Endogenous and exogenous female sex hormones and renal electrolyte handling: effects of an acute sodium load on plasma volume at rest

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1School of Physical Education, University of Otago, Dunedin, New Zealand; 2Stanford Prevention Research Center, Stanford University, Stanford, California; and 3Department of Human Nutrition, and 4Preventive and Social Medicine, University of Otago, Dunedin, New Zealand

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Sims ST, Rehrer NJ, Bell ML, Cotter JD. Endogenous and exogenous female sex hormones and renal electrolyte handling: effects of an acute sodium load on plasma volume at rest. J Appl Physiol 105: 121–127, 2008. First published April 24, 2008; doi:10.1152/japplphysiol.01331.2007.—This study was conducted to investigate effects of an acute sodium load on resting plasma volume (PV) and renal mechanisms across the menstrual cycle of endurance-trained women with natural (NAT) or oral contraceptive pill (OCP) controlled cycles. Twelve women were assigned to one of two groups, according to their usage status: 1) OCP [n = 6, 29 yr (SD 6), 59.4 kg (SD 3.2)], or 2) NAT [n = 6, 24 yr (SD 5), 61.3 kg (SD 3.6)]. The sodium load was administered as a concentrated sodium chloride/citrate beverage (164 mmol Na+/l, 253 mosmol/kgH2O, 10 ml/kg body mass) during the last high-hormone week of the OCP cycle (OCPhigh) or late luteal phase of the NAT cycle (NAThigh) and during the low-hormone sugar pill week of OCP (OCPlow) or early follicular phase of the NAT cycle (NATlow). The beverage (~628 ml) was ingested in seven portions across 60 min. Over the next 4 h, PV expanded more in the low-hormone phase for both groups (time-averaged change): OCPlow 6.1% (SD 1.1) and NATlow 5.4% (SD 1.2) vs. OCPhigh 3.9% (SD 0.9) and NAThigh 3.5% (SD 0.8) (P = 0.02). The arginine vasopressin increased less in the low-hormone phase [1.63 (SD 0.2) and 1.30 pg/ml (SD 0.2) vs. 1.82 (SD 0.3) and 1.57 pg/ml (SD 0.5), P = 0.0001], as did plasma aldosterone concentration (~64% lower, P = 0.0001). Thus PV increased more and renal hormone sensitivity was decreased in the low-hormone menstrual phase following sodium/fluid ingestion, irrespective of OCP usage.

oral contraceptive pill; citrate; hypervolemia; hyperhydration; estradiol; progesterone

BODY WATER AND ELECTROLYTE balance are critical for normal cellular function and maintaining adequate blood and plasma volume (PV) and osmolality, yet natural and synthetic female sex hormones have various effects on water and electrolyte balance. Thus understanding the interactions of female sex hormones and their synthetic analogs and the fluid regulatory system is crucial. The two most influential female sex hormones are estrogen and progesterone, both of which change in concentration across the menstrual cycle and are governed by oral contraceptive pill (OCP) usage. These two hormones influence sodium and water distribution and thus fluid compartment volumes and dynamics. Primarily, it is known that estrogens favor fluid retention by activating the renin-angiotensin-aldosterone system and that progesterone is able to antagonize this event (21). Estrogen enhances vasodilation and capillary permeability and acts centrally to lower the operating set point of plasma osmolality (Posm) (a leftward shift in AVP sensitivity) (21, 22, 28, 30, 38). Progesterone competes directly with the same mineralocorticoid receptor as aldosterone, which may cause a transient natriuresis (20).

Although the effects of estrogen and progesterone on PV in women are relatively well known via acute infusions and manipulation of hormone concentrations, there is limited research on the effects of the chronic perturbations of menstrual cycle hormones on water and sodium handling. Moreover, these effects may not be the same with the chronic use of OCPs, where adaptations may be evident with regard to fluid regulatory functions. Combined OCP exhibit three to five times the bioactivity of endogenous estrogen; the progesterin component of OCP does not compete with the mineralocorticoid receptor (8, 17, 20). Thus unopposed effects of ethinyl estradiol on fluid regulation may induce extracellular fluid expansion at a greater volume than observed with natural endogenous estrogen (17β-estradiol). The “placebo week” of OCP regimes is of additional interest, as it is often referred to as “low hormone” or “hormone free.” This concept is erroneous, as OCP agents do not produce complete ovarian suppression. Residual ovarian activity has been observed in women taking preparations containing 50 mg ethinyl estradiol, and lower estrogen doses have been associated with even less ovarian suppression (5, 9, 27). Coupled with the secondary effects of residual metabolites in other tissues (e.g., the kidney), fluid dynamics of this placebo week are still unknown.

The main purpose of this project was to investigate fluid balance perturbations, renal-sodium sensitivity, and responses during hormonal “extremes” of the menstrual cycle, particularly with regard to the impact of chronic OCP usage during the placebo week on sodium and water regulation. This was evaluated by inducing a sodium-mediated PV expansion using a high-sodium beverage at rest during the last high-hormone week of the OCP cycle (OCPhigh) or the late luteal phase of the natural cycle (NAThigh) and during the low-hormone sugar pill week of the OCP cycle (OCPlow) or during the early follicular phase of the natural cycle (NATlow). It was hypothesized that hypervolemia would occur in both phases of the menstrual cycle, regardless of pill usage, with the greatest expansion occurring in OCPlow followed by the NATlow. It was also hypothesized that the renal responses to the sodium load would be blunted in the luteal and high-hormone phases due to the resetting of baseline osmotic and AVP sensitivity.
METHODS

Participants

Thirteen healthy, eumenorrheic, endurance-trained female cyclists [peak aerobic power (V\textsubscript{O}\textsubscript{2peak}) 52 ml·kg\(^{-1}\)·min\(^{-1}\) (SD 2); 26 yr (SD 6), 60.8 kg (SD 4.8)], aged 18–35 yr, with no history of cardiovascular or renal disease, no contraindications to OCPs, and taking no other medication, were recruited. Twelve women completed the study: six were on triphasic OCPs (OCP, Table 1), and six were not on any contraceptive pill (NAT). All women had regular menstrual cycles (28 days, 26–29 days). All women on the triphasic OCP had been following the same schedule of pills for at least 12 mo before testing. Before participation, all participants were informed of the nature and demands of the investigation, after which they gave written, informed consent. The study was approved by the Human Ethics Committee of the University of Otago. All participants were familiar with the experimental protocols and conditions, and all had participated in previous laboratory trials.

Preliminary Testing

All participants initially underwent an incremental cycling test to exhaustion to ensure that they met the criteria for being categorized as “well trained” [train ≥ 5 times/wk and have V\textsubscript{O}\textsubscript{2peak} > 50 ml O\textsubscript{2}·kg body mass (BM)\(^{-1}\)·min\(^{-1}\)]. The V\textsubscript{O}\textsubscript{2peak} test was conducted on a separate day, in temperate conditions (19 ± 2°C), 1–2 wk before experimental testing. The test comprised incremental increases in work rate to exhaustion, on an electromagnetically braked bicycle ergometer (Velotron, Racermate, Seattle, WA) during which O\textsubscript{2} consumption, CO\textsubscript{2} production, and heart rate were measured.

Experimental Testing

Each participant performed two identical sodium-loading trials: one in NAT\textsubscript{low}, or OCP\textsubscript{low} and one in NAT\textsubscript{high}, or OCP\textsubscript{high}. Sodium loading was via ingestion of a concentrated sodium beverage (3), as described below. Experimental trials were on days 4–6 and 21–22 for an endogenous 28-day cycle, and on days 18–20 (end of the third week of active pills high-hormone phase) and days 24–26 (days 3–5 of placebo week) for a triphasic OCP cycle. Participants were asked to self-monitor menstrual cycle by recording the brand name and of placebo week) for a triphasic OCP cycle. Participants were asked to self-monitor menstrual cycle by recording the brand name and cycle of the pill or, in nonpill users, by recording basal temperature. Women were required to walk for 2 min before every urine sample, after the blood samples were taken 10 min after blood sampling. Participants were required to walk for 2 min before every urine sample, after the blood sampling, to ensure posture standardized, but also minimally artificial, effects on PV (Fig. 1).

Blood and Urine Analysis

All blood samples (17 ml each) were separated into aliquots for analysis of hematocrit (Hct), hemoglobin concentration ([Hb]), plasma sodium concentration ([Na\textsuperscript{+}]P), Posm, plasma creatinine ([Cr\textsubscript{p}]P), plasma arginine vasopressin ([AVP]P), and aldosterone ([ALD]P). A 2-ml aliquot was analyzed immediately for [Hb] (Hemoximeter, OSM3 Radiometer, Copenhagen, Denmark) and Hct, in quadruplicate. Blood for Hct was drawn into capillary tubes and centrifuged for 6 min at 3,000 rpm (Hawksley Microcentrifuge, Sussex, UK) and read using a modified microcapillary tube reader (Damon/IEC division, Needham Heights, MA); the measurement error was ±0.25%. One of the remaining three additional aliquots of blood (5 ml each) was transferred into a tube containing heparin for Posm determination. The last two aliquots were transferred into tubes containing EDTA for determination of [AVP]P, [ALD]P, creatinine, [E\textsubscript{2}P], and progesterone and progestins ([P\textsubscript{4}P]). All three tubes were then centrifuged for 10 min at 6°C and 3,000 rpm (model GS-15R Centrifuge, Beckman-Coulter, Fullerton, CA).

USG was measured in triplicate with a hand refractometer (ATAGO, Tokyo, Japan). Plasma and urine samples were put on ice during the protocol and then stored at −80°C until analyses for

<table>
<thead>
<tr>
<th>Participant</th>
<th>Brand Name</th>
<th>Dose OCP\textsubscript{high}, mg</th>
<th>Dose OCP\textsubscript{low}, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Triphasil*</td>
<td>0.02 0.125</td>
<td>0.03 0.05</td>
</tr>
<tr>
<td>B</td>
<td>TRIFEME*</td>
<td>0.03 0.125</td>
<td>0.03 0.05</td>
</tr>
<tr>
<td>C</td>
<td>Triquilar ED†</td>
<td>0.03 0.125</td>
<td>0.03 0.05</td>
</tr>
<tr>
<td>D</td>
<td>Triquilar ED†</td>
<td>0.03 0.125</td>
<td>0.03 0.05</td>
</tr>
<tr>
<td>E</td>
<td>Triphasil*</td>
<td>0.02 0.125</td>
<td>0.03 0.05</td>
</tr>
<tr>
<td>F</td>
<td>Triphasil*</td>
<td>0.03 0.125</td>
<td>0.03 0.05</td>
</tr>
</tbody>
</table>

OCP\textsubscript{high} and OCP\textsubscript{low}, high- and low-hormone week of oral contraceptive pill cycle, respectively; EE, ethinyl-estradiol; progestin, levonorgestrel. *Wyeth (New Zealand) Ltd. †Bayer (New Zealand) Ltd.
osmolalities and electrolyte and hormone concentrations, conducted after completion of the study. Posm was measured using vapor point depression (Osmometer, model Vapo5520, Wescor, Logan, UT). Urine and plasma electrolyte and hormone concentrations were measured at the local health board medical laboratory (Otago Southern Community Laboratories) using indirect ion-specific electrode technique (Aeroset/c8000 Indirect Ion Specific Electrodes analyzer, Abbott, Chicago, IL). Creatinine clearance was determined through log-linear equation of [Cr]P/creatinine concentrations in urine ([Cr]U) (Jaffe reaction, Abbott reagents). The [AVP]P was measured using an “in house” antiserum, with synthetic AVP (Ferring or Sigma) used for standards and preparation of 125I-labeled AVP using chloramine T and purification by HPLC. Samples were extracted with acetonitrile (1:2 acetonitrile-plasma), and the supernatant was dried before assay.

A 3-day preincubation step at 4°C is followed by a further 3 days at 4°C after the addition of the 125I-labeled AVP. Separation of bound and free hormone is by polyethylene glycol plus-globulin precipitation. The [ALD]P was measured using the solid-phase antibody RIA method (Biosource Europe). The [E2]P was measured via a Sorin (sensitive) RIA kit (Sorin Biomedica Diagnostics, Saluggia, Italy). The [P4]P was measured using the commercial conjugate-antibody method (ELISA kit, Assay Designs, Ann Arbor, MI), with sample concentrations determined against a standard curve. Intra- and inter-assay coefficients of variation, respectively, for the midrange standards were for [AVP]P 23.2 pg/ml 5.10 and 9.80%; [ALD]P 147 pg/ml 5.48 and 6.52%; [E2]P 115 pg/ml 2.80 and 6.00%, and [P4]P 1.5 ng/ml 3.61 and 4.80%.

Calculations

Changes in PV from baseline were estimated from changes in Hct and [Hb] using the following equation (6):

\[
\% \Delta PV = 100\left( Hb_b/Hb_t \right) \times \left[ \left( 1 - Hct_t \right) / \left( 1 - Hct_b \right) \right] - 100
\]

where subscripts t and 0 denote measurements at time t and at baseline, respectively. Hb is in g/100 ml, and Hct is a fraction. Hct was multiplied by 0.96 and then 0.91 to correct for trapped plasma and the venous-to-whole blood Hct excess, respectively.

\[
GFR \text{ (m}^{-1} \text{·min}^{-1} \cdot \text{m}^{-2}) = \left( [Cr]_U \times U_{\text{vol}} \right) / \left( [Cr]_P \times t \right)
\]

Where [Cr]U and [Cr]P are in mg/dl; Uvol is urine collection volume in ml, and t is urine collection time in minutes and is normalized to body surface area of each individual from height and mass (7).

Urine Na+ excretion was calculated as the product of urine sodium concentration ([Na+]U) and Uvol (ml). The fractional excretion of water (FEH2O) was calculated as

\[
FE_{\text{H2O}} = \left( U_{\text{vol}} / GFR \right) - 100
\]

and the fractional excretion of Na+ (FENa+) as:

\[
FE_{\text{Na}^+} = \frac{\text{[Na+]_U} - \text{[Na+]_P}}{\text{[Na+]_P}}
\]

Mixed models were used to model each of the outcomes as a function of time and hormonal state. The repeated-measures measures of the study design were taken into account by using the covariance structures available in the SAS (version 9.1) procedure MIXED. Measurements were assumed to be more highly correlated within than between participants and also within than between treatments within a subject.

Each outcome was modeled with a mixed model that included the order (first or second trial), the hormonal state (2 levels), time (5 levels), and the interaction of hormonal state with time. A significant (P < 0.05) interaction would indicate a difference in the profiles across time of the outcome between the two hormone states. Covariates of female sex hormones (progesterone, estrogen, OCP, or NAT), renal hormones, and the interaction of the main effects were included in the model. If the interaction term was not significant, a model, which included treatment and the main effects of time and hormone state, was computed. Differences in least squares means for each of the outcomes and 95% confidence interval (CI) were calculated from the model and were considered statistically significant at P < 0.05. Means are given with SD in parentheses.

Sample size calculation. The desired statistical test is two-sided at an α-level of 0.05, with 80% power to detect a difference. On the basis of pilot work, 80% power was determined sufficient to detect a significant alteration in PV expansion, [AVP]P, [ALD]P, Posm, and [Na+]U for a two-sided test, the calculated sample size is six participants per group.

RESULTS

Participant Compliance

To ensure participant compliance, training, diet, temperature logs (NAT), and pill usage (OCP) were collected and reviewed the morning of the second experimental session. All participants were deemed euhydrated based on USG (≤1.015). All participants completed all documentation and standardization procedures requested. Participant baseline characteristics are reported in Table 2.

Acute PV Changes

There were significant phase, but not group, differences with regard to the effect of sodium loading on PV expansion. Across the 4-h postloading time, there was greater PV expansion in OCPlow and NATlow vs. OCPhigh and NAThigh [change (Δ) 6.14 (SD 1.12) and 5.41% (SD 1.16) vs. Δ3.88 (SD 0.85) and 3.45% (SD 0.83), P = 0.0178; 95% CI: Δ3.39, Δ4.34; Fig. 2]. OCP usage did not alter the hypervolemic response (P = 0.27), and this was not dependent on phase of cycle (P = 0.32).

Renal Responses and Na+ Regulating Hormones

Across the experimental session, there was an increase of AVP with the sodium loading in the high-hormone phase of both OCPhigh and NAThigh A/V P: 1.82 (SD 0.3) and 1.57 pg/ml (SD 0.5) compared with OCPlow and NATlow [1.63 (SD 0.2) and 1.30 pg/ml (SD 0.2); 95% CI: 0.27, 0.12 pg/ml; Figs. 3 and 4]. There were significant differences in Posm between phases [OCPhigh
and NAThigh: 284.7 (SD 2.1) and 288.0 mosmol/kgH2O (SD 2.2); OCPlow and NATlow: 289.1 (SD 1.6) and 290.8 mosmol/kgH2O (SD 1.2), P = 0.001; 95% CI: 4.22, 5.82 mosmol/kgH2O), but no difference in the magnitude of response over time (P = 0.11) was observed. The AVP response in the high-hormone phase of both OCPhigh and NAThigh correlated with a lower Posm (P = 0.00; NAThigh vs. OCPhigh 101.9 pg/ml, 110.8 pg/ml (95% CI: 163.3, 52.5 pg/ml; OCPlow vs. OCPlow 101.9 pg/ml, 110.8 pg/ml, 95% CI: 10.98, 8.44 pg/ml), in contrast to the low-hormone phase.

### Renal Water and Sodium Handling

Means (SD) are presented in Table 4. There were significant differences in urinary output across the 5-h experimental sessions, with a greater urinary output in NAT across phases [NAThigh and OCPhigh: 1,068 (SD 90) vs. 928 ml (SD 88), P = 0.03; 95% CI: 119, 298 ml; NATlow and OCPlow: 1,133 (SD 108) vs. 938 ml (SD 20), P = 0.03; 95% CI: 180, 279 ml]. No significant differences were found between groups in GFR (P > 0.05, Table 4), although significant increased FENa+ (P = 0.03; 95% CI: 180, 279 ml).
Observed between NATlow and OCPlow (likely via their actions on the capillary endothelium to increase PV expansion occurred. Alteration of AVP sensitivity and/or action in the kidney stimulation of the renin-angiotensin-aldosterone system and an low-hormone phase was observed, which indicated that stim-

Loading was examined in women across the endogenous and exogenous menstrual cycle. Thus, in the present investigation, the efficacy of sodium loading was similar; however, FEH₂O was different between phases, with a difference in FEH₂O between the two groups.

**DISCUSSION**

This investigation is the first to document that an acute sodium-fluid load expands PV at rest in both high-hormone and low-hormone phases of an endogenous or exogenous driven menstrual cycle of endurance-trained women. The PV expansion observed in women is similar to that observed by 10.220.33.5 on October 1, 2017 http://jap.physiology.org/ Downloaded from

### Table 4. Renal characteristics

<table>
<thead>
<tr>
<th></th>
<th>Triphasic OCP</th>
<th>Natural 28-day Cycle</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>OCPhigh</td>
<td>OCPlow</td>
</tr>
<tr>
<td>GFR, ml/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80 min</td>
<td>118 (8)</td>
<td>110 (6)</td>
</tr>
<tr>
<td>120 min</td>
<td>121 (9)</td>
<td>116 (9)</td>
</tr>
<tr>
<td>180 min</td>
<td>95 (9)</td>
<td>90 (11)</td>
</tr>
<tr>
<td>300 min</td>
<td>88 (11)</td>
<td>85 (8)</td>
</tr>
<tr>
<td>Uᵣₐ, ml/min†</td>
<td>3.1 (1.2)</td>
<td>3.3 (1.1)</td>
</tr>
<tr>
<td>FEH₂O, %</td>
<td>2.9 (0.3)*</td>
<td>3.3 (0.5)</td>
</tr>
<tr>
<td>FE₈O⁺, % g</td>
<td>1.8 (0.2)</td>
<td>1.5 (0.1)</td>
</tr>
</tbody>
</table>

Values are means (SD). *Over the experimental time, postdrinking. GFR, glomerular filtration rate; Uᵣ, urinary excretion; FEH₂O, fractional excretion of water; FE₈O⁺, fractional excretion of sodium. *P < 0.05 between phases.

The results of the present study illustrate a greater AVP response to the sodium loading in the high-hormone phase of both groups, concomitant with a lower Po and higher [E₂]p. In humans, it has been established that basal Posm is higher in the follicular than in the luteal phase, with the threshold for AVP release lowest in the luteal phase (29, 31–32). Moreover, plasma 17β-estradiol concentrations of OCPlow were similar to those of NATlow in the baseline data of both groups; thus we would have expected a similar response in fluid retention (duration and %expansion) between OCPlow and NATlow. With the observed drop in PV expansion of OCPlow at 180 min (not NATlow), it may indicate residual levonorgestrel may have antagonized the estradiol effects on fluid retention and renal sodium retention activity of aldoste-

### AVP and Free Water Clearance

The results of the present study illustrate a greater AVP response to the sodium loading in the high-hormone phase of both groups, concomitant with a lower Posm and higher [E₂]p. In humans, it has been established that basal Posm is higher in the follicular than in the luteal phase, with the threshold for AVP release lowest in the luteal phase (29, 31–32). Moreover, estrogens upregulate the number of AVP binding sites (28, 32, 38), which increase the pressor response in the renal vascular bed. These observations are further supported by the result of the present study. We observed a lower Posm and elevated [AVP]p in the high-hormone state, regardless of pill or no pill usage, from resting throughout the experiment period. A slight increase in [AVP]p was also observed in response to the sodium load. The free water clearance between groups was similar; however, FEH₂O was different between phases, with a lower FEH₂O observed in the high-hormone phase of both

**PV Expansion**

It is well known that estrogens cause PV expansion, most likely via their actions on the capillary endothelium to increase the transcapillary escape of proteins and thus water (22, 36). These changes in oncotic pressure will induce changes in body fluid distribution within the extracellular fluid, independent of sodium concentration. In the present study, a high-sodium beverage did induce a transient hypervolemia in trained women cyclists, and there was a difference of the %PV change between phases of the menstrual cycle. The greatest expansion was found in the sugar pill phase of OCP (OCPlow). However, this expansion was transient, and no differences were observed between OCPlow and the high-hormone groups at 300 min. To note, although the PV expansion of the NATlow was slightly less than that of the OCPlow, this expansion was not transient. At 300 min, the PV expansion of NATlow was ~3% greater than that of the other three groups.

This discrepancy in expansion between the low-hormone groups may indicate residual metabolite activity of levonorgestrol and ethinylestradiol in the renal tissue. To review, OCP agents do not induce complete ovarian suppression during the placebo week (5, 16, 27). Moreover, plasma 17β-estradiol concentrations of OCPlow were similar to those of NATlow in the baseline data of both groups; thus we would have expected a similar response in fluid retention (duration and %expansion) between OCPlow and NATlow. With the observed drop in PV expansion of OCPlow at 180 min (not NATlow), it may indicate residual levonorgestrel may have antagonized the estradiol effects on fluid retention and renal sodium retention activity of aldoste-

**Table 3. Aldosterone concentrations at baseline (0 min) and end (300 min)**

<table>
<thead>
<tr>
<th>[ALD]p, pg/ml</th>
<th>Triphasic OCP</th>
<th>Natural 28-day Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OCPhigh</td>
<td>OCPlow</td>
</tr>
<tr>
<td>Baseline</td>
<td>122 (46)*</td>
<td>107 (12)</td>
</tr>
<tr>
<td>End</td>
<td>61 (19)*</td>
<td>49 (10)</td>
</tr>
</tbody>
</table>

Values are means (SD). *P < 0.05 between phases.
groups (concomitant with a higher urine osmolality and an attenuated urine flow volume). This difference may be due to a resetting of osmoregulatory mechanisms (i.e., downward resetting of Posm and elevated resting [AVP]p) and the subsequent effects on the translocation of aquaporin-2 (AQP-2). AVP exerts its antidiuretic effect in the collecting ducts of the kidney by activating the water channel AQP-2. Our baseline data illustrated a phase difference of resting [AVP]p (elevated in the high-hormone phase of both groups), which may have influenced an increase in AQP-2 expression, which was further indicated by the reduced FEH2O in the high-hormone groups.

GFR and FE\textsubscript{Na+}

Nitric oxide (NO) is an important regulator of glomerular hemodynamics in the kidney. Specifically, NO synthase activity is important to the overall function of the tubuloglomerular feedback system, as a modulator of sodium transport, as well as blood flow and GFR. NO within the kidney is known to contribute to low renal vascular resistance and stimulate diuresis and natriuresis, independent of renal perfusion pressure (4). Additionally, inhibition of renal NO synthase has been shown to reduce the pressure-natriuresis curve, which may increase natriuresis in all tubular segments (4, 18). This is consistent with the increased FE\textsubscript{Na+} and [Na\textsuperscript{+}]\textsubscript{U} of our participants in the sugar pill week and high-hormone phase, regardless of whether it was an endogenous or an OCP-mediated cycle. The increased FE\textsubscript{Na+} may be due to a few pressure-mediated interactions. Pechere-Bertschi et al. (23) reported there was no blood pressure increase with a sodium + water volume load in OC users, as a salt-induced renal vasodilation was observed (an increase in GFR coupled with an increase in filtration fraction, but no change in renal blood flow). As we observed a drop in GFR across all conditions, we may conclude that a decrease in renal perfusion pressure occurred concomitant with an increased filtration fraction. It is well known that estrogen increases endothelium-dependent vasodilation via NO, but estrogen also induces an increase in NO in the renal tissues, in particular the vasa recta capillaries. This precapillary vasodilation will increase medullary hydrostatic pressure, which, with NO, will reduce sodium reabsorption (increase in FE\textsubscript{Na+}) and increase fluid reabsorption (as observed by the decreased renal free water clearance).

General Conclusions and Recommendations

The purpose of this study was to examine how the OCP and NAT menstrual cycle affect sodium and volume regulatory mechanisms and to examine efficacy of a highly concentrated sodium (164 mmol/l) beverage as a means to induce acute hypervolemia across the endogenous and exogenous menstrual cycle. PV expansion across both types and phases of the menstrual cycle occurred; however, the differences between the high- and low-hormonal states indicate that alterations to renal responses to a sodium load occur across the menstrual cycle. The present data indicate that adaptation to OCPS may result in a new baseline set point for body fluid regulation, although this study was not designed to allow distinction to be drawn on the relative effects of the different estrogens and progestrogens. Further research is needed to investigate the complex interactions and any adaptations that may occur with chronic OCP use; in particular, any adaptations that may either contribute to or protect women from fluid balance conditions like hypertension and deep vein thrombosis over the long term.

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GRANTS

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REFERENCES


