Plasma Aldosterone Concentration at Delivery and during the Newborn Period

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ABSTRACT Aldosterone concentrations in plasma of women on normal sodium intake undergoing cesarean section were 3.7 ±1.4 ng/100 ml (mean ±1 SD). These values were significantly lower ($P < 0.001$) than those observed in mothers on normal sodium diet, delivered by the vaginal route (14.9 ±7.0 ng/100 ml). A significant elevation ($P < 0.001$) of the concentrations was found if the mothers had been on sodium restriction and/or diuretics (44.9 ±24.2 ng/100 ml). In supine position, adult nonpregnant subjects have aldosterone concentrations in plasma of 1.7 ±1.4 ng/100 ml on normal sodium intake and of 16.7 ±8.1 ng/100 ml on low sodium diet.

Simultaneous determinations of aldosterone levels in cord blood showed that cord values were significantly higher than those of the corresponding mother ($P <$ 0.01 by paired t test). However, values in cord blood of infants born to mothers on a normal sodium intake were significantly lower ($P < 0.005$) than those of infants whose mothers had required low sodium diet and/or diuretics during their pregnancy.

Aldosterone concentrations in plasma of infants 1–72 hr of age and born to mothers on normal sodium intake were 25.9 ±11.7 ng/100 ml (mean ±1 SD). These values were significantly lower ($P < 0.005$) than those of infants born to mothers on restricted sodium intake with or without diuretics (80.3 ±54.4 ng/100 ml). The concentrations at birth were not significantly different from those observed during the first 3 days of life ($P > 0.6$).

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INTRODUCTION

It is known that aldosterone excretion (1–8) and secretion increases during pregnancy (9–13). Plasma aldosterone levels have also been shown to be elevated (14). We have previously reported elevated plasma aldosterone concentrations in women at term undergoing cesarean section (15). In each instance, the levels of aldosterone in cord plasma were significantly higher than those in maternal circulation. A dramatic increase in both the maternal and cord levels was observed in a mother who had been on sodium restriction and diuretics.

The secretion rate of aldosterone during the 1st wk of life was found to be significantly lower than later in life (16). However, at the present time, there is no information available on the plasma aldosterone concentrations during the newborn period. The reason for this is that extremely large amounts of blood in relation to the body size of an infant were necessary for determinations by double isotope dilution methods (17–19). The development of the radioimmunoassay for aldosterone has now made such studies possible (20).

We undertook the present study to extend the above observations. Plasma aldosterone concentration was measured in women at term undergoing vaginal delivery. Simultaneous determinations of aldosterone in cord plasma were done. The mothers had been either on normal or restricted sodium intake with or without diuretic therapy. Plasma aldosterone concentration was also measured in newborn infants ranging in age from 1 to 72 hr born to mothers on normal or restricted sodium intake or diuretics.

METHODS

Patients

Mothers. Healthy pregnant women ranging in age from 14 to 38 yr who had attended the Prenatal Clinic at the

University of Maryland Hospital were studied. According to their clinical states, normal diet or sodium restriction to 4 g NaCl per day had been recommended. In addition, in some cases the use of diuretics such as: Esidrix[1] (hydrochlorothiazide), Dyazide[2] (triamterene and hydrochlorothiazide), Naturetin[3] (bendroflumethiazide), and Enduron[4] (methyclothiazide) were recommended. This information was obtained from a study of the hospital charts and from patient interviews but it cannot be ascertained whether in every case the recommendations were adhered to, specifically as to dose and duration of treatment.

Six of these mothers were studied previously under a protocol described elsewhere (15). They underwent elective cesarean section after a period of 8 hr of recumbency, either on their side or back. During the 2 hr before delivery they were supine, under close supervision. They were given either epidural anesthesia or general anesthesia with nitrous oxide until delivery and then halothane. Heparinized blood samples were obtained from the mother and cord at the time of delivery. Another 18 women were studied at the time of vaginal delivery. The conditions before delivery and length of labor varied. They received either small amounts of analgesic or epidural anesthesia. All underwent uncomplicated delivery and blood samples were obtained simultaneously from the mother and cord at delivery.

In 7 cases, maternal samples alone were obtained and in 11, cord samples alone were collected as shown in Table II.

Newborns. Normal newborns ranging in age from 1 to 72 hr were studied from the Newborn Nursery of the University of Maryland Hospital. Heparinized blood samples were obtained, centrifuged within 30 min and the plasma stored at −20°C. Unfortunately, it was not possible to do serial studies on the same newborn. The weights had been recorded at time of birth and at the time of the test. Most babies had been fed glucose water (D_5W) in the first 24 hr and had been started on Similac[5] (S_{20}) formula by 36 hr. In each instance the baby had been fed 30–150 min before the blood drawing. In all cases except for two, where the baby was crying, the babies were either asleep or quietly awake.

Experimental procedures

The plasma aldosterone concentrations were determined by either double isotope technique (19) or radioimmunoassay (20). In the latter method, aldosterone-3-carboxymethoxime-18,21 diacetate was coupled to rabbit albumin and antibodies produced in rabbits. 0.5–1 ml of plasma was extracted and subjected to paper chromatography. After equilibration the bound and free fractions were separated using Florisil.[6] Good correlation between the two methods was present.

Statistical evaluation was done by using *t* test and paired *t* test (21).

RESULTS

Cesarean section (Table I). The plasma aldosterone concentrations in maternal and cord blood with the mother on a normal sodium intake undergoing elective cesarean section have been reported previously (15) and are represented in Table I. The mean of the maternal plasma concentration was 3.7 ±1.4 ng/100 ml (SD) which was significantly lower than the mean of the cord blood aldosterone concentration of 17.2 ±9.5 ng/100 ml (SD) ($P < 0.02$). The maternal plasma aldosterone concentration was higher than the mean of normal recumbent adults on normal sodium intake (1.7 ±1.4 ng/100 ml) as shown in Fig. 1.

TABLE I

*Aldosterone Concentrations in Maternal and Cord Plasma with Mother on Normal Sodium Intake Undergoing Cesarean Section**

Number	Plasma aldosterone	
	Maternal	Cord
	ng/100 ml	
1	1.7	3.4
2	2.0	24.0
3	4.6	20.3
4	5.0	26.7
5	4.4	11.8
Mean ±SD	3.7 ±1.4	17.2 ±9.5

* These values have been reported previously (15).

Vaginal delivery (Table II). If the mothers had been on a normal sodium intake before uncomplicated vaginal delivery their mean plasma aldosterone concentration was 14.9 ±7.0 ng/100 ml (SD) which was significantly higher ($P < 0.001$) than the mean concentration obtained at cesarean section (Fig. 1). The mean plasma aldosterone concentration in the cord blood specimens obtained at vaginal delivery of 22.9 ±17.3 μg/100 ml (SD) was not significantly higher ($P > 0.30$) than the maternal value.

If the mother had been on sodium restriction with or without additional diuretics before vaginal delivery the mean plasma aldosterone concentration in the maternal blood was 44.9 ±24.2 ng/100 ml (SD). This was significantly higher than the plasma aldosterone concentration during vaginal delivery in mothers on normal sodium intake ($P < 0.001$). The mean plasma aldosterone concentration in the cord blood when the mothers were on sodium restriction was 75.2 ±51.6 ng/100 ml (SD). This was significantly higher than the corresponding mean maternal aldosterone concentration ($P < 0.05$). Aldosterone concentrations in cord plasma of infants delivered by elective cesarean section and by vaginal delivery when the mothers were on normal sodium intake were similar. However, values of cord blood were significantly higher ($P < 0.005$) when the mothers had been on restricted sodium diet with or

[1] Ciba Pharmaceutical Company, Summit, N. J.
[2] Smith, Kline & French Laboratories, Philadelphia, Pa.
[3] E. R. Squibb & Sons, New York.
[4] Abbott Laboratories, North Chicago, Ill.
[5] Ross Laboratories, Columbus, Ohio.
[6] Floridin Co., Tallahassee, Fla.

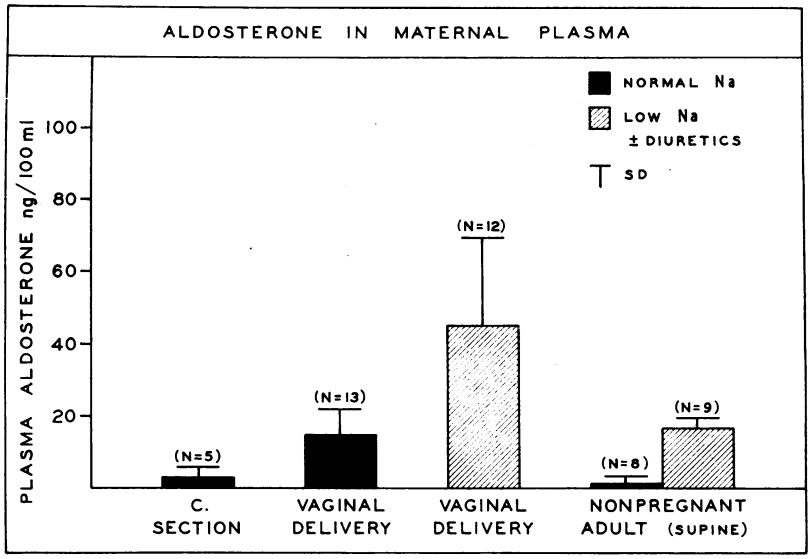

FIGURE 1 Aldosterone concentration in maternal plasma at the time of delivery by cesarean section and vaginal route. Bars represent mean plasma aldosterone concentrations expressed as nanograms per 100 ml ±1 SD.

TABLE II

Aldosterone Concentrations in Maternal and Cord Plasma during Vaginal Delivery

Mother on normal sodium intake			Mother on restricted sodium diet with or without diuretics		
	Plasma aldosterone			Plasma aldosterone	
Number	Maternal	Cord	Number	Maternal	Cord
	ng/100 ml			*ng/100 ml*	
6	10.9	21.0	25*	29.4	112.0
7	9.2	12.2	26	30.0	86.6
8	15.3	24.0	27	75.7	34.7
9	17.2	54.9	28	96.7	91.3
10	19.3	17.9	29	62.1	97.9
11	29.2	28.0	30	25.3	26.5
12	13.1	7.6	31	26.5	56.7
13	2.8	5.8	32	34.9	27.6
14	17.9	—	33	30.9	66.6
15	14.4	—	34	68.0	95.0
16	9.2	—	35	29.0	—
17	11.0	—	36	30.0	—
18	24.6	—	37	—	42.0
19	—	24.0	38	—	215.0
20	—	12.7	39	—	124.4
21	—	61.8	40	—	34.4
22	—	11.0	41‡	—	18.0
23	—	33.5			
24	—	6.3			
Mean ±SD	14.9 ±7.0	22.9 ±17.3		44.9 ±24.2	75.2 ±51.6

* Cesarean section.

‡ Pitocin induction.

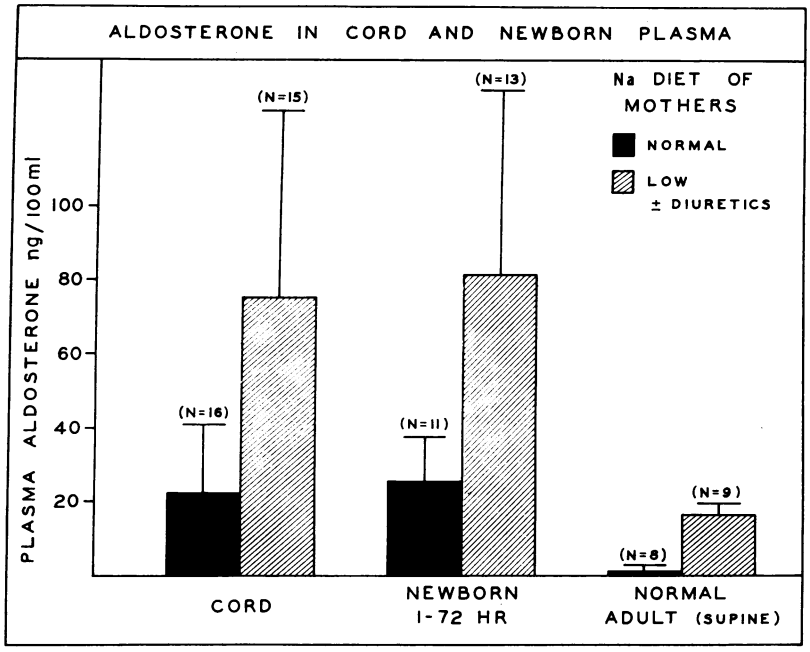

FIGURE 2 Aldosterone concentration in cord and newborn plasma. The mothers had been on normal or low sodium intake or diuretics before delivery. These values are compared to values obtained on normal, nonpregnant adults in supine position on similar dietary conditions.

without diuretics, as shown in Fig. 2. One mother on low sodium intake (No. 25) underwent elective cesarean section. Her plasma aldosterone concentration and that in cord blood of her infant were not different from those observed in vaginal delivery. The lowest plasma aldosterone concentration in a cord blood was obtained in a case where the mother had an induction by means of a Pitocin [7] drip.

Newborns. Table III represents the plasma aldosterone concentrations obtained in infants from 1 to 72 hr of age who had been born to mothers on normal sodium intake. All the infants were healthy newborns of approximately the same weight. All were fed dextrose water during the first 24 hr and then started on formula. The mean plasma aldosterone concentration was 25.9 ±11.7 ng/100 ml.

Table IV represents similar data on newborn infants of mothers on sodium restriction with or without diuretics. The mean plasma aldosterone concentration was 80.3 ±54.4 ng/100 ml. This value was significantly higher ($P < 0.005$) than that for infants born of mothers on normal sodium intake (see Fig. 2).

When mothers were on normal sodium intake, the aldosterone concentrations in cord plasma of infants born by either cesarean section or vaginal delivery were not significantly different ($P > 0.8$) from those of newborns 1–72 hr of age (Fig. 2). When the mothers had been on sodium restriction, with or without diuretics, there was no significant difference between the plasma aldosterone concentration of the infants at the time of birth or during the first 72 hr of life ($P > 0.6$).

[7] Parke, Davis & Company, Detroit, Mich.

DISCUSSION

Aldosterone during pregnancy. Aldosterone excretion and secretion is increased during pregnancy. Even though there is considerable variation in salt and water retention of normal pregnant women, Watanabe, Meeker, Gray, Sims, and Solomon (10) were able to show that during the last month of pregnancy there was increased retention of sodium coinciding with increased aldosterone secretion. We have also demonstrated that plasma aldosterone concentrations during the last trimester of pregnancy were significantly elevated when compared to normal individuals under similar conditions of sodium intake and posture (Fig. 1). The reason for this phenomenon has not been clearly elucidated.

The increase in aldosterone during pregnancy could be mediated by the renin-angiotensin system. Raised plasma renin levels have been demonstrated in all stages of pregnancy (22–28). Further increases have been demonstrated after sodium restriction and upright posture (29). Brown, Davies, Doak, Lever, and Robert-

TABLE III

Aldosterone Concentrations in Plasma of Newborns Whose Mothers Had Been on Normal Sodium Intake

Number	Sex of baby	Weight	Feeding	Hr after delivery	Aldosterone
		g			*ng/100 ml*
42	F	3005	None	1–24	6.6
43	M	3062	D_5W	1–24	32.5
44	F	3402	D_5W	1–24	39.5*
45	M	2920	D_5W	1–24	42.3*
46	M	4508	S_{20}	24–48	29.1
47	F	2778	S_{20}	24–48	13.3
48	F	2863	D_5W	24–48	34.2
49	F	3005	S_{20}	24–48	22.7
50	F	3515	S_{20}	24–48	21.3
51	M	2580	S_{20}	48–72	11.8
52	F	2948	S_{20}	48–72	31.1
Mean ±SD		3144 ±522			25.9 ±11.7

* Crying.

son (30) have also reported that at delivery the renin levels in the amniotic fluid were much higher than those in the umbilical plasma which were higher than those in the peripheral plasma of the corresponding mother.

The origin of renin in the various compartments of the maternal-placental-fetal unit is not known. The fetal kidney has been shown to contain renin and could therefore be the source of some of this hormone (31–33). Symonds, Stanley, and Skinner (34) found that the chorion laeve cells were capable of renin production in large amounts in vitro and this could explain the high levels of the amniotic fluid. Myometrial cells were also able to secrete renin (34), while the renin persisting in some nephrectomized nonpregnant women was thought to be uterine in origin (35, 36).

The elevated rate of progesterone secretion (37) and elevated plasma progesterone levels in pregnancy (38–40) could also influence the plasma aldosterone concentration. Landau et al (41–43) demonstrated that sodium excretion is increased when progesterone is given to nonpregnant subjects in doses comparable to

TABLE IV

Aldosterone Concentrations in Plasma of Newborns Whose Mothers Had Been on Sodium Restriction with or without Diuretics

Number	Sex of baby	Weight	Feeding	Hr after delivery	Aldosterone
		g			*ng/100 ml*
53	M	3388	None	1–24	12.8
54	M	3742	None	1–24	108.4
55	F	3232	None	1–24	149.0
56	M	3260	D_5W	1–24	62.7
57	M	2977	None	1–24	21.5
58	F	3218	D_5W	1–24	11.8
59	F	2466	S_{20}	24–48	106.0
60	F	3289	S_{20}	24–48	163.2
61	F	3260	S_{20}	24–48	39.3
62	F	3219	S_{20}	24–48	20.3
63	F	3515	S_{20}	24–48	109.8
64	M	3232	S_{20}	48–72	129.1
65	F	3572	S_{20}	48–72	110.4
Mean ±SD		3259 ±306			80.3 ±54.4

the rate of secretion in pregnancy. This was attributed to the antagonism between progesterone and aldosterone at the renal tubular level (44, 45). Estradiol and estriol have been shown to increase aldosterone secretion and excretion in normal nonpregnant women (46, 49). Whether estrogens are sufficiently elevated during pregnancy to contribute to the hyperaldosteronism is not known (46). Another hypothesis was that because of the increased glomerular filtration rate observed during pregnancy, increased sodium loss could occur causing secondary aldosterone elevation (49), but it has not been found to be a positive correlation (50).

The plasma levels of aldosterone obtained after 10 hr of recumbency and cesarean section were significantly lower than those obtained during vaginal delivery. In addition to an uncontrolled period of recumbency during vaginal delivery the stress of natural labor may cause a greater and more prolonged release of ACTH. Migeon et al. (51–53) have shown that plasma 17-hydroxycorticoids are significantly higher in maternal and cord plasma after vaginal delivery as compared to cesarean section. ACTH is known to cause acute stimulation of the adrenal with subsequent aldosterone release (13, 54–63). In animals uterine ischemia causes increased renin release (64). Whether this is true in the human at term is not known. If it were so, this could be another factor causing the elevation of plasma aldosterone concentration in women undergoing vaginal delivery compared to cesarean section.

If the pregnant woman had been on sodium restriction or diuretics before the time of delivery the plasma aldosterone concentrations were significantly higher irrespective of mode of delivery. These results agree with the data of Watanabe et al. (10) who showed that aldosterone secretion in pregnancy responded normally to changes in dietary sodium.

Aldosterone in cord plasma. In this study we were able to demonstrate that at the time of birth the cord plasma aldosterone concentration was even higher than the maternal in the majority of instances. This was significant in infants born of women on normal or low sodium intake undergoing cesarean section and of infants born by vaginal delivery of mothers on low sodium intake with or without diuretics; however, it was not significant when the mothers were on normal sodium diet. The plasma aldosterone concentrations remained high and significantly unaltered in infants during the first 72 hr of life. If the mother had been on sodium restriction or had used diuretics before delivery, then the baby's plasma aldosterone concentration was and remained significantly higher than if the mother had been on a normal sodium intake. All plasma aldosterone concentrations were significantly elevated when compared to normal supine individuals on normal or low sodium intake (Fig. 2).

Dufau and Villee (65) have shown that the fetal adrenal is capable of converting corticosterone to aldosterone as early as 15 wk of gestation in vitro. In a previous study (15) we were able to demonstrate that at term a significant amount of the fetal aldosterone was secreted by the fetus and only a small portion of the total fetal aldosterone crossed the placenta from the mother.

Normally in the human being the concentration of sodium ions is the same in the maternal and fetal circulation. Sodium ions move across the placenta more slowly than water and exert an appreciable osmotic effect. Studies of the transfer rate of Na^{24} from mother to fetus during gestation have shown a rise of sodium in the fetus at a maximum at about $\frac{9}{10}$ of gestation with subsequent fall (66). Whether sodium transfer across the placenta can explain the results obtained in infants born of sodium restricted mothers remains to be demonstrated.

Aldosterone in the newborn period. After birth a physiologic weight loss of about 7% of total body weight occurs during the first 3–5 days of life. Both intracellular and extracellular fluid are lost (67). Even though intake is virtually sodium-free, a loss of both water and sodium continues. The kidneys are able to concentrate urine to about half the full capacity (66). High circulating levels of progesterone may also aggravate sodium loss (68, 69).

No information was previously available in regard to plasma aldosterone concentrations during the newborn period. Several investigators have reported excretion rates of aldosterone in young children but a wide range of values is found (70–74). This is probably due to the variable percentage of the 3-oxoconjugate which is excreted (16, 72, 73). Weldon, Kowarski, and Migeon (16) reported aldosterone secretion rates (ASR[8]) in seven newborns ranging in age from 3 to 168 hr. In all cases the ASR was low when compared to older infants or children. The highest value of 41 μg/24 hr was obtained in an infant whose mother was treated with chlorothiazide for several months before delivery. The half-life of cortisol has been shown to be prolonged during the neonatal period (75) and this could also be true for aldosterone due to inefficient, developing enzyme systems. Thus, the aldosterone excretion and secretion studies did not reflect the true aldosterone homeostasis. Studies of aldosterone half-life, turnover, and metabolic clearance will be necessary for additional and more precise information.

[8] *Abbreviation used in this paper:* ASR, aldosterone secretion rate.

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