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Temporal relationships between hormonal and hemodynamic changes in early human pregnancy

Arlene B. Chapman, William T. Abraham, Stacy Zamudio, Carolyn Coffin, Aicha Merouani, David Young, Ann Johnson, Fritz Osorio, Carol Goldberg, Lorna G. Moore, Thomas Dahms, and Robert W. Schrier

Departments of Medicine, Anesthesiology and Anthropology, Preventive Medicine and Biometrics, University of Colorado Health Sciences Center and Department of Anesthesiology, University of St. Louis, St. Louis, Missouri, USA

Temporal relationships between hormonal and hemodynamic changes in early human pregnancy.

Background. The systemic hemodynamic profile of human pregnancy is characterized by a decrease in mean arterial pressure, a rise in cardiac output and plasma volume in association with an increase in renal plasma flow and glomerular filtration rate. The factors and the time course responsible for the initial hemodynamic changes seen in human pregnancy have not been completely documented. We hypothesize that systemic and renal hemodynamic changes occur early, prior to the presence of the fetal-placental unit.

Methods. Thirteen women were studied prior to and immediately following conception in identical fashion at gestational weeks 6, 8, 10, 12, 24 and 36. Individuals underwent mean arterial pressure, cardiac output, inulin and PAH clearance determinations.

Results. Mean arterial pressure decreased by six weeks gestation (mid follicular 81.5 ± 2.6 vs. six weeks 68.7 ± 2.0 mm tig, $P < 0.001$) in association with a significant increase in cardiac output, a decrease in systemic vascular resistance and an increase in plasma volume. Renal plasma flow and glomerular filtration rate increased by six weeks gestation. Plasma renin activity and aldosterone concentration increased significently by six weeks, whereas norepinephrine levels did not change throughout pregnancy. Atrial natriuretic peptide levels increased later, at 12 weeks gestation. Plasma cGMP levels decreased and cGMP clearance increased by six and eight weeks, respectively.

Conclusions. Peripheral vasodilation occurs early in pregnancy prior to full placentation in association with renal vasodilation and activation of the renin-angiotensin-aldosterone system. Plasma volume expansion occurs early, followed later by increases in ANP concentration, suggesting that ANP increases in response to changes in intravasular volume.

Key words: gestation, mean arterial pressure, cardiac output, plasma volume, glomerular filtration rate, cGMP, renin-angiotensin-aldosterone system, vasodilation.

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Normal human pregnancy is characterized by a decrease in mean arterial pressure accompanied by an increase in cardiac output and a decrease in systemic vascular resistance [1–3]. The hemodynamic changes found in human pregnancy have been proposed to be primarily due to systemic vasodilation [4] similar to other sodium and water retaining states [5, 6]. These hemodynamic changes have been documented longitudinally during pregnancy in non-primate animal species [7–9], in the baboon [10] and in part in humans [11]. However, the temporal sequence of peripheral vasodilation, increased cardiac output and plasma volume expansion in the initial phases of human pregnancy remains to be described. Importantly, the magnitude of these changes is suggested to be maximal in the second trimester of human pregnancy [3, 12]. The majority of these observations have been made with women initially studied after the end of the first trimester and then in the postpartum period [1–3]. Therefore, it is possible that most if not all hemodynamic changes occur much earlier in pregnancy.

Pseudopregnant rats demonstrate systemic hemodynamic changes identical to early pregnancy in the absence of a fetal-placental unit due to the extended function of the corpora lutea [13]. As well, women demonstrate systemic hemodynamic changes in the post-ovulatory or luteal phase of the menstrual cycle qualitatively similar to pregnancy [14]. These changes are exaggerated during ovarian hyperstimulation [15], suggesting that the initial hemodynamic changes of pregnancy may occur early and not require an intact maternal-fetal-placental unit.

Increases in glomerular filtration rate, as measured by creatinine clearance, have been shown to increase as early as the 6th week of gestation [16–18]. However, more accurate measurements of glomerular filtration rate, such as inulin clearance as well as measures of renal plasma flow, have not been performed at this early stage of human pregnancy, nor have simultaneous measurements of systemic and renal hemodynamics been performed in human

pregnancy to determine if the initial peripheral vasodilation of pregnancy is accompanied by similar changes in renal hemodynamics.

Activation of the renin-angiotensin-aldosterone system has been consistently found in human pregnancy [19–21], where increased and unchanged sympathetic activity [22, 23], and increased, decreased and unchanged atrial natriuretic peptide concentrations have been reported [24–27]. Whether changes in these vasopressor systems are directly related to the peripheral vasodilation of pregnancy has not been studied longitudinally or extensively in the first trimester of human pregnancy.

Vasodilating substances responsible for the hemodynamic changes found in human pregnancy have been sought. Nitric oxide (NO) and its second messenger, cyclic guanosine 3′,5′-monophosphate (cGMP), have been shown to increase in animal pregnancy [28–30]. Moreover, when inhibitors of NO production such as N^{ω}-nitro-L-arginine methylester (L-NAME) are given to pregnant rodents, the hemodynamic changes found in normal pregnancy are completely reversed [31]. In human pregnancy, much less information is available concerning NO and its second messenger cGMP [32–34].

We hypothesize that prior to fully functional placentation, normal human pregnancy is characterized by primary systemic and renal vasodilation as well as vasopressor activation associated with subsequent plasma volume expansion. The present study was therefore undertaken to examine systemic and renal hemodynamics, the renin-angiotensin-aldosterone and sympathetic nervous systems, as well as plasma volume and atrial natriuretic peptide levels: (*1*) in the mid-follicular phase of the menstrual cycle; (*2*) immediately after conception; and (*3*) serially throughout gestation. The role of NO in the peripheral vasodilation of pregnancy was also indirectly evaluated in this study by measuring second messengers of NO including plasma and urinary cGMP levels.

METHODS

Healthy subjects planning a pregnancy were studied on the General Clinical Research Center (GCRC) at the University of Colorado Health Sciences Center between January 1990 and July 1996. Women were eligible to participate if they were between the ages of 21 and 40 years, and did not have a history of hypertension, diabetes mellitus, or cardiac or renal disease. Women with a previous history of preeclampsia or pregnancy-induced hypertension were not eligible for study. Women taking oral contraceptive medications discontinued use at least four cycles prior to study. After signing informed consent to procedures approved by the University of Colorado Multiple Institutional Review Board, patients underwent identical protocols during the mid-follicular phase of the menstrual cycle and after successful conception. Follicular phase measurements were obtained between the second and ninth day after onset of menstruation. After completion of the non-pregnant studies, subjects contacted the investigators after successful conception and were studied at gestational week 6, 8, 10, 12, 24 and 36. All subjects were asked not to begin vitamin supplementation until after the 12th week of gestation.

Subjects collected a 24-hour urine sample the day prior to each study. During collection, subjects kept the urine refrigerated and completed the collection after admission to the GCRC. Urine samples were immediately processed and frozen at −70°C until further measurement. Urinary creatinine and cGMP excretion rates were determined. Creatinine concentrations were performed to determine adequate collection. The subjects were admitted to the GCRC in the morning having ingested only water after midnight. Following determination of height and weight, total blood and plasma volumes were determined using a modified carbon monoxide rebreathing technique previously described [14, 35]. Seated subjects rebreathed a gas mixture initially containing 100% O_2 in a closed circuit with a noseclip in place and a CO_2-absorber and 5-liter anesthesia bag placed in the line to which 100% O_2 was added continuously during the rebreathing procedures. Baseline blood samples were drawn via an intravenous line in the antecubital vein after five minutes of rebreathing and 10 and 15 minutes following the addition of 50 ml (ATP) carbon monoxide to the rebreathing system. Arterial O_2 saturation was monitored throughout the rebreathing procedures and found to remain greater than 95%. Carbon monoxide concentration was determined in triplicate using gas chromatography [35]. Total blood volume was calculated as previously reported [35]. Red cell mass was calculated as total blood volume multiplied by hematocrit. Plasma volume was obtained by subtracting red cell mass from total blood volume.

Patients were then placed in the left lateral decubitus position in a quiet room for 60 minutes. After thirty minutes, four blood pressures were determined at five minute intervals using a sphygmomanometer. The Korotkoff V sound was used for determining diastolic blood pressure [36]. Mean arterial pressure was calculated using the formula: diastolic pressure plus one-third the pulse pressure. While still in the left lateral decubitus position, cardiac output (CO) was determined using standard echocardiographic techniques reported by our laboratory and elsewhere [14, 37, 38]. Systemic vascular resistance (SVR) was calculated from the formula: $SVR = MAP \times 80/CO$.

Following blood pressure and cardiac output measurements and after an uninterrupted 30 minutes of rest, blood was withdrawn from an indwelling catheter without a tourniquet for the determination of serum creatinine and electrolyte concentrations, serum osmolarity, estradiol, progesterone, human choriogonadotropin, prolactin, aldosterone concentrations, and plasma norepinephrine, atrial natriuretic peptide, cGMP and plasma renin activity. Tubes

used for the collection of plasma renin activity were kept at room temperature until separated and were immediately frozen to avoid cryoactivation [21].

With the subjects in the left lateral decubitus position, inulin (C_{In}) and para-aminohippurate (C_{PAH}) clearances were performed to determine glomerular filtration rate and effective renal plasma flow, respectively [39]. An initial loading dose of 3.0 gm inulin and 500 mg PAH were given followed by a constant infusion of 1.5 g inulin/hr and 400 mg PAH/hr. Inulin and PAH were premixed in 5% glucose in water and infused at a rate of 1 ml/min. Subjects ingested 300 ml water/hr during the study to maintain urine output above 3 ml/min. One hour after the initial infusion when steady state levels were achieved, three thirty-minute clearances were performed with the subjects spontaneously voiding. Blood samples were obtained in the mid-point of each clearance period for the determination of plasma inulin and PAH concentrations. Renal blood flow (RBF) was determined using C_{PAH} divided by one minus the fraction of hematocrit divided by 100 [$RBF = C_{PAH}(1 - Hct/100)$]. Renal vascular resistance was calculated as the ratio between MAP and renal blood flow multiplied by the constant 79,920 [$(MAP/RBF) \times 79{,}920$].

Serum and urinary electrolytes and reproductive hormones were measured by standard laboratory techniques on the GCRC. Serum and urine creatinine measurements were performed using the Jaffé reaction and a Beckman 2 autoanalyzer. Serum osmolarity was determined by freezing point depression. Serum and urine inulin and PAH concentrations were determined colorimetrically [40]. Urine and plasma cGMP, serum aldosterone, plasma atrial natriuretic peptide concentrations and plasma renin activity (PRA) were determined by radioimmunoassay [41–44]. Samples were thawed once prior to measurement of PRA. Norepinephrine concentrations were determined radioenzymatically [45]. Progesterone, estradiol, prolactin, and human choriogonadotropin levels were measured by radioimmunoassay as reported elsewhere [14]. All variables of the study group were compared using the linear random-effects model discussed by Laird and Ware [46]. The latter model is appropriate for repeated measures data, accommodates missing values and assesses variability between subjects as well as variability between multiple observations on the same subject. The data were modeled by fitting constants, or first or second order polynomial regression lines for each variable versus week of gestation, validating the best-fitting lines with likelihood ratio tests, and superimposing the best fit lines on the mean ± SEM values for visual inspection and interpretation. The resulting response curves were compared throughout pregnancy using an extension of Scheffe's method for multiple comparisons, which permits each point along the response curve to be compared to the value observed during mid-follicular phase, and the resulting adjusted *P* value obtained [47]. All analyses were implemented with SAS Stat and SAS IML statistical software [48].

Table 1. Demographic characteristics of eleven pregnant women

Variable	Value
Age *years*	30.9 ± 0.9
Race *White:Afro-American*	10:1
Nulliparous %	9 (82.5)
Smokers %	1 (8.3)
Family history of preeclampsia	0 (1 unknown)
Time from initial study to conception *months*	7.83 ± 2.6 (0.8–24.4)
Length of pregnancy *weeks*	39.0 ± 0.5 (36.8–40.7)
Birth weight *kg*	3.1 ± 0.1

RESULTS

Thirteen subjects enrolled in the study and eleven were successful in becoming pregnant. The demographic characteristics of the women who became pregnant are shown in Table 1. Subjects were studied on day 5.4 ± 0.5 (range 1 to 9) of the follicular phase, week 5.9 ± 0.2 (5.0 to 6.7), 8.0 ± 0.2 (7.1 to 8.7), 10.0 ± 0.3 (8.6 to 11.4), 12.4 ± 0.2 (11.6 to 13.6), 24.2 ± 0.3 (23.6 to 25.7) and 36.4 ± 0.2 (35.7 to 37.6) of gestation. Three subjects developed complications during their pregnancies. One subject, who had a history of two previous first trimester spontaneous abortions, miscarried at 8.5 weeks gestation; her data are not included in the data analysis. A second patient developed asthma at gestational week 16 and required theophylline and inhaled corticosteroid therapy. She was not studied after that point, suffered no further maternal or fetal complications, and delivered a full-term healthy baby. Her data are presented and included in the data analysis. A third subject developed preeclampsia with blood pressures greater than 140/90 mm Hg and 1.2 g/day urinary protein excretion at week 36 gestation. This patient was not studied in the second or third trimester. Her data are included in the analysis. One subject had a twin gestation that was uncomplicated. Her data are included in the data analysis.

Figure 1 demonstrates the systemic hemodynamics throughout pregnancy. Mean arterial pressure decreased significantly compared to the mid-follicular phase by week six gestation. Cardiac output increased as compared to the mid-follicular phase by the sixth week of gestation with a simultaneous decrease in systemic vascular resistance. Maximum cardiac output occurred in the second and third trimesters while systemic resistance was at a minimum in the middle of the first trimester. Plasma and blood volume increased significantly from the non-pregnant state at six weeks gestation, reaching maximal levels at week 36 gestation (Fig. 2). These changes were accompanied by a significant increase in weight.

Renal plasma flow and glomerular rate filtration increased and renal vascular resistance decreased significantly by the first measurement of gestation (Fig. 3).

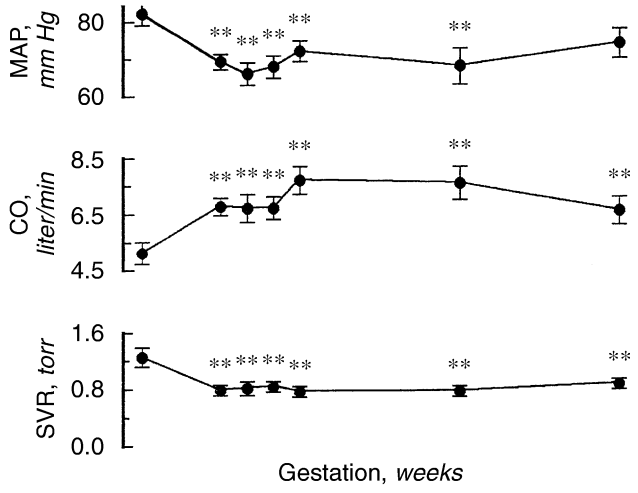

Fig. 1. Systemic hemodynamic changes throughout early human pregnancy. Ten women were studied in the mid-follicular phase of the menstrual cycle and weeks 6, 8, 10, 12, 24, and 36 gestation. Mean arterial pressure (MAP) decreased and cardiac output (CO) increased significantly by week 6 gestation in association with a decrease in systemic vascular resistance (SVR). $^{*}P < 0.05$, $^{**}P < 0.001$.

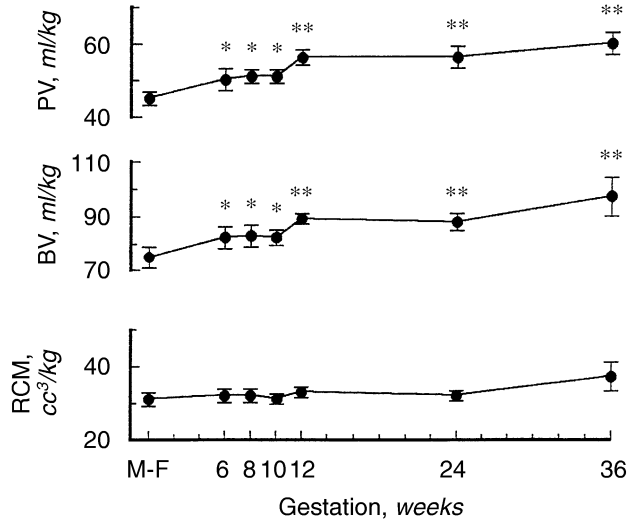

Fig. 2. Plasma volume (PV), blood volume (BV), and red cell mass (RCM) determinations in early pregnancy. Ten women were studied in the mid follicular phase of the menstrual cycle and weeks 6, 8, 10, 12, 24 and 36 gestation. Plasma and blood volume increased significantly by week 6 gestation. Red cell mass remained unchanged throughout pregnancy. $^{*}P < 0.05$, $^{**}P < 0.0001$.

Maximal renal plasma flow and minimal renal vascular resistance occurred at the eighth week gestation, whereas the peak glomerular filtration rate occurred in the second trimester. Filtration fraction decreased significantly by week six of gestation and remained lower than non-pregnant values until the 36th week of pregnancy (data not shown). Twenty-four-hour urinary creatinine excretion remained unchanged throughout gestation.

Serum electrolyte and hematocrit data are presented in

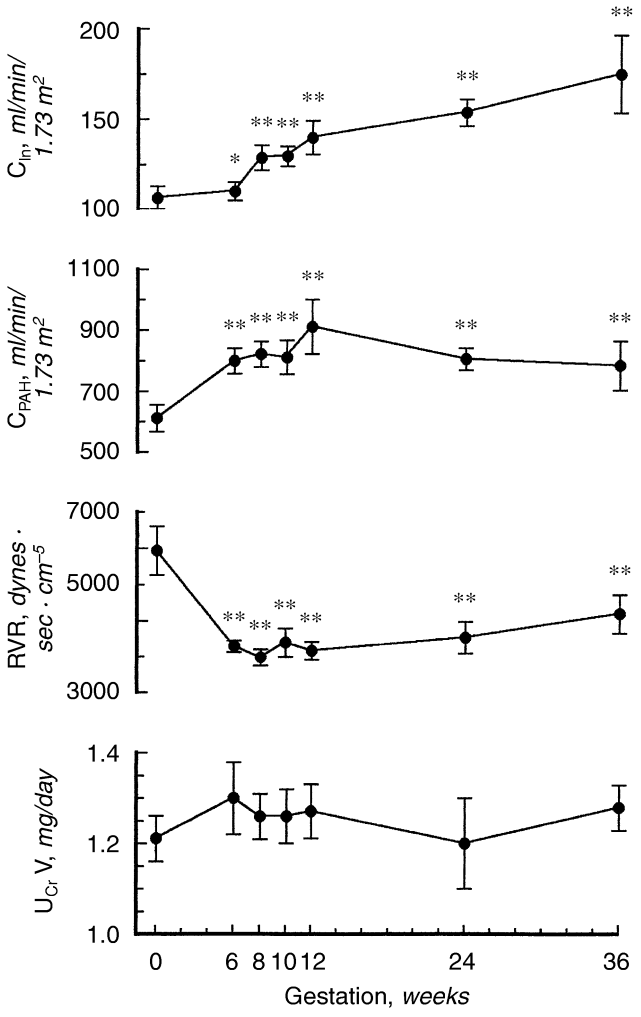

Fig. 3. Renal hemodynamic changes throughout early human pregnancy. Ten women were studied in the mid-follicular phase of the menstrual cycle and weeks 6, 8, 10, 12, 24 and 36 gestation. Renal plasma flow and glomerular filtration rate increased significantly in association with a decrease in renal vascular resistance by week 6 gestation. Twenty-four-hour urinary creatinine excretion remained unchanged throughout gestation. Abbreviations are: C_{In}, inulin clearance; C_{PAH}, para-aminohippurate clearance; RVR, renal vascular resistance; $U_{Cr}V$, urinary creatinine excretion. $^{*}P < 0.05$, $^{**}P < 0.001$

Table 2. Serum sodium, chloride, total carbon dioxide, creatinine, blood urea nitrogen concentrations and serum osmolarity decreased significantly by the first measurement or the sixth week of gestation. Hematocrit decreased significantly by week 10 gestation. All values remained lower than non-pregnant levels for the remainder of pregnancy. Reproductive human data are shown in Table 3. All values were within the expected range for gestational age.

Vasopressor hormone profiles are shown in Figure 4. Plasma renin activity and plasma aldosterone concentrations increased significantly by the sixth week of gestation. Plasma aldosterone levels increased further in the third trimester of pregnancy. Atrial natriuretic peptide concentrations increased from non-pregnant values at the 24th

Table 2. Serum electrolyte, creatinine, blood urea nitrogen and osmolarity profiles of women undergoing pregnancy

Variable	Mid follicular	Weeks gestation					
		6	8	10	12	24	36
Na *mEq/liter*	139.5 ± 0.5	137.6 ± 0.2[a]	136.3 ± 0.4[a]	136.6 ± 0.7[a]	135.7 ± 0.6[a]	135.6 ± 0.6[a]	137 ± 0.5[a]
Cl *mEq/liter*	107.3 ± 1.2	106.2 ± 0.8[a]	105.0 ± 1.5[a]	105.5 ± 0.8[a]	104.6 ± 0.9[a]	104.9 ± 0.6[a]	106.7 ± 1.4[a]
CO_2 *mEq/liter*	24.7 ± 0.4	21.3 ± 1.0[a]	20.5 ± 0.6[a]	20.5 ± 0.9[a]	20.4 ± 0.81[a]	19.9 ± 0.8[a]	18.9 ± 0.9[a]
K *mEq/liter*	3.9 ± 0.1	4.0 ± 0.1	3.7 ± 0.1	3.7 ± 0.1	3.8 ± 0.1	3.7 ± 0.1	3.6 ± 0.1[a]
S Osm M *Osm/kg*	288 ± 1.2	277 ± 1.4[a]	276 ± 1.6[a]	275 ± 0.8[a]	275 ± 1.0[a]	274 ± 1.4[a]	275 ± 1.7[a]
BUN *mg/dl*	11.8 ± 1.0	10.4 ± 1.0[a]	9.8 ± 1.1[a]	8.9 ± 0.6[a]	8.6 ± 0.5[a]	8.6 ± 0.1[a]	7.5 ± 0.8[a]
S_{Cr} *mg/dl*	0.8 ± 0.1	0.8 ± 0.05	0.7 ± 0.1[a]	0.7 ± 0.1[a]	0.7 ± 0.04[a]	0.6 ± 0.04[a]	0.55 ± 0.04[a]
Hct *%*	38.7 ± 0.8	38.2 ± 0.6	38.3 ± 0.2	37.2 ± 0.9[a]	37.0 ± 0.8[a]	36.6 ± 0.6[a]	37.0 ± 0.8[a]
Weight *kg*	61.5 ± 2.6	61.0 ± 2.9	62.3 ± 3.2[a]	64.4 ± 3.0[a]	64.6 ± 2.6[a]	72.7 ± 0.1[a]	79.2 ± 3.2[a]

[a] $P < 0.05$ compared to mid follicular values

Table 3. Reproductive hormones during human pregnancy

	Mid-Foll	Weeks gestation					
		Week 6	Week 8	Week 10	Week 12	Week 24	Week 36
Estradiol *pg/ml*	54.8 ± 8	486.3 ± 83	743 ± 141	1,004 ± 133	1,615 ± 173	7,470 ± 897	13,894 ± 2,122
Progesterone *ng/ml*	0.21 ± 0.03	20.4 ± 3.0	30.1 ± 6.2	21.4 ± 3.9	29.5 ± 3.8	166 ± 82	224 ± 36.6
BHCG mIU	0	10,727 ± 4,586	100,038 ± 17,973	116,128 ± 8,606	78,426 ± 12,000	18,953 ± 2,954	26,358 ± 9,920
Prolactin *ng/ml*	9.2 ± 1.3	29.4 ± 10.6	33.1 ± 7.3	27.9 ± 2.2	36.3 ± 4.9	21 ± 3.3	145 ± 13.5

All pregnancy values significantly greater than mid-follicular, $P < 0.001$.

and 36th weeks of gestation. Plasma norepinephrine concentrations did not change from the non-pregnant state throughout pregnancy.

Plasma concentrations of cGMP and cGMP clearance are shown in Figure 5. Plasma cGMP levels decreased significantly throughout pregnancy as early as the sixth week of gestation as compared to the non-pregnant state. A significant increase in cGMP clearance throughout pregnancy was apparent by week six of gestation.

DISCUSSION

This is the first study, to our knowledge, which rigorously and simultaneously evaluates the initial systemic and renal hemodynamic and neurohumoral changes of human pregnancy. A significant decrease in systemic vascular resistance associated with an increase in cardiac output resulting in a decrease in mean arterial pressure prior to placentation was found. These changes have been shown to occur, but to a lesser degree, during the menstrual cycle following ovulation in non-pregnant women [14]. Previous studies during early pregnancy by other investigators have not been as conclusive for a number of reasons. In the present study, blood pressure measurements were carefully standardized. Measurements were performed after one hour in the left lateral decubitus position in the morning, at the same time of day under quiet, controlled conditions. The Korotkoff V sound was used to determine diastolic blood pressure, which may be more reliable than the Korotkoff IV sound in pregnancy [34]. Importantly, women were initally studied prior to conception and immediately after becoming aware they were pregnant, ensuring early measurements no later than six weeks gestation [1–3]. During non-pregnant measurements, the phase of the menstrual cycle was also controlled and performed in the mid-follicular phase, since hemodynamic changes in the post-ovulatory or luteal phase of the menstrual cycle are significant [14, 15]. This study design allowed for the same subjects to be studied longitudinally with appropriate control of many variables known to affect systemic and renal hemodynamic measurements.

As other investigators have demonstrated, changes in cardiac output and systemic vascular resistance occurred early in the first trimester of pregnancy [37, 38]. Differences across studies in cardiac output measurements have previously been demonstrated with some showing an increase in heart rate [37] and others, an increase in stroke volume [38] accounting for the increased cardiac output found. In this study, increases in stroke volume in the second and third trimesters predominated, accounting for the changes in cardiac output seen (data not shown).

The present findings indicate that complete placentation is not necessary for the initial hemodynamic changes to occur in normal human pregnancy. Placentation, which initially begins between weeks 6 and 8 gestation, is usually complete by the 12th week [49], well after systemic and renal hemodynamic changes were observed in the present study. Therefore, it is likely that maternal factors, possibly related to changes in ovarian function or extended function of the corpora lutea, are responsible for the initial peripheral vasodilation found in human pregnancy. These observations are further supported by the changes in systemic vascular resistance and blood pressure found in pseudopregnant rats [13], in women in the luteal as compared to the follicular phase of the menstrual cycle [14], as well as women undergoing ovarian hyperstimulation [15].

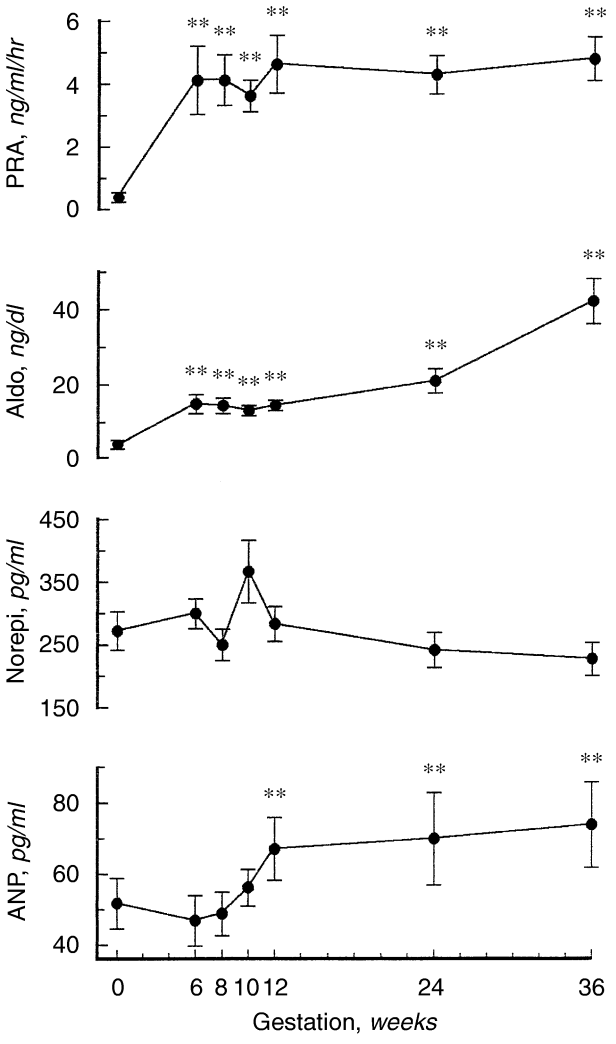

Fig. 4. Vasopressor hormone profiles throughout early human pregnancy. Ten women were studied in the mid-follicular phase of the menstrual cycle and weeks 6, 8, 10, 12, 24 and 36 gestation. Plasma renin activity (PRA) and aldosterone (Aldo) levels increased by week 6 gestation. Norepinephrine (Norepi) concentrations did not change throughout gestation. Atrial natriuretic peptide (ANP) concentrations increased significantly by week 12 gestation. $^{**}P < 0.001$.

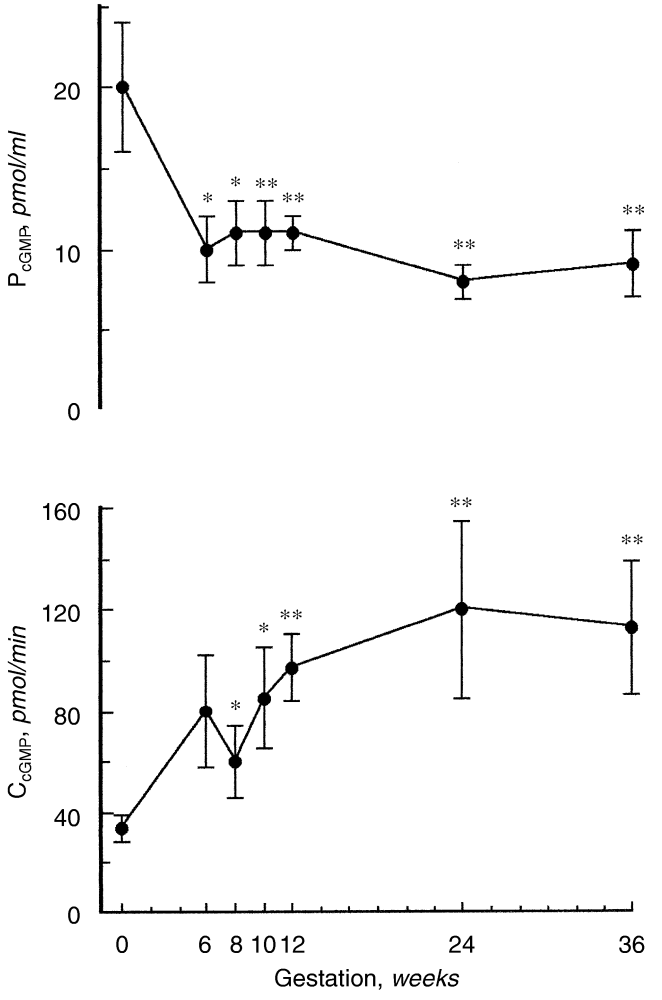

Fig. 5. Plasma and clearance values for cGMP, the second messenger for atrial natriuretic peptide (ANP) and nitric oxide (NO), throughout early human pregnancy. Ten women were studied in the mid-follicular phase of the menstrual cycle and weeks 6, 8, 10, 12, 24 and 36 gestation. Plasma cGMP levels decreased and cGMP clearance increased significantly by weeks 6 and 8 gestation. respectively. $^{*}P < 0.05$, $^{**}P < 0.001$.

Effective renal plasma flow and glomerular filtration increased, resulting in decreased renal vascular resistance. Filtration fraction decreased significantly, indicating a greater rise in effective renal plasma flow consistent with primary renal vasodilation. These findings are also found in the rat model of gestation where initial renal hemodynamic changes are found early in gestation, between days five and nine [50]. In contrast to other investigators [16, 17], a consistent but nonsignificant 6% increase in urinary creatinine excretion was found during gestation with no decrease found in the third trimester. Although others have shown a significant and greater (approximately 10%) increase in creatinine excretion during gestation, the fall in plasma creatinine concentration has always been greater, accounting for the 45% increase in creatinine clearance seen during pregnancy [16, 17]. Others have demonstrated a decrease in urinary creatinine excretion in the third trimester and followed their subjects weekly, well past the 36th week of gestation [51]. This study therefore may not have detected significant decreases in urinary creatinine excretion closer to term.

Other conditions of peripheral vasodilation, such as sepsis, cirrhosis, and high output congestive heart failure, result in no change or decreases in renal plasma flow and increases in renal vascular resistance [5, 6]. This suggests that the hormonal changes associated with pregnancy have a specific renal vasodilating effect, overriding secondary activation of other renal vasoconstricting systems such as the renin-angiotensin system (RAS). This conclusion is supported by the relative systemic pressor resistance to angiotensin II, norepinephrine and vasopressin found in pregnancy [8, 13].

The RAS was activated early as shown by increased PRA and plasma aldosterone concentrations. In this regard, it is known that peripheral vasodilation results in activation of the RAS [19–21]. Although estrogen increases angiotensinogen or renin substrate and can activate the RAS through non-hemodynamic mechanisms [19], PRA and plasma aldosterone levels are increased during pregnancy out of proportion to the enhanced substrate availability [19–21]. Further evidence for the hemodynamic activation of RAS during pregnancy is that angiotensin converting enzyme inhibition lowers blood pressure in pregnant women [52].

In other longitudinal studies of the renin-angiotensin system in women undergoing normal pregnancy and *in vitro* fertilization, PRA were greater than those found in this study [20, 21]. The change from the non-pregnant state in PRA and urinary aldosterone excretion in women undergoing ovarian stimulation correlated most closely with increases in estradiol levels, and were equivalent to a gestational age of 18 weeks [21]. Why less dramatic changes were found in the present study is unclear; however, they may reflect the supine as opposed to the seated position of the patient, differences in dietary sodium intake, and differences between assays. In the present study plasma aldosterone levels continued to rise during the last trimester independent of a change in PRA, suggesting that factors other than hemodynamic activation of the RAS, such as markedly increased progesterone levels, may be important in the later stages of pregnancy.

Plasma atrial natriuretic peptide levels remained unchanged during the first trimester as compared to the non-pregnant state. We and others have previously shown a decrease in plasma ANP concentrations during the mid-luteal phase of the menstrual cycle [14, 53]. In the present study, increases in plasma volume were greater by week six gestation as compared to the previously reported non-pregnant mid-luteal phase [14], potentially accounting for the lack in plasma ANP change in early pregnancy. However, plasma ANP levels increased 35% by the second trimester. In previous studies, plasma ANP concentration has been shown to increase, decrease or not change in the third trimester of human and rat pregnancy [23–25]. The present results are similar to a recent meta-analysis of 14 studies where plasma ANP increases significantly in the later stages of pregnancy in association with increased plasma volume [25]. These results suggest that plasma ANP changes found in pregnancy are secondary to increases in plasma volume, rather than playing a primary role in the hemodynamic changes found.

Nitric oxide, a potent vasodilator that acts through its second messenger cGMP, plays an important role in the systemic and renal hemodynamic changes found in rodent pregnancy [26–29]. In the present study, cGMP clearance increased in the setting of decreased plasma cGMP levels, indicating increased nephrogenous cGMP production. Most rodent pregnancy studies carefully performed have demonstrated an increase in both plasma and urinary excretion of cGMP [27]. However, in human studies, increased plasma cGMP has not been consistently found while increases in urinary excretion of cGMP are invariably present [30–32]. This is similar to the increase in cGMP clearance found in the present study. These results provide preliminary evidence that renal production of NO or other natriuretic substances may account for the increase in cGMP clearance found.

In summary, peripheral vasodilation occurs early in pregnancy, prior to fully complete placentation. This vasodilation causes a fall in mean arterial pressure associated with a rise in cardiac output. Increases in plasma volume also occur during the same time. Renal vasodilation occurs simultaneously with the systemic vasodilation as renal plasma flow and glomerular filtration increase, and renal vascular resistance and filtration fraction decrease. Activation of the renin-angiotensin-aldosterone system was found in association with peripheral vasodilation. Cyclic GMP clearance increased in the setting of decreased plasma cGMP levels in the first trimester of pregnancy. Further studies are needed to confirm and identify the vasodilating substances responsible for the initial systemic and renal hemodynamic changes found in early human pregnancy.

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Reprint requests to Arlene B. Chapman, M.D., Emory University School of Medicine, WMB Room 338, 1639 Pierce Drive, Atlanta, GA 30322, USA.
E-mail: arlene_chapman@emory.org

REFERENCES

1. Atkins AFJ, Wat JM, Milan P, Davies P, Crawford JS, A longitudinal study of cardiovascular dynamic changes throughout pregnancy. *Eur J Obstet Gynecol Reprod Bio* 12:215–224, 1981
2. Macgillivray I, Rose GA, Rowe B: Blood pressure survey in pregnancy. *Clin Sci* 37:395–398, 1969
3. Page EW, Christianson R: The impact of mean arterial pressure in the middle trimester upon the outcome of pregnancy. *Am J Obstet Gynecol* 125:740–745, 1976
4. Schrier RW, Briner VA Peripheral arterial vasodilation hypothesis of sodium and water retention in pregnancy: Implication for pathogenesis of preeclampsia-eclampsia. *Obstet Gynecol* 77:632–369, 1991
5. Schrier RW: Pathogenesis of sodium and water retention in high-output and low-output cardiac failure, nephrotic syndrome, cirrhosis and pregnancy. *N Engl J Med* 319:1065–1072, 1988
6. Abraham WT, Schrier RW: Cardiac failure, liver disease and nephrotic syndrome, in *Diseases of the Kidney*, edited by Schrier RW, Gottschalk C, Boston, Little, Brown and Co., 1997, pp 2353–2392
7. Conrad KP: Possible mechanisms for changes in renal hemodynamics in pregnancy. *Am J Kidney Dis* 9:253–256, 1987
8. Paller MS: Decreased pressure responsiveness in pregnancy: Studies in experimental animals. *Am J Kidney Dis* 9:308–311, 1987

9. Baylis C: The mechanism of the increase in glomerular filtration rate in the 12 days pregnant rat. *J Physiol (Lond)* 305:405–408, 1980
10. Phippard AF, Harvath JS, Glynn EM: Circulatory adaptation to pregnancy-serial studies of hemodynamics, blood volume, renin and aldosterone in the baboon. *J Hypertens* 4:733–738, 1986
11. Dunlop W: Serial changes in systemic hemodynamics during normal human pregnancy. *Br J Obstet Gynecol* 88:1–9, 1981
12. Chesley LC, Annitto JW: Pregnancy in the patient with hypertensive disease. *Am J Gynecol* 53:372–376, 1947
13. Paller MS, Gregorini G, Ferris TF: Pressure responsiveness in pseudopregnant and pregnant rats; role of maternal factors. *Am J Physiol* 257:R866–R871, 1989
14. Chapman AB, Zamudio S, Woodmansee W, Merouani A, Osono F, Johnson A, Moore LG, Dahms T, Coffin C, Abraham WT, Schrier RW: Systemic and renal hemodynamic changes in the luteal phases of the menstrual cycle mimic early pregnancy. *Am J Physiol* 273:F777–F782, 1997
15. Balasch J, Jiminex W, Arroyo V, Pare JC, Carmona F, Vanrell JA: Severe ovarian hyperstimulation syndrome: Role of peripheral vasodilation. *Fertil and Steril* 56:1077–1083, 1991
16. Davison JM, Noble McB: Serial changes in 24 hour creatinine clearance during normal menstrual cycles and in the first trimester of pregnancy. *Br J Obstet Gynecol* 88:10–17, 1980
17. Davison JM: Renal hemodynamics and volume homeostasis in pregnancy. *Scand J Clin Lab Invest* 169(Suppl):15–24, 1984
18. Barron WM, Lindheimer MD: Renal function during pregnancy. (abstract) *Contemp Obstet Gynecol* 2:179–186, 1983
19. Wilson M: Blood pressure, the renin aldosterone system and sex steroids throughout pregnancy. *Am J Med* 68:97–102, 1980
20. August P, Lenz T, Ales KL, Druzin ML, Edersheim TG, Hutson M, Muller FB, Laragh JH, Sealey JE: Longitudinal study of the renin-angiotensin-aldosterone system in hypertensive pregnant women: Deviations related to the development of superimposed preeclampsia. *Am J Obstet Gynecol* 163:1612–1621, 1990
21. Sealey JE, Itskovitz-Eldon J, Rubattu S, James GD, August P, Thaler I, Levron J, Laragh JH: Estradiol-and progestrone-related increases in the renin-aldosterone system: Studies during ovarian stimulation and early pregnancy. *J Clin Endo Metab* 79:258–264, 1994
22. Tunbridge RDG, Donnai P: Plasma noradrenaline in normal pregnancy and in hypertension of late pregnancy. *Br J Obstet Gynecol* 88:105–108, 1981
23. Schobel HP, Fischer T, Henszer K, Geiger H, Schmeider RE: Preeclampsia - A state of sympathetic over-activity. *N Engl J Med* 335:1480–1485, 1996
24. Castro LC, Arora CP, Krakow DE, Allen RJ: Atrial natriuretic peptide metabolism during pregnancy in the rat. *Am J Obstet Gynecol* 170:1184–1188, 1994
25. Lowe SA, MacDonald GJ, Brown MA: Regulation of atrial natriuretic peptide in pregnancy: Response to posture. *Am J Obstet Gynecol* 165:591–595, 1991
26. Castro LC, Hobel CJ, Gornbein J: Plasma levels of atrial natriuretic peptide in normal and hypertensive pregnancies: A meta-analysis. *Am J Obstet Gynecol* 171:1642–1651, 1994
27. Irons DW, Baylis PH, Davison JM: The metabolic clearance of atrial natriuretic peptide during human pregnancy. *Am J Obstet Gynecol* 175:449–454, 1996
28. Conrad KP, Joffe GM, Krusayma H, Rochelle LG, Smith RP, Chavez JE, Mosher MD: Identification of increased nitric oxide biosynthesis during pregnancy in rats. *FASEB J* 7:566–571, 1993
29. Conrad KP, Vernier VA: Plasma levels, urinary excretion and metabolic production of cGMP during gestation in rats. *Am J Physiol* 257:R847—R853, 1989
30. Weiner CP, Liza Soain I, Baykis SA, Knowles RG, Charles IG, Moncada S: Introduction of calcium-dependent nitric oxide synthase by sex hormones. *Proc Natl Acad Sci USA* 91:5212–5216, 1994
31. Deng A, Engels K, Baylis C: Impact of nitric oxide deficiency on blood pressure and glomerular hemodynamic adaptations to pregnancy in the rat. *Kidney Int* 50:1132–1138, 1996
32. Manninen A, Vucivnen P, Laippala P, Tiumala R, Vaapatalo H: Atrial natriuretic peptide and cyclic guanosine-3′,5′-monophosphate in hypertensive pregnancy and during nifedipine treatment. *Pharm Toxicol* 74:153–157, 1994
33. Rey E, Larochelle P, Gutkowska J, Thibailt G, Trembley J, Hamet P: ANF and head-out water immersion in normotensive and essential hypertensive pregnant women. *Clin Exp Hypertens* B11:45–47, 1992
34. Miyamoto S, Shimokawa H, Sumioki H, Nakario H: Physiologic role of endogenous human atrial natruiretic peptide in preeclamptic pregnancies. *Am J Obstet Gynecol* 160:155–160, 1989
35. Zamudio S, Palmer SK, Dahms TE, Berman JC, McCollough RG, McCullough RE, Moore LG: Blood volume expansion, preeclampsia and infant birth weight at high altitude. *J Appl Physiol* 75:1566–1573, 1993
36. Villar J, Repke J, Markush L, Calvert W, Rhoads G: The measuring of blood pressure during pregnancy. *Am J Obstet Gynecol* 161:1019–1024, 1989
37. Lee W, Rokey R, Cotton DB: Noninvasive maternal stroke volume and cardiac output determination by pulsed Doppler echocardiography. *Am J Obstet Gynecol* 158:505–510, 1988
38. Robson SC, Hunter S, Boys RJ, Dunlop W: Serial study of factors influencing changes in cardiac output during human pregnancy. *Am J Physiol* 356:H1060—H1065, 1989
39. Chapman AB, Johnson A, Gabow PA, Schrier RW: The renin-angiotensin-aldosterone system and autosomal dominant polycystic kidney disease. *N Engl J Med* 323:1091–1096, 1991
40. Walser M, Davidson DG, Orloff J: The renal clearance of alkali-stable inulin. *J Clin Invest* 34:1520–1530, 1955
41. Antunes JR, Dale SL, Melby JC: Simplified radioimmunoassay for aldosterone using antisera to aldosterone-gamma-lactone. *Steroids* 28:621–630, 1976
42. Lang RE, Thiken H, Ganten D, Luft FC, Rushoaho H, Unger TH: Atrial natriuretic factor - A circulating hormone stimulated by volume loading. *Nature* 314:264–266, 1985
43. Stockigt JR, Collins RD, Biglieri EG: Determination of plasma renin concentration by angiotensin I immunoassay: Diagnostic import of precise measurement of subnormal renin in hyperaldosteronism. *Circ Res* 28(Suppl 2):175–191, 1971
44. Kopp L, Paradiz G, Tucci JR Jr: Urinary excretion of cyclic 3′,5′-adenosine monophosphate and cyclic 3′,5′-guanosine monophosphate during and after pregnancy. *J Clin Endcor Metab* 44:590–594, 1977
45. Passon PG, Peuler JD: A simplified radiometric assay for plasma norepinephrine and epinephrine. *Anal Biochem* 51:618–631, 1973
46. Laird NM, Ware JH: Random-effects models for longitudual data. *Biometrics* 38:963–974, 1982
47. Young DA, Zerbe BO, Hay WW Jr: Fieller's theorem, Scheffe's simultaneous confidence intervals, and ratios of the parameters of linear and monlinear mixed-effects models. *Biometrics* 53:114–123, 1997
48. *SAS/1M1* (Version 6.12). SAS Institute, Inc., Cary, 1996
49. Trudinger B: Fetal-placental circulation and placentation in normal and hypertensive pregnancies, in *The Principles and Practice of Nephrology* (2nd ed), edited by Jacobsen H, Striker G, Klahr S, 1995, pp 431–435
50. Baylis C: Glomerular filtration and renal plasma flow in gravid animal models. *Bailliere's Clin Obstet Gynecol* 8:235–264, 1994
51. Davison JM, Dunlop W, Ezimokhai M: Twenty four hour cratinine clearance during the third trimester of normal pregnancy. *Br J Obstet Gynecol* 87:106–109, 1980
52. Taufield AP, Mueller FB, Edersheim TG, Druzin M, Laragh JH, Sealey JE: Blood pressure regulation in normal pregnancy: Unmasking the role of the renin-angiotensin system with captopril. (abstract) *Clin Res* 35:433A, 1988
53. Jensen LK, Svaneguard J, Husby H: Atrial natriuretic peptide during the menstrual cycle. *Am J Obstet Gynecol* 161:951–952, 1989