiley & Sons [3])

so that the rising plasma concentration with advancing pregnancy presumably results in roughly comparable increases in the biologically active free steroid. Nonetheless, the substantial increment in urinary aldosterone excretion observed in pregnancy is only partly a reflection of the elevation of the circulating level of aldosterone, but is accounted for largely by the much greater proportion of aldosterone that is metabolized and excreted as the acid-labile conjugate during pregnancy, which ultimately is included in usual urinary measurements [8]. Thus, the aldosterone secretion rate is elevated substantially in pregnancy but not nearly to the same degree as is the urinary excretion rate.

Plasma renin activity, renin substrate (Fig. 2), and concentrations of renin and angiotensin II (AII) are also elevated throughout normal gestation [2, 3]. The increase in renin activity parallels aldosterone levels only in early pregnancy, when it rises rapidly to a plateau level. Renin activity remains unchanged in the second and third trimesters, whereas plasma aldosterone continues to increase [3]. This suggests that factors other than renin activity and AII may directly stimulate or modulate the production of aldosterone in gestation. It has been assumed that most of the increased plasma renin in pregnancy exists in an inactive form that is activated when plasma is acidified [9]. Nonetheless, the plasma concentration of active renin is considerably higher throughout gestation than it is in nonpregnant women, although it declines somewhat towards term. Renin-like enzymes, found in the uterus and amniotic fluid, do not respond to stimulation by hemorrhage or acute hyponatremia and therefore are not believed to enter the maternal circulation [10]. Increased plasma levels of renin activity and angiotensin in pregnant women depend therefore entirely upon renin secreted by the kidney.

Despite the very high levels of aldosterone, pregnant women are quite sensitive to the increased

sodium-retaining activity that follows the administration of mineralocorticoids or adrenocorticotropic hormone (ACTH) [11, 12]. Prolonged treatment of normal third trimester women with these agents results in marked cumulative sodium retention, and aldosterone excretion is drastically reduced from very high baseline rates down toward the normal nongravid range. A representative study of the effects of DOCA (DOC acetate) in a pregnant woman is shown in Fig. 3. The lack of refractoriness to the induced increases in sodium-retaining activity suggests that the very high pretreatment aldosterone levels were not excessive, because otherwise chronic volume hyperexpansion should have resulted in "escape" from the effects of further increments in mineralocorticoid activity. The fact that the increased excretion of aldosterone was so readily suppressed by volume hyperexpansion resulting from mineralocorticoid administration also argues against excessive aldosterone secretion.[1]

In contrast to results of comparable studies in normal nongravidas, as shown in Fig. 3, mineralocorticoid-induced sodium retention in pregnancy is not accompanied by kaliuresis, even when sodium intakes are very high [11]. Refractoriness to the kaliuretic action of mineralocorticoids during pregnancy has been attributed to the inhibitory effect of progesterone. Attenuation of the kaliuretic influence of mineralocorticoids by progesterone would also account for the amelioration of hypokalemia that occurs in women with primary aldosteronism when they become pregnant [14].

Aside from observations that aldosterone excretion is readily suppressed by mineralocorticoid-induced volume hyperexpansion, numerous studies provide additional evidence that aldosterone secretion is regulated by normal mechanisms during pregnancy. Aldosterone secretion and excretion in pregnant women vary inversely with changes in salt intake and increase further in response to volume depletion by diuretics [15–18]. The degree of change induced by these maneuvers is comparable to that observed in nongravidas. Other studies indicate that the elevated levels of aldosterone and plasma renin activity in pregnancy also are responsive to postural changes [19–21]. When third trimester women in one reported study assumed a supine-upright posture after a period of lateral recumbency, sodium retention occurred, associated with a concurrent increase in aldosterone excretion and plasma renin activity [21]. The increment in aldosterone excretion and renin activity that occurs when pregnant women assume the supine-upright posture was similar to that observed in nongravid individuals when they changed to the upright position after being recumbent.

Because aldosterone secretion in pregnancy responds normally to physiologic stimuli, it can be concluded that it is regulated by normal mechanisms and that it increases in normal gestation only to the extent necessary to maintain sodium balance and volume homeostasis. Conversely, failure to maintain the elevated aldosterone levels should result in salt wasting and hypovolemia. This hypothesis was tested by studies in which aldosterone secretion was directly inhibited without concurrent volume hyperexpansion by administration of a heparinoid [22]. Heparin and several related heparinoid derivatives, which are relatively devoid of anticoagulant activity, selectively impair aldosterone production by means of an undefined mechanism. When the elevated secretion of aldosterone in normal gravidas was reduced by prolonged treatment with a heparinoid, marked sodium loss ensued, as shown in a representative study (Fig. 4). One subject developed clinical manifestations of volume depletion, characterized by postural weakness and a slight rise in blood urea nitrogen as aldosterone remained depressed. It is remarkable that sodium loss occurred during treatment, although aldosterone excretion, even though greatly diminished as compared with baseline levels, never was reduced below normal nonpregnant values. After discontinuation of the heparinoid, the natriuresis induced by treatment did not subside until the aldosterone excretion rate returned to the very high baseline rate. The occurrence of marked sodium loss despite higher-than-normal aldosterone excretion provides strong evidence that increased aldosterone secretion is needed in pregnancy to maintain sodium balance. Moreover, it supports the proposition that potent factors oppose the sodium-retaining effects of aldosterone during gestation.

Thus, it is noteworthy that when third trimester pregnant women were studied during extreme dietary sodium deprivation, urinary sodium excretion was reduced to a similar degree, and resultant weight loss was the same as in nongravidas [7]. At first glance, these observations seem to offer reassurance that the postulated sodium-losing factors in pregnancy can be countered effectively by compensatory mechanisms. Gravidas normally should

[1] A sharp decline in the aldosterone excretion rate is noted also during ACTH administration in pregnant women, which is similar to the response observed in nongravidas, where the resultant depression of aldosterone secretion has not necessarily been related to the degree of sodium retention [12, 13].

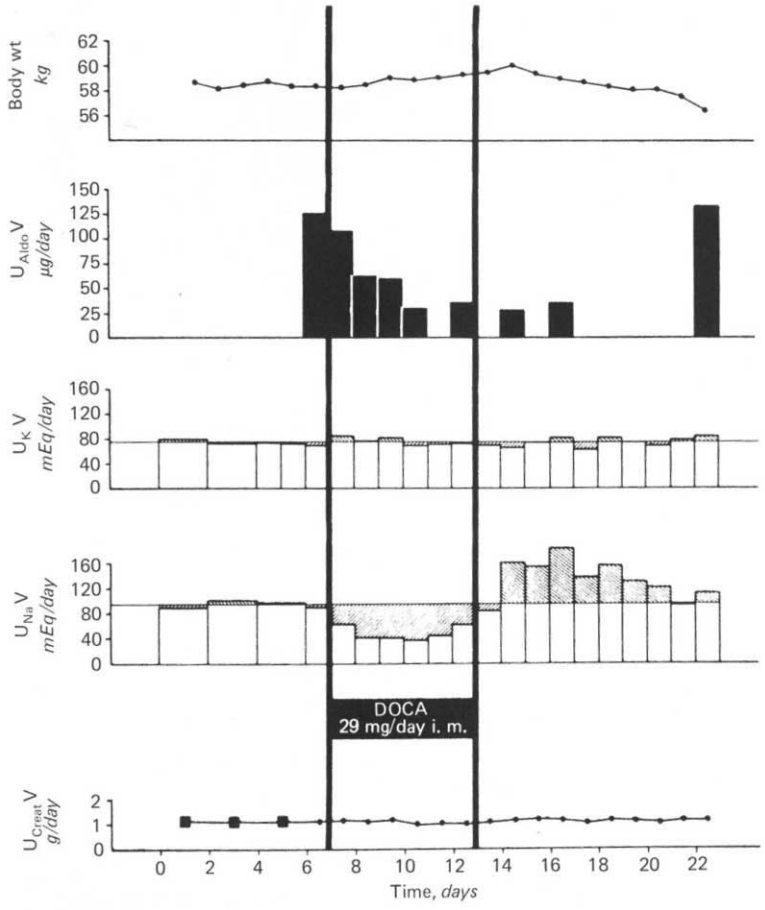

Fig. 3. *Metabolic and aldosterone responses to administered mineralocorticoid in a normal third trimester woman.* DOCA is desoxycorticosterone acetate. (Reprinted with permission from The Rockefeller University Press [11])

retain 4 to 5 mEq of sodium daily to meet fetal requirements, however, and there should be a weight gain of 1 lb or more weekly during the third trimester [23]. Therefore, the fact that urinary sodium excretion and weight loss were no less than they were in nongravidas suggests that the maximum sodium-conserving capability may be impaired in pregnancy.

Several known factors in pregnancy promote sodium loss and therefore could evoke compensatory responses, including the rise in aldosterone secretion. The GFR increases by as much as 50%, resulting in an increment in the filtered load of sodium of 5000 to 10,000 mEq each day [24]. If enhanced filtration were not countered by a commensurate increase in reabsorption, sodium depletion would rapidly ensue. Assuming that glomerulotubular balance is maintained in pregnancy as in nongravid individuals, there still would be a substantial increase in the amount of sodium presenting to distal tubular sites, where a portion of sodium reabsorption is aldosterone dependent. The sodium-retaining action of aldosterone at these distal sites is inhibited, however, by progesterone, which is secreted in large amounts during pregnancy. The inhibitory effect of progesterone, as demonstrated by Landau and Lugibihl in an early study in an Addisonian subject, is presented in Fig. 5 [25]. Furthermore, progesterone may also exert a natriuretic effect that is independent of mineralocorticoid inhibition. Studies of renal hemodynamics and intrarenal sodium handling during administration of progesterone to normal men show that progesterone may also inhibit sodium reabsorption at proximal sites in the nephron [26]. Thus, aldosterone would have to increase just to offset the combined sodium-losing effects of the increased GFR and the natriuretic actions of progesterone. That progesterone is at least in part responsible for the rise in aldosterone secretion is supported by the direct correlation that has been observed between progesterone and aldosterone secretion in normal pregnant women [8, 27, 28]. Furthermore, administration of progesterone to normal men results in an initial natriuresis, which sub-

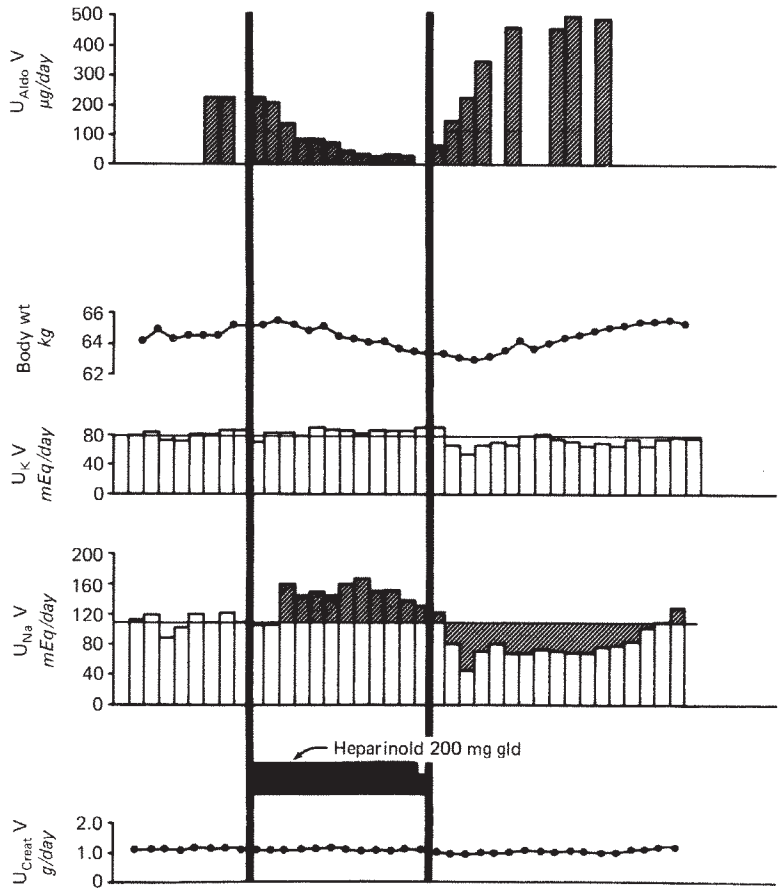

Fig. 4. *Metabolic and aldosterone responses to administration of the heparinoid R01-8307 to a normal third trimester woman.* (Reprinted with permission from the C. V. Mosby Company [22])

sides promptly as the rate of aldosterone excretion rises [27]. In addition to countering the above noted sodium-losing factors, however, normal pregnant women must retain 500 to 900 mEq of sodium during the course of normal gestation to meet the requirements of the developing conceptus and to provide for the physiologic increase of the maternal interstitial and intravascular fluid volumes [23]. The need to retain this additional quantity of sodium imposes a further stress upon sodium-conserving mechanisms and provides an additional stimulus for augmented aldosterone secretion.

The increase in activity of the renin-angiotensin system and in aldosterone secretion in pregnancy cannot be attributed entirely to a compensatory response to threatened sodium depletion. In one reported study, aldosterone excretion, although markedly suppressed by prolonged mineralocorticoid administration, remained above the normal nongravid rate even though treatment resulted in cumulative sodium retention of 280 mEq or more [11]. In another study, plasma renin activity and aldosterone concentrations were significantly higher in pregnant women after 6 days on a 300-mEq sodium diet than they were in nonpregnant controls [7]. Gravidas take longer to come into balance and retain more sodium, however, than do nongravidas when given high-sodium diets, consistent with the proposition that they are relatively sodium depleted at the outset. Nevertheless, it seems unlikely that any appreciable degree of sodium depletion still was present in the pregnant women at the end of the treatment periods, because they were then in sodium balance. Therefore, it must be assumed that factors other than sodium depletion contributed to the higher levels of renin activity and aldosterone secretion that were noted in the pregnant women.

In normal gestation, vascular smooth muscle tonus and pressor responsiveness to AII are reduced, presumably due to the action of vasodepressor prostaglandins and progestins [29, 30]. Systemic peripheral resistance is decreased, and blood pres-

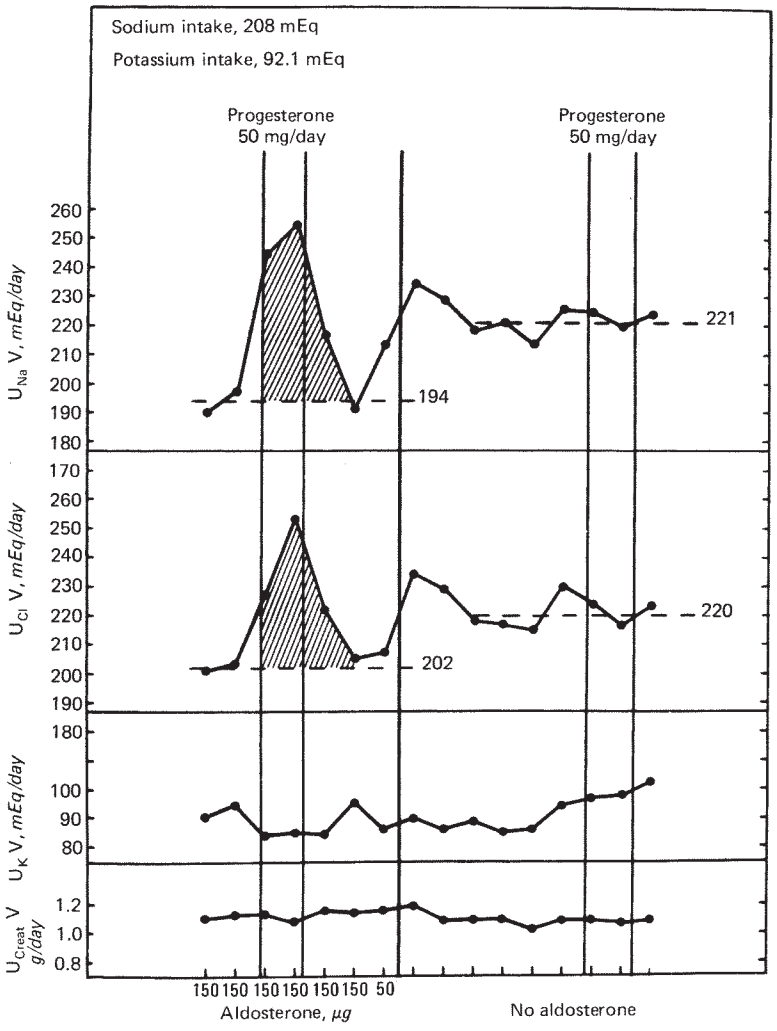

Fig. 5. *Effects of progesterone on the urinary excretion of sodium, chloride, potassium, and creatinine in a patient with Addison's disease.* Throughout these observations, the patient received 50 mg of cortisone acetate per day. *Broken horizontal lines* indicate averages of control values; *oblique hatching* indicates significant shifts. (Reprinted with permission from The J. B. Lippincott, Co. [25])

sure falls significantly despite a 25 to 50% increment in cardiac output. Although the extracellular fluid volume is expanded by 4 to 6 liters, enough to produce overt edema, heightened activity of the renin-angiotensin-aldosterone system still is increased further by changes from lateral recumbent to supine or upright posture. The briskness of these responses reflects the marked reduction in the effective blood volume that occurs when pregnant women are changed in position from supine recumbency, possibly because of enhanced vascular distensibility and orthostatic pooling of blood from compression of the inferior vena cava by the gravid uterus. Even though the renin-angiotensin-aldosterone system remains extremely responsive to postural changes, the lowest levels of serum renin activity and rates of aldosterone excretion noted in pregnant women on normal sodium intakes after 3 days of lateral recumbency still were much higher, however, than they were in nongravidas, suggesting that renin release in this instance was being stimulated or modulated by factors not directly related to decreased vascular tonus [21].

Plasma and urinary prostaglandin E may be increased considerably in normal pregnancy [7]. Aside from their vasodepressor action, prostaglandins of the E type have been shown to enhance renin release and also possibly to increase aldosterone secretion directly [31, 32]. Thus, heightened activity of the renin-angiotensin-aldosterone system induced by elevated levels of prostaglandins in pregnancy might be expected to promote sodium re-

tention whereas blood pressure remains normal because of the associated vascular refractoriness to the pressor action of angiotensin. As noted previously, however, the striking sensitivity of the renin-angiotensin system to postural stimuli observed in pregnant women is more consistent with a tendency toward functional volume depletion rather than excessive sodium retention, and it is doubtful that the elevated levels of plasma renin activity and aldosterone in pregnancy would be so readily suppressible if either or both were stimulated directly by increased prostaglandins. On the other hand, studies in nongravidas seem to indicate that vasodepressor prostaglandins tend to enhance responses of the renin-angiotensin-aldosterone system to sodium restriction or diuretic administration [33–36]. Thus, the increased synthesis of vasodepressor prostaglandins in pregnancy may play an important role not only in regulation of blood pressure by modifying sensitivity of vascular smooth muscle to the pressor effect of angiotensin, but also in volume homeostasis by modulating responsiveness of the renin-angiotensin-aldosterone system to volume-depleting influences. (See contribution by Gant et al, in this Symposium.)

Desoxycorticosterone in pregnancy

Secretion of desoxycorticosterone (DOC) is greatly increased in the third trimester of normal pregnancy as reflected by elevated levels of plasma DOC and increased excretion of urinary free DOC as well as of the urinary metabolite, tetrahydrodesoxycorticosterone [4, 12]. In the one reported instance where DOC production was measured by a urinary metabolite isotope dilution method, the production rate exceeded 8000 μg/day toward term and fell to a normal value of 174 μg/day on the third day after delivery [4]. Sequential measurements of plasma DOC during normal gestation reveal that only modest increases occur in the first two trimesters; the most dramatic increments were noted in the third trimester when mean DOC concentrations rose to 60.6 ng/dl compared with 11.2 ng/dl in the nongravid state, as shown in Fig. 1. Because, however, DOC is bound to CBG with almost the same avidity as is cortisol, it would not immediately be apparent whether the measured increments in total plasma DOC concentration are accounted for entirely by the higher levels of CBG that occur in pregnancy, or whether the biologically active free moiety is raised above nonpregnant levels. Thus, it is noteworthy that the free DOC index, which accurately reflects relative differences in plasma concentrations of free DOC, was greatly increased above the normal nonpregnant range when measured in the third trimester women [37]. Furthermore, the markedly elevated rate of urinary free DOC excretion, 770 ng/day in late pregnancy compared with 90 ng/day in nongravid controls, provides additional evidence that the plasma free DOC concentration is greatly increased, because the amount of unconjugated, free steroid excreted in the urine is related directly to the circulating level of unbound steroid [38, 39].

The mechanisms responsible for the increased secretion of DOC in pregnancy have not been defined. In nongravidas, DOC secretion is not affected directly by factors that influence aldosterone secretion, but increases in response to ACTH stimulation and is reduced by dexamethasone suppression [40]. Thus, it has been assumed that the small amount of DOC secreted in nonpregnant individuals is mainly a byproduct of cortisol biosynthesis, and accordingly, that it is ACTH-dependent. When effects of prolonged administration of ACTH were studied in third trimester women, there was marked cumulative sodium retention, which was attributed to enhanced DOC secretion because the high baseline rate of urinary tetrahydrodesoxycorticosterone excretion increased sharply during treatment, but aldosterone was depressed [12]. In later studies, however, elevated plasma DOC in third trimester gravidas not only was unresponsive to changes in salt intake, but, surprisingly, failed to respond to either ACTH or dexamethasone administration, whereas plasma cortisol concentrations rose and fell in normal fashion [37]. The apparent discrepancy between reponses of urinary tetrahydrodesoxycorticosterone and plasma DOC to ACTH was reconciled by a study that took into consideration binding interactions of DOC and cortisol with CBG in plasma [37]. Results of this study show that the free DOC concentration in pregnant subjects rose significantly during ACTH administration due to displacement of DOC from CBG by the ACTH-induced increment in cortisol, even though the total plasma DOC concentration was virtually unchanged (Fig. 6). The increase in biologically active free DOC not only could contribute to the sodium retention that occurred during ACTH administration but also would be available for hepatic metabolism to tetrahydrodesoxycorticosterone, thereby accounting for the increased urinary excretion of this metabolite. These steroid-binding interactions have important implications going beyond the scope of this study, because they identify an additional mechanism, aside from those regulating secretion, whereby biologic activity of steroids in

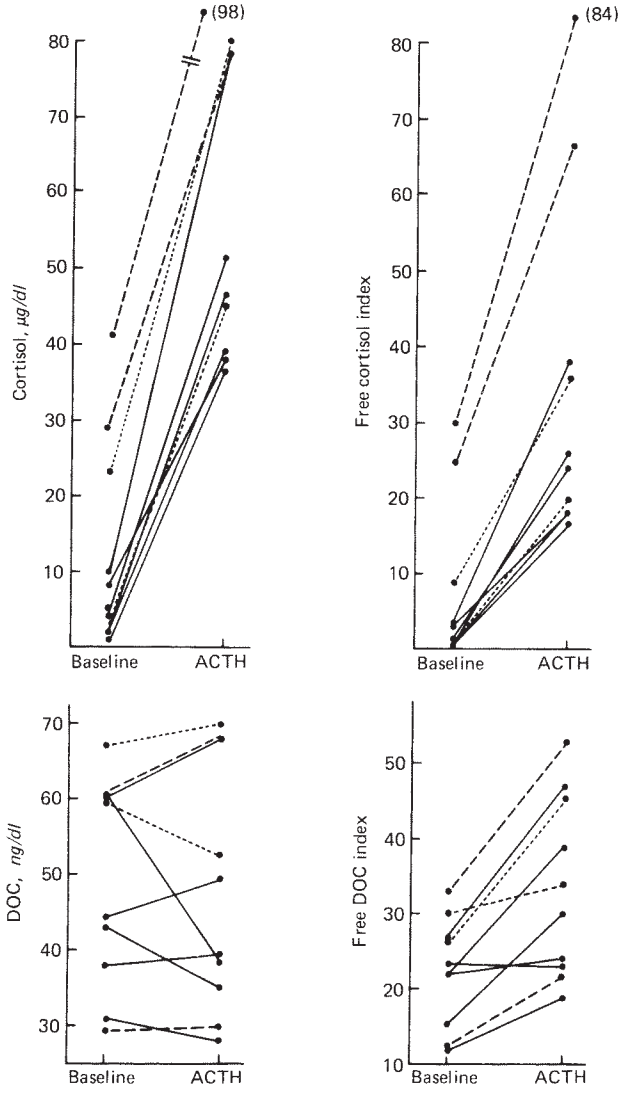

Fig. 6. *Plasma concentrations and free indexes of cortisol and desoxycorticosterone (DOC) in normal third trimester pregnant women before and after administration of ACTH.* Six subjects (•——•) were treated initially with dexamethasone (2 mg/day in divided doses for 7 days) and subsequently with ACTH (20 U i.m. every 12 hours for 7 days). Two subjects (• · · · · •) received an i.m. injection of 0.25 mg of ACTH, after overnight suppression with a single dose of 1 mg of dexamethasone. Two subjects (• ---- •) were given a 6-hour infusion of 40 U of ACTH. (Reprinted with permission from The C. V. Mosby Company [37])

plasma may be modulated. These observations also underscore the need to use measurements that reflect the free steroid fraction, particularly in pregnancy where increased quantities of circulating cortisol and progestins compete for binding sites on elevated CBG levels.

The source of increased DOC secreted in pregnancy has not been localized precisely. Non-suppressibility of DOC by dexamethasone administration or during long-term high-salt intake suggests that the increased DOC does not arise from either glucocorticoid or mineralocorticoid pathways of the maternal adrenals [37]. Rather, the much higher concentrations of DOC and DOC sulfate found in mixed cord blood, compared with maternal venous blood (Table 1), seem to point to the fetoplacental unit as a source of the increased DOC [38]. The fetal-maternal gradient for *free* DOC would be even steeper than assumed from the 2 to 3:1 ratio between measured concentrations of total DOC, because CBG levels are negligible in fetal blood [4, 38]. The extremely high concentrations of DOC sulfate noted in cord blood also are consistent with the proposition that increased DOC is produced within the fetoplacental unit, because it is assumed that steroid sulfurylation is exclusively a fetal process, which in this instance leads to inactivation of DOC [41, 42]. Thus, it is tempting to speculate that sulfurylation may afford a protective mechanism limiting the quantity of active DOC contributed to the maternal circulation by the fetus. On the other hand, the above arguments do not necessarily exclude the possibility that there also might be significant maternal production of DOC. Recently, Winkel et al presented evidence that a substantial amount of DOC is produced within the maternal compartment by extra-adrenal 21-hydroxylation of progesterone [43]. In view of the very high plasma levels of progesterone that occur in pregnancy, it will be interesting to determine if individual differences in the conversion ratio might occasionally result in pathologic elevations of DOC from this maternal source.

Regardless of the source, it is apparent that secretion of DOC is elevated substantially in the third trimester of normal pregnancy and that it is not influenced by factors that normally regulate adrenocortical function. Thus, it is remarkable that normal third trimester gravidas not only seem to tolerate very high circulating levels of biologically active

Table 1. Desoxycorticosterone (DOC) and desoxycorticosterone sulfate (DOC-S) in mixed cord blood obtained after vaginal delivery and in the plasma of six term gravidas and of six nonpregnant female controls[a]

	Plasma DOC *ng/dl*	Plasma DOC-S *ng/dl*
Fetus	166.0 ± 6.0[b]	553.0 ± 72.0[b]
Pregnant	57.5 ± 8.1[b]	37.5 ± 12.5[b]
Nonpregnant	10.3 ± 3.4	undetectable

[a] Values are the means ± SEM.
[b] $P < 0.001$.

free DOC, but continue to show signs of functional hypovolemia, that is, a reduced effective blood volume. Perhaps the mineralocorticoid activity of the increased DOC is mitigated to some extent by the inhibitory action of progesterone, but pregnant women still are quite sensitive to the sodium-retaining effect of administered DOC, despite their high levels of progesterone. Thus, excessive increases of DOC production during pregnancy could lead to manifestations of mineralocorticoid excess, particularly sodium retention and hypertension. Moreover, the very high levels of mineralocorticoid activity, which seem to be well tolerated in normal pregnancy, might begin to express themselves in abnormal circumstances and lead to pathologic consequences. Accordingly, with the development of preeclampsia, aldosterone is depressed, but nonsuppressible DOC, although reported to be no higher than it is in normotensive subjects, might then be excessive relative to the existing state of sodium balance [4].

Salt restriction and diuretics in pregnancy

As opinion has shifted toward the view that normal pregnancy is associated with a tendency toward volume depletion, there has been a reappraisal of previously advocated practices of restricting sodium intake and prescribing diuretics during pregancy as prophylaxis against the development of preeclampsia. Several recent reviews, as well as the report of an Ad Hoc Committee of the American College of Obstetricians and Gynecologists, have presented strong admonitions against these practices [23, 44–47]. Accordingly, it seems appropriate to restate some of these precautions in the light of the physiologic concepts presented above.

Although the maternal plasma and interstitial fluid volumes are increased substantially in pregnancy, maternal volume receptors apparently sense these alterations as normal. As noted above, when salt restriction or diuretic therapy offsets or limits the physiologic expansion of these extracellular fluid spaces, compensatory responses of the renin-angiotensin-aldosterone system, and presumably, of other sodium-conserving mechanisms are similar to those occurring in volume-depleted nonpregnant subjects. Thus, even though routine treatment with diuretics or sodium-restricted diets in pregnancy would seem to be ill-advised, some might argue that normal compensatory responses would rise to the occasion, and there would be only a momentary exaggeration of the normal hypovolemic tendency. There are animal studies, however, that suggest that the double stress of pregnancy and sodium restriction may exceed the adaptive capacity of the renin-angiotensin-aldosterone system; exhaustion of adrenal glomerulosa cells occurs, and the animals become salt depleted [48]. Similarly, the interruption of normal gestational weight gain observed in human subjects during prolonged periods of dietary sodium deprivation suggests that the maximum sodium-conserving capability may be impaired slightly in pregnancy, enough to result in insidious sodium wasting when challenged by chronic sodium-depleting stresses. Thus, treatment with diuretics or sodium restriction may lead to a sufficient reduction in the intravascular volume to compromise placental perfusion. Diuretic therapy has been shown to reduce the metabolic and placental clearances of dehydroepiandrosterone sulfate, which presumably reflect diminished fetoplacental function [49]. Another serious concern, exemplified by several reported cases, is that salt depletion in pregnancy has resulted in severely impaired renal function. This complication could easily be misinterpreted as an evidence of the occurrence or deterioration of preeclampsia, and the need for salt repletion and cessation of diuretic therapy could be overlooked [50, 51].

Claims that prophylactic therapy with thiazide diuretics reduces the incidence of preeclampsia have not been substantiated by later studies. Because proof of benefit currently is lacking and associated risks are well documented, treatment with diuretics should be avoided in pregnancy except for heart disease. Similarly, because routine restriction of dietary sodium has not been shown to prevent preeclampsia and may produce complications of sodium depletion, pregnant women should be advised to salt their food according to taste. If the physician feels compelled to treat asymptomatic edema, bed rest with the patient positioned in lateral recumbency usually promotes adequate diuresis, and if preeclampsia is suspected, bed rest in the hospital with careful observation is preferable to diuretic therapy.

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