FERTILITY AND STERILITY
Vol. 50, No. 5, November 1988

Printed in U.S.A.

Atrial natriuretic peptide, plasma renin activity, and aldosterone in women on estrogen therapy and with premenstrual syndrome*

Bert J. Davidson, M.D., Ph.D.†
Christopher D. Rea, B.A.
Guillermo J. Valenzuela, M.D.

Department of Gynecology and Obstetrics, Loma Linda University Medical Center, Loma Linda, California

Estrogens are known to increase the renin–angiotensin–aldosterone system and to produce fluid retention, while atrial natriuretic peptide (ANP) induces an increase of the urinary output and tends to return the fluid balance to normal. The aim of this study was to test whether the levels of ANP were decreased during chronic estrogen and progestin administration, thereby possibly decreasing the amount of fluid excreted. The authors also studied women with premenstrual syndrome (PMS), because of the associated fluid retention often described with this syndrome. Levels of ANP, plasma renin activity (PRA), and aldosterone were determined in premenopausal women in the early follicular phase (EFP) and on low-dose oral contraceptives (OC), in postmenopausal patients with and without estrogen replacement therapy (ERT), and in women with PMS associated with fluid retention. The concentrations of ANP and PRA were enhanced in the women on OC, but those of aldosterone were unchanged. No differences were observed in the women on ERT or with PMS. It is concluded that the levels of PRA and ANP are affected by estrogen or progesterone therapy or the combination of the two and this response is dose dependent or additive. Furthermore, ANP and PRA do not seem to play a direct role in PMS. Fertil Steril 50:743, 1988

Women retain significant amounts of fluid during their reproductive years, especially in relation to the use of exogenous estrogens[1] or during pregnancy.[2] The reasons for this fluid retention during pregnancy are unknown. One theory is that the changes during pregnancy may be related to the 100-fold increase in the plasma concentration of circulating estradiol (E_2), which would produce an increase in the renin–angiotensin–aldosterone system, which in turn would produce water retention.[3] Possibly the 10-fold increase of progesterone in pregnancy could have that effect. Castration of ewes affects several cardiovascular functions including a decrease in blood volume, systemic vascular and interstitial fluid compliance, and lymph flow rate.[4] These results would suggest that even physiological amounts of estrogen are important factors in blood volume regulation.

Atrial natriuretic peptide (ANP) is the latest hormonal addition to the complex mechanisms involved in the maintenance of fluid and salt homeostasis, which also includes renin, angiotensin II, and aldosterone. ANP is released by the heart in response to increase in atrial pressure; an ANP infusion produces, among other effects, an increase in urinary flow, hypotension, and a decrease in the adrenal secretion of angiotensin II.[5]

The present study aimed to evaluate the interrelations among ANP, plasma renin substrate

Received February 8, 1988; revised and accepted July 26, 1988.

* Presented at the Forty-Second Annual Meeting of The American Fertility Society and the Eighteenth Annual Meeting of The Canadian Fertility and Andrology Society, September 27 to October 2, 1986, Toronto, Ontario, Canada.

† Reprint requests: Bert J. Davidson, M.D., Ph.D., Department of Gynecology and Obstetrics, Loma Linda University Medical Center, Loma Linda, California 92350.

(PRA), and aldosterone after exogenous estrogen with and without progestin administration. This is important because a decrease in the concentration of a hormone that increases the urinary output in case of excessive fluid would explain the fluid retention associated with estrogen and progestin excess. To accomplish this objective, we tested women with higher-dose estrogen and progestin treatment as oral contraceptives (OC) and lower-dose estrogen and progestin replacement therapy (ERT) in the menopause. We also studied women with significant premenstrual syndrome (PMS) who complained about water retention.

MATERIALS AND METHODS

Patients

All participants were healthy and of average weight, did not take any medications except for the ones studied, and had no kidney disease or hypertension. All premenopausal women were under 35 years of age. In all patients, informed consent was obtained.

Oral Contraceptives

All women (n = 17) were taking pills containing 35 μg of ethinyl estradiol (EE) and various dosages of 19-nortestosterone derivatives. Blood was drawn between 10 and 15 days after starting the monthly regimen. As a control group, 17 normally cycling premenopausal women were studied in the early follicular phase (EFP), days 3 to 7 of the cycle.

Estrogen Replacement Therapy

All women (n = 17) were postmenopausal and between the ages of 50 and 60. They were taking 0.625 mg of conjugated equine estrogens (CEE) day 1 to 25 of each month; 10 mg of medroxyprogesterone acetate (MPA) was added day 16 through 25. Blood was drawn between day 10 and 15 of the cyclic regimen before the addition of the progestin. As a control group, 13 postmenopausal women in the same age group without estrogen replacement therapy were studied.

Premenstrual Syndrome

Seven women were selected with recurrent premenstrual symptoms as recorded on a symptoms chart. In all of them, there were signs of water retention described as "bloating," headaches, and breast engorgement, in addition to other symptoms. Samples were obtained in the EFP, when there were no complaints, and in the late luteal phase (LLP), when symptoms were present, within 1 week of the menstrual period. All women in this group were between the ages of 28 and 35.

Specimen Collection and Processing

Blood was drawn while the patients were fasting with low suction to prevent hemolysis and immediately transferred to ice-cooled tubes. For aldosterone, blood was allowed to clot in glass containers; for PRA, it was collected in plastic tubes to which 1.5 mg/ml of ethylenediaminetetraacetic acid (EDTA) was added; for ANP, in 1.5 mg/ml EDTA Safety-Monovett syringes containing 50 U/ml of trasylol, obtained from Sigma Company (St. Louis, MO). All samples were separated within 20 minutes of collection and stored at −20°C until assay.

Assays

All samples were tested in one assay for each individual compound. ANP was assayed without extraction with a radioimmunoassay (RIA) kit purchased from Amersham Corporation (Arlington Heights, IL). Inter-assay and intra-assay coefficients of variation (COVs) were 9.1% and 9.9%, respectively. PRA was determined with the use of a RIA kit from Travenol-Genentech Diagnostics (Cambridge, MA). COVs were 6.0% and 6.9%.

Aldosterone was measured by RIA obtained from Diagnostic Products Corporation (Los Angeles, CA), with COVs of 7.1% and 5.1%.

Statistical Analysis

For comparisons between groups, unpaired Student's *t*-tests were utilized; whereas for comparisons within groups, paired *t*-tests were applied.

RESULTS

All hormone values are expressed as the mean ± standard error of the mean (SEM).

Figure 1 shows the levels of ANP in pg/ml in women in the EFP (35.7 ± 3.4), on OC (57.7 ± 5.8), and in the menopause without (42.8 ± 5.8) or with ERT (52.7 ± 7.7). The women on OC had significantly higher levels than those in the early follicular phase ($P = 0.002$). Women on ERT had levels not different from those without treatment.

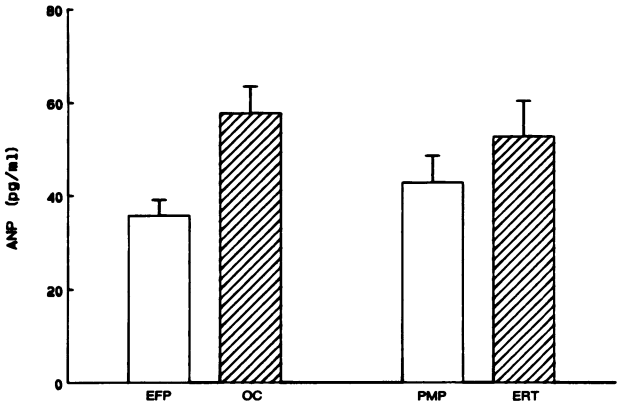

Figure 1 Mean (±SEM) ANP in women in the EFP, on OC, and in the menopause without (PMP) or with ERT. Women on OC had significantly higher levels than those in the EFP ($P = 0.002$). Women on ERT had levels not different from those without treatment.

Figure 2 depicts the levels of PRA in ng/ml/hr in women in the EFP (2.96 ± 0.7), on OC (5.26 ± 0.59), and in the menopause without (2.48 ± 1.21) or with ERT (5.08 ± 1.57). The women on OC had significantly higher levels than those in the EFP ($P = 0.028$). Women on ERT had levels not different from those without treatment.

Figure 3 represents the levels of aldosterone in pg/ml in women in the EFP (122.3 ± 22.0), on OC (117.8 ± 23.7), and in the menopause without (86.1 ± 13.9) or with ERT (156.7 ± 30.9). No significantly different levels were found between the groups.

Table 1 shows the levels of ANP and PRA in women with significant PMS in the EFP and the LLP. No significant differences were observed between the levels of both hormones.

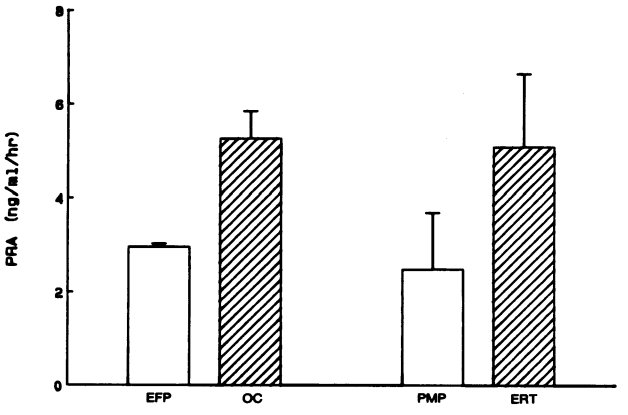

Figure 2 Mean (±SEM) PRA in women in the EFP, on OC, and in the menopause without (PMP) or with ERT (ERP). Women on OC had significantly higher levels than those in the ($P = 0.028$). Women on ERT had levels not different from those without treatment.

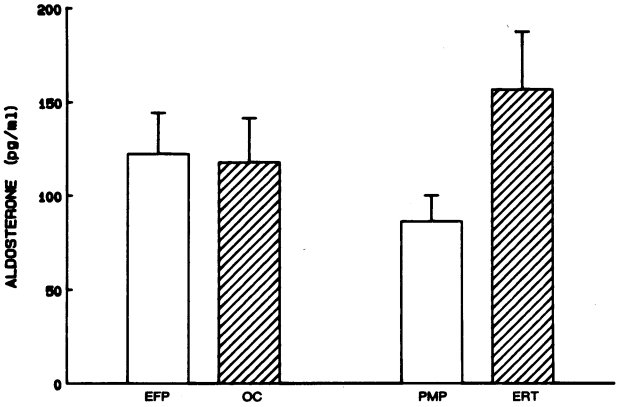

Figure 3 Mean (±SEM) aldosterone in women in the EFP, on OC, and in the menopause without (PMP) or with ERT. No significantly different levels were found between the groups.

DISCUSSION

The renin–angiotensin–aldosterone axis responds to decreases in circulatory volume and is able to adjust very precisely to reductions in salt intake by increasing these hormones and diminishing renal salt excretion. ANP appears to play a role in a homeostatic feedback system that regulates fluid balance. Pressors and salt- and volume-retaining stimuli increase ANP, which in turn decreases blood pressure; antagonizes renin, angiotensin, aldosterone, and antidiuretic hormone; and increases natriuresis.[5]

In this study, we evaluated levels of ANP, PRA, and aldosterone in women on OC containing 35 μg of EE and ERT with 0.625 mg of CEE. Mashchak et al.,[6] comparing equivalent amounts of synthetic and natural estrogens and their effects on angiotensinogen, estimated the potency of EE to be about 70 times that of CEE. For the doses used in this study, EE was almost four times as potent as CEE for this component of the renin–angiotensin–

Table 1 Levels of ANP and PRA in Women with Significant PMS in the EFP and the LLP[a]

	EFP	LLP	*P*
ANP (ng/ml)	30.7 ± 4.7	26.7 ± 3.1	NS[b]
PRA (ng/ml/hr)	2.16 ± .86	1.34 ± .62	NS

[a] No significant differences were observed between the levels of hormones.

[b] NS, not significant.

aldosterone–ANP axis, so women on OC received four times the amount of estrogen that the postmenopausal women ingested daily. While the women on OC received progestins, those on ERT were studied while on CEE alone.

Levels of ANP and PRA, but not those of aldosterone, were significantly increased in the users of OC but not in the women on ERT, suggesting an estrogen dose response or an effect from the progestin in the OC medication. The lack of increase in the circulating levels of aldosterone observed with the chronic estrogen administration are in agreement with experimental observations in castrated sheep, in whom the chronic administration of E_2 increased PRA and aldosterone initially but later on only PRA continued to be elevated.[7] The present findings of an increase of ANP after the administration of estrogen and progestin may help explain the increase of ANP in human pregnancy described by Yamaji et al.,[8] in which there are a 100-fold increase of circulating E_2, a 10-fold increase of progesterone, and a several-fold increase of ANP over the nonpregnant state.

The present results did not confirm our original hypothesis that a decrease of ANP would be responsible for the fluid retention observed during estrogen administration. One possible reason for the increase in circulating ANP is that it is secondary to the increase in the renin–angiotensin–aldosterone system after estrogen and progestin administration. It is possible that if this increase of ANP would not have occurred, the fluid retention could have been much more marked, so a higher set-point was reached.

PMS is a frequent complaint of premenopausal women, and the pathophysiology is under much speculation. In addition to the psychologic and behavioral complaints, there are physical symptoms, of which fluid retention or a fluid shift is the most prevalent. Women perceive this fluid retention or change in fluid distribution as abdominal bloating, swelling of the extremities and breasts, headaches, and periodic weight gain. Most studies agree that there are no changes in circulating steroid hormones in PMS sufferers.[9] This study evaluated the role of two of the major hormones involved in fluid and salt homeostasis, PRA and ANP, in women with PMS who specifically complained about water retention. According to some authors, levels of PRA, angiotensin II, and aldosterone are elevated in the luteal phase.[10] Abraham[11] reports that aldosterone is enhanced manyfold in the luteal phase of women with PMS associated with increased extracellular fluid, but that is not confirmed by all authors.[12] If PRA or aldosterone were to be elevated, conceivably a defect in the secretion of ANP with its strong natriuretic effect could be responsible for the symptoms in this manifestation of PMS. However, in this study, no changes of either PRA or ANP were observed.

In conclusion, high estrogen and progestin doses are associated with an increase in the levels of some of the hormones associated with fluid balance, as PRA and ANP. This study confirms that chronic estrogen and progestin administration does not maintain elevated levels of aldosterone. PRA and ANP are unchanged in PMS.

REFERENCES

1. Speroff L, Glass RH, Kase NG: Steroid contraception. In Clinical Gynecological Endocrinology and Infertility, 3rd edition. Baltimore, Williams & Wilkins, 1983, p 409
2. Hytten FE: Water storage in normal pregnancy. Int J Gynecol Obstet 8:343, 1970
3. Longo LD: Maternal blood volume and cardiac output during pregnancy: a hypothesis of endocrinological control. Am J Physiol (Regulatory Integr Comp Physiol 14) 245: R720, 1983
4. Valenzuela GJ, Brace RA, Longo LD: Lymphatic and vascular responses to fluid infusion in castrated and non-castrated sheep. Am J Physiol (Regulatory Integr Comp Physiol 21) 252:R1114, 1987
5. Laragh JH: Atrial natriuretic hormone, the renin–aldosterone axis, and blood pressure–electrolyte homeostasis. N Engl J Med 313:1330, 1985
6. Mashchak CA, Lobo RA, Dozono-Takano R, Eggena P, Nakamura RM, Brenner PF, Mishell DR: Comparison of pharmacodynamic properties of various estrogen formulations. Am J Obstet Gynecol 144:511, 1982
7. Valenzuela GJ, Hewitt CW, Longo LD: Estradiol effects on plasma renin activity, aldosterone, and cardiac output in chronically catheterized castrated sheep. (Abstr 69P.) Presented at the Thirty-fourth Annual Meeting of the Society of Gynecological Investigation, Atlanta, Georgia, March 18 to 21, 1987
8. Yamaji T, Hirai N, Ishibashi M, Tekaku F, Yanaihara T, Nakayama T: Atrial natriuretic peptide in umbilical cord blood: evidence for a circulating hormone in human fetus. J Clin Endocrinol Metab 63:1414, 1986
9. O'Brien PMS: The premenstrual syndrome, a review. J Reprod Med 30:113, 1985
10. Katz FH, Rohm P: Plasma aldosterone and renin activity during the menstrual cycle. J Clin Endocrinol 34:819, 1972
11. Abraham GE: Nutritional factors in the etiology of the premenstrual tension syndromes. J Reprod Med 28:446, 1983
12. Munday M, Brush MG, Taylor RW: Progesterone and aldosterone levels in premenstrual syndrome. J Endocrinol 73:21P, 1977