Changes in the Metabolic Clearance of Vasopressin and in Plasma Vasopressinase throughout Human Pregnancy

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Abstract

Metabolic clearance rates (MCR) of arginine vasopressin (AVP) were measured serially in five women starting before conception, during gestational weeks 7–8 (early), 22–24 (middle), and 36–38 (late pregnancy), and again 10–12 wk postpartum. Hormonal disposal rates were determined after water loading to suppress endogenous AVP release using a constant infusion method designed to achieve three different steady-state concentrations of plasma AVP (P_{AVP}) on each test occasion. Dose schedules were altered in mid- and late pregnancy to obtain comparable AVP levels at each stage of the protocol. Prehydration decreased plasma osmolality sufficiently to suppress AVP release, as circulating AVP-neurophysin measured serially in three of the women was undetectable. The MCR of AVP was similar before conception (0.75±0.31, 0.79±0.34, and 0.76±0.28 liters/min at P_{AVP} of 2.6±1.9, 4.7±2.4, and 8.3±3.9 pg/ml), in early pregnancy (0.89±0.34, 0.97±0.04, and 0.95±0.40 liters/min at P_{AVP} of 2.2±2.1, 3.9±3.2, and 7.9±3.4 pg/ml), and postpartum (0.70±0.21, 0.69±0.24, and 0.75±0.20 liters/min at P_{AVP} 3.5±1.8, 5.1±3.7, and 9.1±4.2 pg/ml). Values at mid-pregnancy (2.8±1.3, 3.0±1.2, and 2.7±1.2 liters/min at P_{AVP} 2.3±2.2, 4.0±3.6, and 7.7±3.9 pg/ml) and late pregnancy (3.2±1.4, 3.3±1.4, and 2.9±1.2 liters/min at P_{AVP} 1.9±2.0, 3.8±2.6, and 7.4±4.1 pg/ml) increased 3–4-fold (all $P < 0.01$). Plasma vasopressinase, undetectable at 7–8 gestational wk, increased markedly by mid- and slightly more by late gestation. Finally, relationships between P_{AVP} and urine osmolality were similar before, during, and after pregnancy. We conclude that marked increments in the MCR of AVP occur between gestational weeks 7 and 8 and mid-pregnancy, which parallel the period of greatest rise in both trophoblastic mass and plasma vasopressinase. There was no evidence of a renal resistance to AVP during gestation.

Introduction

Human gestation is characterized by profound alterations in osmoregulation. Plasma osmolality (P_{osmol})[1] and osmotic thresholds for thirst and arginine vasopressin (AVP) release decrease ~ 10 mosmol/kg during the first trimester. These decrements are maintained till term (1–3). Another interesting osmoregulatory change is that the rise in circulating AVP levels provoked by increases in body tonicity ($\Delta P_{AVP}/\Delta P_{osmol}$), unaltered early in gestation, is markedly decreased in the third trimester (3). This latter event could represent a reduced secretory response to osmotic stimuli, but might also reflect an increase in hormonal metabolic clearance rates (MCR). Indeed, in a preliminary report we have noted that the MCR are increased fourfold during the third trimester compared with measurements postpartum (4). The present study extends this latter observation. MCR of AVP were measured serially in volunteers, starting before conception, continuing throughout pregnancy, and again 10–12 wk postpartum. This study was designed to determine hormonal disposal rates at three different steady-state plasma concentrations during each test. Furthermore, by manipulating exogenous AVP infusion rates we succeeded in duplicating these levels and were able to compare their influence both on the MCR and urine osmolality (U_{osmol}) first before, three times during, and again after pregnancy. Results were also correlated with circulating levels of cystine-aminopeptidase (EC 3.4.11.3; vasopressinase), an enzyme recently implicated in the etiology of transient vasopressin-resistant diabetes insipidus (DI) of pregnancy (5).

Methods

Subjects

Serial studies were performed on five normotensive healthy subjects once before conception, between gestational weeks 7 and 8, 22 and 24, 36 and 38 (designated as early, mid-, and late pregnancy), and again 10–12 wk postpartum, when none were breast feeding or ingesting oral contraceptives. In addition, two women with a single kidney, one subject carrying twins and another triplets, were studied but only in late pregnancy and postpartum. All volunteers gave informed consent in writing to protocols approved by both the Ethical Committee of Newcastle Health Authority and the Clinical Investigation Committee of the University of Chicago Pritzker School of Medicine. All subjects had successful pregnancies.

Protocols

Fig. 1 is a schema of the protocol. Each study began at 9:00 a.m. with the volunteers seated comfortably. Control blood samples were obtained and an infusion of normal saline (0.03 ml/kg per min) was started, after which the subject drank 20 ml/kg of tap water. Clearance measurements began 1 h later and after U_{osmol} had decreased below 100 mosmol/kg. Three AVP (Argipressin; Parke-Davis, Detroit, MI) delivery rates, each preceded by a priming dose, were used during each test (Fig. 1).[2] Each infusion was maintained for 75 min, urine collected at

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1. *Abbreviations used in this paper:* DDAVP, 1-desamino-[8-D-arginine] vasopressin; DI, diabetes insipidus; MCR, metabolic clearance rates; P_{AVP}, plasma arginine vasopressin; P_{osmol}, plasma osmolality; U_{osmol}, urine osmolality.

2. Dose schedules, altered in mid- and late pregnancy to obtain comparable levels at each stage of the protocol, were based on preliminary

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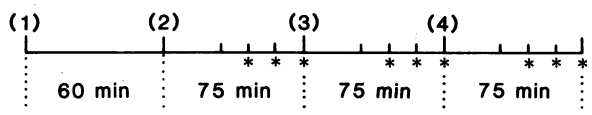

(1) Ingest water load (20 ml/kg) and begin sustaining infusion. After 60 min., priming dose followed by constant AVP infusion

	(*denotes blood sampling)	PRIME (pg/kg)	DELIVERY (pg/kg/min)
(2)	nonpregnant; early pregnancy	35	24
	midgestation; late pregnancy	120	84
(3)	non pregnant: early pregnancy	60	42
	midgestation: late pregnancy	210	144
(4)	nonpregnant: early pregnancy	105	72
	midgestation: late pregnancy	360	246

Figure 1. Schema of infusion protocol.

15-min intervals during the last 45 min, and blood samples obtained at 45, 60, and 75 min, respectively (Fig. 1). Constancy of the delivery rate was verified at frequent intervals using a calibrated burette within the intravenous set-up, while P_{osmol} were maintained at 270 mosmol/kg during pregnancy and 275 mosmol/kg preconception and postpartum, by periodic ingestion of water. These tonicities should be sufficiently low to ensure suppression of endogenous AVP release, but to confirm this, plasma AVP-neurophysin levels were determined in three of the subjects on 15 test occasions. Finally, vasopressinase levels were monitored starting with the initial test, and then every 2–3 wk until the postpartum study.

Analytical procedures

Blood for osmolality and vasopressinase activity was collected in chilled heparinized tubes, small portions were immediately drawn for microhematocrit determination, and the remainder was centrifuged at 4°C. Osmolality was determined by freezing point depression on an osmometer (model 3DII; Advanced Instruments, Inc., Needham Heights, MA) on freshly separated plasma, and the remaining sample was stored at −20°C until used. Blood for AVP determination was collected in a 10-ml syringe containing 0.1 ml phenanthroline (1-20-phenanthroline monohydrate; Sigma Chemical Co., St. Louis, MO) solution (60 mg/ml) and then rapidly added to chilled heparinized tubes, centrifuged in the cold, and extracted within 3 h of venipuncture. Validation of this technique, which immediately inactivates the high concentrations of cystine aminopeptidase (vasopressinase) present in the plasma of gravidas, is detailed elsewhere (2).

RIA of AVP. Details of our extraction technique and assay procedures have been published (2). Briefly, plasma is extracted by a modification of the acetone method and 200-μl samples are assayed by a nonequilibrium method. The tracer has a high specific activity (> 1,000 Ci × μg^{-1}); highly purified AVP (potency, 400 U/mg, lot 800207; Ferring Arzneimittal GbhG, Wittland, FRG) is used for iodination and standards, and our antiserum (10169) is quite specific and sensitive. Assay sensitivity is 0.1 pg/assay tube, while its 50% displacement is 1.6 pg/assay tube.

Vasopressinase activity. An index derived from the rapidity by which the enzyme degraded the ^{125}I-AVP tracer was used to monitor vasopressinase activity during and after pregnancy (5, 6). Phenanthroline-free plasma (1.0 ml) was incubated at 22°C with tracer (2×10^5 cpm). 50-μl aliquots were drawn before and 5, 10, 15, 30, and 60 min after incubation, and immediately diluted in 1 ml chilled 4°C assay buffer containing phenanthroline (60 mg/ml), a step that inactivated the enzyme (2). Degradation of the iodinated tracer was measured by loss of binding to excess AVP antiserum and residual activity (at 60 min) expressed as percentage of bound tracer from the aliquot obtained before incubation (usually > 95%). Sensitivity of this index was compared with that of a standard photometric fluorometric assay that uses 5-benzyl-L-cystine-*p*-nitroanilide as a substrate (7).

AVP-neurophysin. Preparation of the antiserum, iodination of tracer, and RIA for AVP (nicotine-stimulated) neurophysin are described in detail elsewhere (8, 9). Briefly, 50 μl of plasma are assayed by a nonequilibrium technique, the minimal detectable level of neurophysin being 0.5 ng/ml.

Calculations and statistical analysis. MCR was measured by a standard formula: infusion rate (calibrated during each study) multiplied by infusate AVP concentration (verified by RIA), divided by P_{AVP} (mean of three separate determinations obtained after reaching equilibrium). To assess if a steady-state AVP level had been achieved during each of the three constant infusions of AVP per study, a test of piecewise linear trend was used (10, 11). To determine whether or not the MCR was significantly different at the three infusion rates, the values at each rate of infusion within each subject or each of the five test occasions were analyzed using an analysis of variance (ANOVA). From the significance of the F ratio from this analysis, comparison was performed using the *t* test (11). Paired comparisons between test occasions were performed using *t* test. For all analyses, values of $P \leq 0.05$ were considered significant. All data are given as mean±SD.

Results

Table I and Fig. 2 summarize results in all five subjects. Altering infusion rates produced similar P_{AVP} levels at each stage of the serial study. P_{AVP} during the final 30 min of all infusions were quite constant, demonstrating that steady-state levels had indeed been achieved by this time. This constancy is illustrated in Table II, which summarizes the mean variation and its SD for P_{AVP} and P_{osmol} at each infusion rate throughout the study. Not shown coefficients of variations were consistently below 10%. These data again underscore the adequacy of steady-state values used to calculate the MCR in this investigation.

Of particular interest, the MCR in mid- and late pregnancy (3–4 liters/min) were fourfold those measured before conception, early in gestation, or postpartum (all $P < 0.01$; Table I and Fig. 2). Small increases in hormonal disposal rates were noted during the first trimester (when osmotic secretory thresholds are decreasing or have just reached their lowest values, but the AVP response to osmotic stimuli [$\Delta P_{AVP}/\Delta P_{osmol}$] is similar to values in the nongravid state [3]), but these changes were not significant. Similarly, the MCR in late gestation were slightly higher than those in mid-pregnancy, but again these increments did not reach significance. In essence, the greatest changes took place between gestational weeks 6 and 8 and 22 and 24.

Note also that the MCR at any stage was unaltered despite virtually tripling circulating hormone concentrations between the first and final infusion rates of each test. Table I and Fig. 2 depict relationships between P_{AVP} and U_{osmol} during each phase of the study. Similar U_{osmol} were recorded when P_{AVP} was comparable before, during, and after gestation.

Table I also contains AVP-neurophysin levels measured in three volunteers. Values before water loading were similar to those reported in the literature (8, 9) and became undetectable (< 0.5 ng/ml) after hydration.

The MCR in the women with a single kidney and those carrying twins and triplets are summarized in Table III. These

data (4), as well as unpublished observations, which indicated that the delivery of substantially more hormone would be necessary to obtain measurable P_{AVP} as gestation progressed.

Table I. MCR of Infused AVP in Pregnant Women

	Prepregnancy			Early pregnancy			Mid-pregnancy			Late pregnancy			Postpartum		
Infusion (*pg/kg per min*)	Basal	24	42	72	Basal	24	42	72	Basal	84	144	246	Basal	24	42	72
P_{AVP} (*pg/ml*)	0.9 ±0.5	2.6 ±1.9	4.7 ±2.4	8.3 ±3.9	0.8 ±0.5	2.2 ±2.1	3.9 ±3.2	7.9 ±3.4	0.7 ±0.5	2.3 ±2.2	4.0 ±3.6	7.7 ±3.9	1.0 ±0.6	1.9 ±2.0	3.8 ±2.6	7.4 ±4.1	1.1 ±0.6	3.5 ±1.8	5.1 ±3.3	9.1 ±4.2
P_{osmol} (*mosmol/kg*)	286.1 ±2.9	279.2 ±2.1	277.1 ±2.1	272.8 ±2.2	279.1 ±3.4	272.2 ±2.6	268.4 ±2.4	267.1 ±2.2	279.1 ±2.9	271.1 ±2.7	270.2 ±2.4	268.6 ±2.0	278.9 ±3.4	268.4 ±2.1	265.6 ±2.8	264.1 ±2.2	287.8 ±3.1	276.1 ±2.6	276.0 ±2.8	275.7 ±1.9
U_{osmol} (*mosmol/kg*)	594 ±248	619 ±94	742 ±86	842 ±109	608 ±262	648 ±90	841 ±106	977 ±114	519 ±101	544 ±92	781 ±116	829 ±138	500 ±82	489 ±141	658 ±131	742 ±97	628 ±104	641 ±109	774 ±126	848 ±137
U_{vol} (*ml/min*)	—	1.1 ±0.83	0.72 ±0.42	0.52 ±0.41	—	0.86 ±0.61	0.80 ±0.32	0.58 ±0.41	—	0.99 ±0.80	0.72 ±0.59	0.67 ±0.39	—	1.31 ±0.37	0.92 ±0.41	0.70 ±0.36	—	1.29 ±0.71	1.18 ±0.62	0.65 ±0.51
MCR_{AVP} (*ml/min*)	—	754 ±311	786 ±391	761 ±284	—	889 ±342	968 ±414	949 ±402	—	2848 ±1320	3016 ±1162	2742 ±1189	—	3176 ±1412	3284 ±1391	2889 ±1209	—	702 ±214	678 ±243	746 ±201
$P_{Neurophysin}$* (*ng/ml*)	0.94 ±0.61	0.52 ±0.51	<0.5	<0.5	0.81 ±0.72	0.50 ±0.50	<0.5	<0.5	0.91 ±0.59	<0.5	<0.5	<0.5	0.74 ±0.61	<0.5	<0.5	<0.5	0.77 ±0.54	<0.5	<0.5	<0.5

$n = 5$ (mean±SD). * $n = 3$ (see text).

subjects, studied only during the third trimester and postpartum, were evaluated during an early phase of the investigation, before we appreciated the magnitude of the changes in MCR in late gestation, and when the experimental design at that time involved only a two-tier infusion. Not shown, only a single similar steady-state P_{AVP} was achieved before and after pregnancy for each subject.

Fig. 3 compares vasopressinase activity derived by our isotope index and a standard substrate method. Activity was detected earlier in pregnancy using the tracer method (7–8 wk) and then the substrate technique (9–10 wk). Enzyme activity increased 40-fold by mid- and 50-fold by late pregnancy using either assay ($P < 0.001$), while vasopressinase remained detectable for a longer period after gestation using the tracer (5–6 wk) compared with the substrate (4 wk) assay. Not shown on the figure, enzyme levels in the women carrying twins and triplets were consistently at the upper 1 SD boundary, their final values near term being 270 and 281 mIU/ml, respectively.

Discussion

We monitored clearances of exogenously infused AVP in five women starting before conception, continuing throughout pregnancy, and 8–10 wk postpartum. The MCR at mid- and late pregnancy was markedly increased compared with values in the first trimester as well as when the women were not pregnant. Hormonal disposal rates at any phase of the study were uninfluenced by the circulating levels of AVP and the increments observed during mid- and late gestation seemed to correlate with striking increases in vasopressinase activity present at these times. We also measured basal AVP in these subjects, noting that levels were similar throughout pregnancy as well as the nonpregnant state. Thus, hormonal production rates must also have increased by mid-gestation.

The observation that infused AVP is cleared more rapidly during gestation confirms and extends a recent report in which we suggested that the MCR of endogenously secreted hormone was increased in late pregnancy (12). This was based on observations during and after pregnancy in a protocol where P_{AVP} had been increased secondarily to increments in P_{osmol} induced by hypertonic saline infusion after which the subjects drank water, a maneuver that rapidly suppresses endogenous hormone release by an oropharyngeal-neuroendocrine reflex, even in the face of sustained hyperosmolality (12). Within minutes of drinking, AVP levels started to decrease and the hormonal $t_{1/2}$ in late gestation was half that in early pregnancy or postpartum. However, as noted in that report, peak AVP levels attained with hypertonic saline were too low (usually between 5 and 10 pg/ml), and post-drinking blood samples with detectable P_{AVP} too few, to accurately assess the $t_{1/2}$. Nevertheless, these previous observations add confidence to the conclusion that our present infusion clearance data reflect the MCR of endogenously secreted hormone. This is not a moot point for in pregnancy it is conceivable that the intravenous infusion of AVP might activate or increase plasma vasopressinase. In this respect circulating vasopressinase activity measured before, during, or after an infusion was similar in a given subject on any test occasion (Sheills, E. A., and J. M. Davison, unpublished observations).

The reason for the striking increments in MCR in late gestation is not apparent from our data and one can only

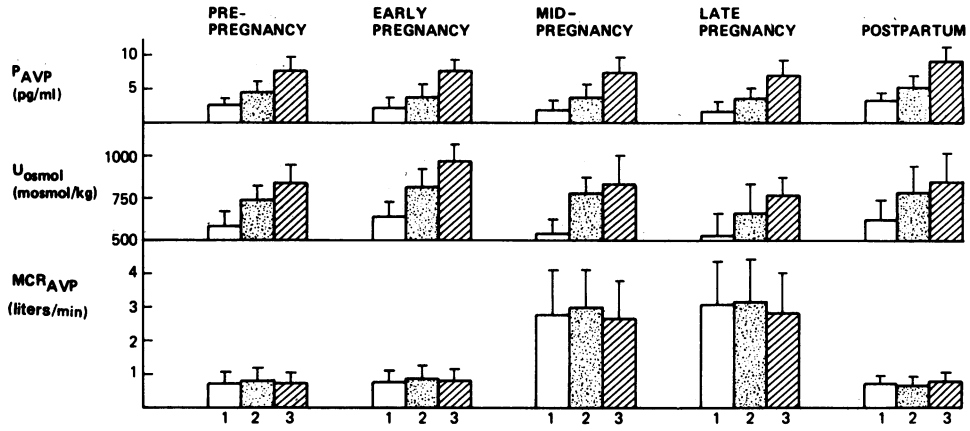

Figure 2. Summary of P_{AVP}, U_{osmol}, and MCR_{AVP}, (±SD) measured serially in all five women starting before conception, then during gestational weeks 6–8, 22–24, and 36–38, as well as 10–12 wk postpartum. The three infusion rates are detailed in Fig. 1.

speculate concerning causality. Renal and hepatic blood flow increase during gestation and the kidney and liver are organs where considerable AVP degradation takes place. Renal hemodynamics, however, increase quite early in pregnancy (at a time when the MCR is hardly altered), and the combined increments in flow to both organs (controversial for the liver and 30–50% for the kidney) are far less than the increase in hormonal disposal recorded in mid- and late gestation (13). Also, the percent rise in MCR noted in the two gravidas with single kidneys was similar to that in the normal volunteers.

The placenta, the mass of which increases throughout gestation, may inactivate substantial quantities of AVP in situ. In preliminary studies we perfused ^{125}I-AVP at rates comparable to in vivo conditions (14). The preparation perfused on the maternal side was capable of inactivating ~ 1 ng/min of tracer, while perfusion of the fetal side was without effect.

Table II. Variation of P_{AVP} and P_{osmol} Measured at 15-min Intervals during Final 45 Min of Each Infusion during 225 Measurements of MCR Performed on Five Patients

		Variation of	
	Infusion	P_{AVP}	P_{osmol}
	pg/kg/min	*pg/ml*	*mosmol/kg*
Prepregnancy	24	0.52±0.29	1.3±0.7
	42	0.44±0.28	0.9±0.7
	72	0.57±0.26	0.9±0.9
Early pregnancy	24	0.42±0.31	1.2±0.9
	42	0.63±0.34	1.1±0.8
	72	0.50±0.29	0.8±0.4
Mid-pregnancy	84	0.64±0.29	0.9±0.9
	144	0.61±0.26	1.4±0.6
	246	0.43±0.27	1.2±0.6
Late pregnancy	84	0.29±0.19	0.9±0.9
	144	0.41±0.20	1.3±0.8
	246	0.34±0.21	1.1±0.8
Postpartum	24	0.56±0.34	1.1±0.7
	42	0.61±0.32	1.1±0.7
	72	0.53±0.34	1.5±0.6

Mean±SD; n = 5 patients.

Thus, the placenta too may account for the increased MCR observed on these studies. Of interest, also, is that estimated trophoblastic mass increases 1,000-fold between gestational weeks 6 and 24, plateauing thereafter (15). Uteroplacental blood flow follows a similar pattern of change, and at term has been estimated to be about 500 ml/min blood flow (16). In these respects the MCR of AVP was almost maximal by 22–24 wk, increasing slightly but not significantly near term.

The placenta is also the source of circulating vasopressinase, an enzyme capable of inactivating large quantities of AVP in vitro. Whether or not this enzyme is active in vivo, however, is unclear, but it is of interest that alterations in the hormonal MCR correlated best with increments in plasma vasopressinase in the present study. Of further interest, pregnant sheep, whose placentae produce no detectable vasopressinase, do not have an increased MCR of AVP during their gestation (17). Currently we are measuring the MCR of 1-desamino-[8-D-arginine]vasopressin (DDAVP), an AVP analogue resistant to enzymatic inactivation by cystine-aminopeptidase (18). If vasopressinase does play a role in the increased MCR of AVP during mid- and late gestation, any increments in the disposal rate of infused DDAVP ought to be considerably less than those observed for the native hormone.

Oxytocin, which differs from AVP by just two amino acids, is also inactivated in vitro by cystine-aminopeptidase, and thus might be expected to be metabolized in a manner similar to vasopressin in pregnant women. Surprisingly, however, Amico et al. observed no differences in the MCR of infused oxytocin into term pregnant subjects compared with nonpregnant vol-

Table III. MCR of AVP in Third Trimester and Postpartum in One Woman with Twins, Another with Triplets, and Two Subjects with a Single Kidney

	Third trimester		Postpartum	
Infusion (*pg/kg per min*)	84	144	42	72
MCR				
Twins (*ml/min*)	3,417	2,994	981	818
Triplets (*ml/min*)	2,627	2,588	812	729
One kidney (*ml/min*)	1,895	2,806	339	550
One kidney (*ml/min*)	2,318	2,103	553	621

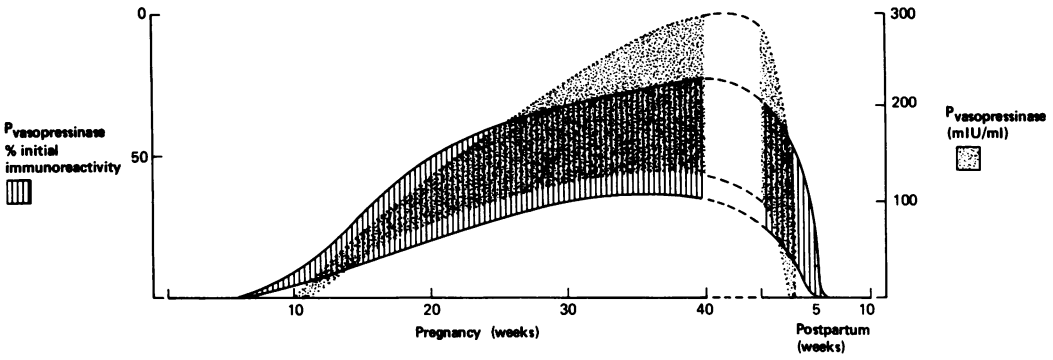

Figure 3. Plasma vasopressinase activity measured serially in the five women who underwent the metabolic clearance studies. Measurements of $P_{vasopressinase}$ started before conception and were repeated at 2–3-wk intervals until postpartum weeks 10–12. Two indices were used, one derived from the rapidity by which the enzyme degraded ^{125}I-AVP tracer (*vertical lines*) and the other by photometry using 5-benzyl-L-cystine-*p*-nitroanilide as substrate (*speckled area*). Solid and dashed lines enclosing the vertical lines and speckled area represent ±1 SD.

unteers (19). However, there is evidence that oxytocin may be more resistant to enzymatic degradation in vivo, especially in the central nervous system (20). Also, and in contrast with observations reported by Amico et al. (19), we have preliminary data that suggest that the MCR of infused oxytocin is increased in a manner similar to that of AVP at term (21).

The increased MCR of AVP in pregnancy may explain certain other changes in osmoregulation during gestation. As noted previously, the rise in circulating hormone provoked by increasing body tonicity ($\Delta P_{AVP}/\Delta P_{osmol}$) decreases in the third trimester. Initially we considered that this might reflect a reduced secretory response to osmotic stimuli, as occurs in certain hypervolemic states such as primary aldosteronism (22), for indeed extracellular volume increases markedly in pregnancy (23). However, the osmotic sensitivity to thirst (Δthirst intensity/ΔP_{osmol}; see reference 3) would also be expected to be decreased in such circumstances (24) and it was not (3). Another possibility considered was that an increase in hormonal disposal rate would explain reductions in the ratio $\Delta P_{AVP}/\Delta P_{osmol}$ with little influence on the relationship between thirst intensity and P_{osmol}. This led to the current study and data supporting the latter hypothesis.

Several problems in water handling known to occur in pregnancy may also relate to our observations. For example, some women with central DI may require more AVP during gestation. There is a syndrome labeled transient DI of pregnancy that usually presents during the second half of gestation and remits postpartum (25). Some of the women with this complication may have subclinical lesions of central DI brought to the fore by the increased hormonal MCR of pregnancy (25–27). Still other patients have been described with transient vasopressin-resistant DI and high circulating levels of vasopressinase, and one of them described by Dürr et al. (5) responded to DDAVP after large doses of AVP had failed to effect U_{osmol}.

Performance of a serial study also allowed us to evaluate the influence of pregnancy on renal effects of AVP. Some have suggested resistance to the hydroosmotic effects of AVP upon the kidney during gestation, both in humans and in two animal species (28–31). Several reasons, including increments during pregnancy in PGE_2 excretion, a hormone that opposes the effects of AVP at the tubular level, have been offered to explain this resistance. Review of the literature, however, reveals that such claims have been based solely on the influence of exogenously administered hormone on U_{osmol}, without noting if such maneuvers achieve similar P_{AVP} levels during the pregnant and nonpregnant states. For example, administration of similar quantities of AVP during the nongravid and pregnant states would be expected to produce lower P_{AVP} values in the latter if either the MCR or volume of distribution were increased in pregnant and control subjects or animals. Our experiments permitted comparison of U_{osmol} at similar AVP levels, measured during steady-state conditions. Similar levels of P_{AVP} produced approximately the same U_{osmol} in early, mid-, and late gestation as well as in the nonpregnant state (Table I and Fig. 2).

Finally, our observations in postpartum subjects are consistent with the MCR for AVP measured in nonpregnant populations and reported by Robertson et al. (32), Beardwell et al. (33), and Moses and Steciak (34), who used constant-infusion techniques, and Engel et al. (35), who performed a single-injection protocol. Moses and Steciak, however, observed increments in the MCR as P_{AVP} increased, but we did not. This discrepancy may be explained by the fact that we measured P_{AVP} at three levels within the physiological range, while even the lowest concentrations observed by Moses and Steciak (34) were supraphysiological.

In conclusion, these data demonstrate that the MCR of AVP similar to nonpregnant values during gestational weeks 7–8 measures fourfold by weeks 22–24 and remains at these elevated levels through term. These rises seem to parallel the periods of rapid increase in both trophoblastic mass and circulating vasopressinase. The increase in hormonal disposal rates may explain the appearance of certain polyuric syndromes in late gestation.

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