Systemic and renal hemodynamic changes in the luteal phase of the menstrual cycle mimic early pregnancy

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Chapman, Arlene B., Stacy Zamudio, Whitney Woodmansee, Aicha Merouani, Fritz Osorio, Ann Johnson, Lorna G. Moore, Thomas Dahms, Carolyn Coffin, William T. Abraham, and Robert W. Schrier. Systemic and renal hemodynamic changes in the luteal phase of the menstrual cycle mimic early pregnancy. Am. J. Physiol. 273 (Renal Physiol. 42): F777–F782, 1997.—Blood pressure decreases during early pregnancy in association with a decrease in peripheral vascular resistance and increases in renal plasma flow and glomerular filtration rate. These early changes suggest a potential association with corpora lutea function. To determine whether peripheral vasodilatation occurs following ovulation, we studied 16 healthy women in the midfollicular and midluteal phases of the menstrual cycle. A significant decrease in mean arterial pressure in the midluteal phase of the cycle (midfollicular of 81.7 ± 2.0 vs. midluteal of 75.4 ± 2.3 mmHg, P < 0.005) was found in association with a decrease in systemic vascular resistance and an increase in cardiac output. Renal plasma flow and glomerular filtration rate increased. Plasma renin activity and aldosterone concentration increased significantly in the luteal phase accompanied by a decrease in atrial natriuretic peptide concentration. Serum sodium, chloride, and bicarbonate concentrations and osmolality also declined significantly in the midluteal phase of the menstrual cycle. Urinary adenosine 3’,5’-cyclic monophosphate (cAMP) excretion increased in the luteal compared with the follicular phase, whereas no changes in urinary cGMP or NO3/NO2 excretion were found. Thus peripheral vasodilatation occurs in the luteal phase of the normal menstrual cycle in association with an increase in renal plasma flow and filtration. Activation of the renin–angiotensin–aldosterone axis is found in the luteal phase of the menstrual cycle. These changes are accompanied by an increase in urinary cAMP excretion indicating potential vasodilating mediators responsible for the observed hemodynamic changes.

Peripheral vasodilation; renal plasma flow; glomerular filtration rate; cardiac output

RECENTLY, A UNIFYING hypothesis of body fluid volume regulation has focused attention on the integrity of the arterial circulation as the primary determinant of renal sodium and water excretion (25). Several sodium- and water-retaining states are associated with arterial underfilling secondary to arterial vasodilatation, whereas congestive heart failure generally involves a diminution in cardiac output (25). Pregnancy has been proposed to be a state in which primary peripheral arterial vasodilatation triggers hemodynamic and hormonal responses that cause sodium and water retention characteristic of normal gestation (25). However, the mediator(s) responsible for, as well as the timeframe involved in, the arterial vasodilatation that occurs in pregnancy is not completely understood. It is suggested, based on studies performed in conscious pregnant baboons, that many systemic hemodynamic changes take place prior to the end of the first trimester of pregnancy and placentation (23).

Pseudo-pregnant rats also demonstrate systemic hemodynamic changes identical to early pregnancy in the presence of extended function of the corpora lutea (21). Given that the placenta is not functional in human pregnancy until the 8th to 12th wk of gestation, hemodynamic changes that occur in the first weeks of gestation are likely the result of the extended function of the corpora lutea and not the result of a functioning maternal-fetal-placental unit. In support of this hypothesis, blood pressure decreases markedly in women undergoing ovarian stimulation (2).

On the basis of these observations, it can be proposed that ovulation and the presence of a corpus luteum during the normal menstrual cycle would be associated with systemic hemodynamic changes similar to those found during the first trimester of pregnancy. However, consistent differences in blood pressure between the follicular and luteal phases of the menstrual cycle have not been clearly documented (9, 13, 31, 34). In addition, systemic vascular resistance and cardiac output, together with plasma volume, have not been systematically studied during the two phases of the menstrual cycle.

In pregnancy, increases in effective renal plasma flow and, to a lesser extent, glomerular filtration rate have also been noted to occur as early as the middle of the first trimester (6). However, there is conflicting information concerning renal hemodynamic changes during the menstrual cycle. One large study of women planning to conceive demonstrates small increases in creatinine clearance during the luteal phase of the menstrual cycle (7), whereas others have demonstrated no change (19), a decline during ovulation (10), or an increase in tubular secretion of creatinine independent of clearance (20). A recent study measuring plasma clearances of inulin and p-aminohippurate (PAH) shows an increase in glomerular filtration rate but no change in renal plasma flow in the luteal phase of the menstrual cycle (31). Simultaneous measurements of glomerular filtration rate and renal plasma flow using timed urine collections have not been performed during the two phases of the menstrual cycle.

A number of vasodilating substances are increased in pregnancy. Prostaglandin production increases in pregnancy (30), and inhibition of prostaglandin with indomethacin production partially reverses the hemodynamic changes found in normal pregnancy (27). Recent
work suggests that nitric oxide (NO) is an important vasodilating substance responsible for the systemic and renal vasodilation found in pregnancy (5). Circulating nitrite/nitrate levels increased during follicle development (24), thus suggesting that NO may play a role in hemodynamic changes found during the menstrual cycle.

We hypothesize, therefore, that peripheral vasodilation occurs during the latter half of the normal menstrual cycle following ovulation, an effect similar to that observed in early pregnancy. This vasodilation results in lower mean arterial pressure (MAP), increased cardiac output, renal plasma flow, and glomerular filtration rate and decreased renal vascular resistance (RVR). On the basis of this background, the present study was undertaken to examine systemic and renal hemodynamics and electrolyte and hormonal profiles during the midfollicular and midluteal phases of the normal human menstrual cycle.

METHODS

Sixteen women were studied between July 1, 1990, and January 20, 1996, at the General Clinical Research Center (GCRC) at the University of Colorado Health Sciences Center. Women were eligible to participate if they were between the ages of 21 and 40 yr and if their menstrual cycles were regular, not varying by more than 2 days between cycles, for more than 6 mo. Those women taking oral contraceptive medications discontinued use and had at least four regular cycles without oral contraceptive medication prior to study. Women with a history of hypertension, diabetes mellitus, and cardiac or renal disease were excluded from the study. After signing an informed consent to procedures approved by the University of Colorado Multiple Institutional Review Board, patients underwent identical protocols during the midfollicular and luteal phases of the menstrual cycle. Women were studied between the 4th and 7th day after onset of menstruation for determination of midfollicular values. Ovulation was determined 12-40 h in advance by identifying luteinizing hormone surges in the urine using ovulatory predictor kits (Becton-Dickinson, Rutherford, NJ). Patients were scheduled for studies between the 4th and 7th day following ovulation.

Patients were asked to collect a 24-h urine sample the day prior to each admission. Samples were refrigerated during collection, and final collections were finished the morning of admission to the GCRC. Urine samples were immediately processed and frozen at −70°C until further measurement. Urinary creatinine, urea nitrogen, osmolality, adenosine 3',5'-cyclic monophosphate (cAMP), cGMP, and NO2/NO3 excretion rates were determined. The patients were admitted to the GCRC in the morning having ingested only water after 12:00 A.M. Following determination of height and weight, total blood and plasma volume was determined using a modified carbon monoxide rebreathing technique previously used in this laboratory (37). This technique has a coefficient of variation between separate measurements in the same individual of 2.7 ± 1.6% and correlates closely with 37 Evans blue plasma dye measurements of plasma volume in 11 male subjects (γ = 1.04x − 0.1; r = 0.88, P < 0.001; personal communication, R. Grover). Briefly, seated subjects rebreathed a gas mixture initially containing 100% O2 from a 5-liter anesthesia bag throughout a closed circuit with one nose clip and a CO2 absorber in place. Baseline blood samples were drawn through an intravenous line from the vein 5 min after the beginning of the rebreathing period and 10 and 15 min following the addition of 50 ml (atmospheres pressure) carbon monoxide to the rebreathing system. Carbon monoxide concentration was determined in triplicate using gas chromatography with a resolution of 0.006 ml carbon monoxide/dl whole blood with a coefficient of variation of 1.7% (37). Microhematocrit and total blood volume were calculated as previously reported (37). Red blood cell mass was calculated as total blood volume multiplied by hematocrit. Plasma volume was obtained by subtracting red blood cell mass from total blood volume, without correction for trapped plasma or whole body hematocrit (17).

Patients were then placed in the left lateral decubitus position in a quiet room for 60 min. After 30 min, four blood pressures were determined at 5-min intervals using a sphygmomanometer. The Korotkoff V sound was used for determining diastolic blood pressure. MAP was calculated using the formula diastolic pressure plus one-third the pulse pressure. While still in the left lateral decubitus position, cardiac output was determined using standard echocardiography techniques (15). Electrode patches were placed to obtain average heart rates. The Hewlett-Packard model 77020A was used with 2.25-MHz transducers for pulse and color Doppler wave determinations and 3.5-MHz transducers for real time two-dimensional measurements. Two-dimensional scanning with color Doppler and M-mode in the parasternal short axis were performed to find the best angles for measurement of the aortic root diameter and to assure that mitral regurgitation, aortic insufficiency, and tricuspid regurgitation were not present. M-mode images were obtained in the parasternal long axis, with a paper speed of 100 mm/s to determine aortic root diameter at the annulus (the base of the leaflets). Inner wall to inner wall measurements were obtained. After using a five-chamber view to find the best Doppler spectral display and the highest signal, pulse wave Doppler was performed at the aortic root to determine the maximal aortic velocity. Time velocity integrals (TVI) were then calculated from Doppler interrogation of the maximal aortic velocity. Cardiac output (CO) was determined from heart rate (HR) and stroke volume (SV) according to the following formula: CO = SV × HR, where SV is cross-sectional area of the aortic root × TVI. Systemic vascular resistance (SVR) was calculated from the formula SVR = MAP × 80/CO. Blinded validation of this procedure was performed by simultaneously measuring cardiac output noninvasively by Doppler echocardiography and invasively by thermodilution in 15 cardiac transplant recipients undergoing surveillance right ventricular biopsies following successful cardiac transplantation. Eighteen simultaneous determinations of cardiac output by Doppler echocardiography and thermodilution were performed and demonstrated good correlation (5.03 ± 0.3 vs. 5.06 ± 0.3 ml/min; P < 0.01, r = 0.82).

Following blood pressure and cardiac output measurements and subsequent resting without interruption for 30 min, blood was then withdrawn from an indwelling catheter without a tourniquet for the determination of serum creatinine and electrolyte concentrations, serum osmolarity, plasma norepinephrine, atrial natriuretic peptide (ANP), cAMP, and cGMP concentrations, and serum aldosterone, estradiol, progesterone, and prolactin concentrations, as well as plasma renin activity. Tubes used for the collection of plasma renin activity were kept at room temperature until separated and were immediately frozen.

Clearances of inulin (ClIn) and PAH (ClPAH) were then performed to determine glomerular filtration rate and effective renal plasma flow, respectively (3). Inulin and PAH were premixed in 5% glucose in water and infused at a rate of 1 ml/min. Subjects drank 300 ml water/h each hour during the
clearance studies to maintain urine output greater than 3 ml/min. Three 30-min urine collections were obtained 1 h after the initiation of inulin and PAH infusion when steady-state serum concentrations had been achieved. Blood samples were obtained at the midpoint of each collection period for the determination of serum inulin and PAH concentrations. Urine output was maintained with oral hydration to replace urine losses. Renal blood flow (RBF) was determined using effective renal plasma flow (C\text{\textit{PAH}}) divided by one minus the fraction of hematocrit (Hct) divided by 100 [i.e., RBF = C\text{\textit{PAH}}/(1 – Hct/100)]. RVR was calculated as the ratio between MAP and renal blood flow multiplied by the constant 79.920 [i.e., (MAP/RBF) × 79.920].

Serum and urinary electrolytes and reproductive hormones were measured by standard laboratory techniques. Serum and urine creatinine concentrations were determined in the core laboratory of the GCRC using the jaffe reaction and a Beckman model 2 autoanalyzer. Serum osmolality and urine osmolality were determined by freezing point depression. Serum and urine inulin and PAH concentrations were determined colorimetrically (33). Urine and plasma cAMP and cGMP, serum aldosterone, plasma ANP concentrations, and plasma renin activity were determined by radioimmunoassay (1, 14, 26, 28). Samples were thawed once prior to measurement of plasma renin activity. Norepinephrine concentrations were determined radioenzymatically (22). Urinary NO\textsubscript{2}/NO\textsubscript{3} concentrations were determined spectrophotometrically (35).

Mann-Whitney signed rank analysis was used to determine change in continuous variables between the two phases of the menstrual cycle. Data are presented as the means ± SE. Significance is defined as a one-tailed P value <0.05, and significant values are given in the text.

RESULTS

The subjects were 30.9 ± 0.9 yr of age (23–37 yr) with a body surface area of 1.71 ± 0.03 m\textsuperscript{2} (1.51–1.95 m\textsuperscript{2}). All menstrual cycles were less than 35 days (26–34 days). Subjects were studied at 5.8 ± 0.5 days (days 2–9) of the follicular phase and at 21.1 ± 0.8 days (days 16–28) of the luteal phase of the menstrual cycle. Eleven of sixteen women were initially studied in the follicular phase. No change in weight was detected throughout the menstrual cycle.

MAP and SVR decreased in the luteal compared with the follicular phase of the menstrual cycle (Table 1). Cardiac output increased significantly in the luteal phase of the menstrual cycle while plasma volume, blood volume, and red blood cell mass remained unchanged throughout the menstrual cycle. Effective renal plasma flow (C\text{\textit{PAH}}) and glomerular filtration rate (GFR) increased and RVR decreased during the luteal compared with the follicular phase of the menstrual cycle (Table 1).

Serum electrolyte data are presented in Table 2. Although all studies were within normal limits, serum sodium, chloride, and carbon dioxide concentrations and osmolality were lower in the midluteal compared with the midfollicular phase of the menstrual cycle.

Plasma progesterone, estradiol, and prolactin concentrations were significantly higher in the luteal compared with the follicular phase and were within reported normal ranges for that phase (Table 3). Plasma renin activity and plasma aldosterone concentrations increased significantly in the luteal compared with the follicular phase of the menstrual cycle (Table 3). Conversely, plasma ANP concentrations decreased in the luteal phase. Plasma norepinephrine concentrations increased in the midluteal phase but did not reach statistical significance (P = 0.06).

Twenty-four-hour urinary cAMP excretions increased significantly in the luteal compared with the follicular phase of the menstrual cycle (Table 4). No significant change in urinary cGMP or NO\textsubscript{2}/NO\textsubscript{3} excretion was found.

DISCUSSION

The present study examined the systemic and renal hemodynamic alterations during the normal menstrual cycle. The results demonstrated the presence of primary arterial vasodilation in the luteal phase of the menstrual cycle, which is qualitatively similar to changes observed in early pregnancy. Using subjects as their own controls, in a controlled environment with standardized measurements, we found that MAP decreased in the midluteal compared with the midfollicular phase of the ovulatory menstrual cycle. Women were studied after ovulation, so as to avoid hormonal changes, which are maximal but short in duration, and

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<th>Table 1. Systemic and renal hemodynamic changes throughout the menstrual cycle</th>
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<td><strong>Follicular</strong></td>
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<td>MAP, mmHg</td>
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<td>SVR, dyn·s·cm\textsuperscript{-5}</td>
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<td>CO, l/min</td>
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<td>HR, beats/min</td>
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<td>PV, ml/kg</td>
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<td>BV, ml/kg</td>
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<td>RCM, cm\textsuperscript{3}/kg</td>
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<td>C\text{\textit{PAH}}, ml·min\textsuperscript{-1}·1.73 m\textsuperscript{2}</td>
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<th>Table 2. Electrolyte, osmolarity, and hematocrit determinations during the follicular and luteal phases of the menstrual cycle</th>
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<td><strong>Follicular</strong></td>
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<td>Serum Na, meq/l</td>
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<td>Serum CO\textsubscript{2}, meq/l</td>
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<td>Osmolarity, mmol/kgH\textsubscript{2}O</td>
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<td>Serum calcium, mg/dl</td>
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Values are means ± SE. MAP, mean arterial pressure; SVR, systemic vascular resistance; CO, cardiac output; HR, heart rate; PV, plasma volume; BV, blood volume; RCM, red blood cell mass; C\text{\textit{PAH}}, clearance of p-aminohippurate; C\text{\textit{IN}}, clearance of inulin; C\text{\textit{Cr}}, clearance of creatinine; RVR, renal vascular resistance; and FF, filtration fraction. NS, not significant.
The presence of decreased SVR in the presence of decreased serum osmolarity in the midluteal phase of the menstrual cycle may account for the changes seen in serum osmolarity, or alternatively, the corpora lutea may release agents that act directly on the hypothalamus to produce a reset osmotic threshold for vasopressin release.

Arterial vasodilation is a known stimulus for the renin-angiotensin-aldosterone system (RAAS) (12). The activation of the RAAS in association with the decrease in SVR during the luteal phase of the menstrual cycle is thus expected. Evidence for the fundamental hemodynamic importance of RAAS activation during pregnancy is also available, given the finding that angiotensin converting enzyme inhibition lowers blood pressure in pregnant women (29).

The specific vasodilator(s) responsible for the hemodynamic changes found in the midluteal phase of the menstrual cycle remains to be identified. Plasma estradiol concentration is increased in the midluteal phase and has been shown to increase local prostacyclin production and to increase nitric oxide synthase (NOS) production (30, 35). In this regard, an increase in urinary cAMP excretion potentially related to increased prostacyclin production was found in the midluteal phase. Although urinary NOx/NO2 levels did not change between the two phases of the menstrual cycle, a preovulatory increase in NOx/NO2 production followed by a postovulatory decrease in NOx/NO2 production has previously been demonstrated (24). We studied women at least 48 h after ovulation and, therefore, we may have missed a periovulatory increase in NOx/NO2 production. Importantly, this observational study did not place the subjects on a low-nitrate diet, so that differences in endogenous nitrate production across the cycle could be accurately determined. Therefore, although our results failed to demonstrate a significant increase in urinary nitrate/nitrite excretion in the midluteal phase, alterations in endogenous NO production throughout the menstrual cycle cannot be excluded.

Plasma ANP, a known vasodilator and stimulator of cGMP production, decreased significantly in the midluteal phase, most likely secondary to venodilation and a decrease in cardiac workload. Urinary NOx/NO2 excretion rates are a marker of NO activity that also increases urinary cGMP levels, rose insignificantly during the glomerular luteal phase. These findings suggest that two independent and opposing processes may account for the absence of change seen in urinary cGMP excretion during the menstrual cycle.
In summary, in the midluteal phase of the menstrual cycle, primary vasodilation causes a fall in MAP that is associated with hemodynamic compensation with a rise in cardiac output in a manner similar to early pregnancy. The peripheral vasodilation of the luteal phase of the menstrual cycle, like early pregnancy, is associated with an increase in effective renal plasma flow and glomerular filtration rate secondary to a decrease in RVR. Activation of the RAAS and a decrease in ANP concentration occurred in the midluteal phase of the menstrual cycle, findings compatible with peripheral vasodilation. Urinary cAMP excretion increased, suggesting that vasodilatory substances such as prostacyclin may be involved in the systemic and renal vasodilation observed during the midluteal phase of the menstrual cycle. Given the hemodynamic alterations that occur during the menstrual cycle, hemodynamic and hormonal changes in early pregnancy may not require an intact functioning fetal-maternal-placental unit but rather may be dependent on ovarian corpora lutea.

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