MINI REVIEW

Osmoregulation, the secretion of arginine vasopressin and its metabolism during pregnancy

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This review stresses changes in osmoregulation as well as the secretion and metabolism of arginine vasopressin during pregnancy, focusing on human gestation. Pregnant women experience a decrease in body tonicity, plasma osmolality decreasing immediately after conception to a nadir ~ 10 mosmol/kg below non-pregnant levels early in pregnancy, after which a new steady state is maintained until term. Data from both human and rodent gestation have led to a formation of how these changes occur. The osmotic thresholds for thirst and antidiuretic hormone release decrease in parallel. Lowering the threshold to drink stimulates increased water intake and dilution of body fluids. Because arginine vasopressin (AVP) release is not suppressed at the usual level of body tonicity, the hormone continues to circulate and the ingested water is retained. Plasma osmolality declines until it is below the osmotic thirst threshold, and a new steady state with little change in water turnover is established. Pregnancy is characterized by increments in intravascular volume, but volume-sensing AVP release mechanisms appear to adjust as gestation progresses so that each new volume status is “sensed” as normal. The metabolic clearance of AVP increases fourfold, the rise paralleling that of circulating cystine aminopeptidase (vasopressinase), and enzyme produced by the placenta. Furthermore, the disposal rate of 1-deamino-8-arginine AVP, and AVP analogue resistant to inactivation by vasopressinase, is unaltered in pregnancy. Thus, the increase in AVP’s metabolism and the high circulating aminopeptidase levels have been implicated in certain forms of transient diabetes insipidus that occur in late pregnancy. Finally, mechanisms responsible for the altered osmoregulation in pregnancy are obscure, but chorionic gonadotropin and relaxin may be implicated in the changes.

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Clinicians are generally aware that plasma sodium (P$_{Na}$) decreases during normal gestation (1–5). Less appreciated is that this represents a decrease in effective osmolality, because when body tonicity is measured serially throughout pregnancy, the following is observed: plasma osmolality (P$_{osmol}$) starts to decrease shortly after conception, the decrement becoming significant by gestational week 5, and continues to decrease, reaching a nadir of 8–10 mosmol/kg by week 10, and thereafter remains unchanged until term, returning to non-pregnant values during the first 2 weeks of the puerperium (5) (Fig. 1). Gravidas, however, are not normally polydipsic and polyuric but concentrate their urines despite P$_{Na}$ and P$_{osmol}$ values below those measured postpartum. Such observations led us to suggest that osmoregulation and vasopressin secretion were altered in pregnancy, topics that our laboratories have explored for over a decade. This review of water handling and AVP release in pregnancy will highlight several observations, namely that the osmotic thresholds for thirst and vasopressin release are altered during gestation, that the metabolic clearance rate (MCR) of antidiuretic hormone increases at midgestation and how studies of these normal physiological adaptations and their mechanisms led to the prediction, search for and description of certain disorders of water handling peculiar to pregnancy.

Arginine vasopressin release and thirst

Decreases in P$_{Na}$ and even P$_{osmol}$ throughout normal human pregnancy were noted several decades ago (1–4), but the relevance of such observations to altered osmoregulation did not appear until the early 1980s when Davison, Vallotton and Lindheimer (5) reported the serial changes in body tonicity during gestation described above (Fig. 1). Also noted in the article was that pregnant women concentrated and diluted their urines around their lower steady-state P$_{osmol}$, and that urinary osmolality (U$_{osmol}$) following either water deprivation or oral hydration was similar during and after pregnancy, the authors hypothesizing that human
pregnancy was accompanied by a “resetting” of the osmotic threshold for vasopressin secretion to a lower body tonicity.

The above postulate obviously would have been more conclusive if both $P_{\text{osmol}}$ and $U_{\text{osmol}}$ had been correlated with circulating levels of AVP, but hormonal measurements were hampered initially because the plasma of gravid women contains large quantities of vasopressinase (a cystine aminopeptidase; EC 3.4.11.3), and enzyme that cleaves rapidly AVP in vitro (6–10). This exaggerated certain analytical problems normally encountered when measuring AVP in non-pregnant subjects, which can be summarized as follows: AVP circulates at extremely low levels ($10^{-12}$ mol/l) and in unextracted plasma there are large quantities of immunoassayable material many times that of the true hormone (11). Changes in body tonicities, which evoke very dilute to maximally concentrated urines ($U_{\text{osmol}} = 30–1200$ mosmol/kg), are associated with $P_{\text{AVP}}$ levels that range from undetectable to only 5 pg/ml. Thus, extraction procedures are critical and antisera of exceptional sensitivity, specificity and precision are required to study vasopressin even in non-pregnant populations. The presence of the cystine aminopeptidase enzyme in sufficient quantities to cleave rapidly nanogram quantities of AVP in vitro, and which could conceivably cause tracer damage that might add to extraction woes and “blank” problems, proved a formidable challenge in efforts to validate the assay. Thus, animal models were sought, and pregnant rats, the blood of which contains no detectable vasopressinase and which also experiences significant decreases in $P_{\text{osmol}}$, proved an ideal species for investigating osmoregulation in pregnancy (12).

Osmotically induced vasopressin secretion during pregnancy

Osmoregulation in the pregnant rat

In 1981 Dürr, Stamoutsus and Lindheimer (12) noted that despite a significant decrement in both $P_{\text{Na}}$ ($\sim 5$ mEq/dl) and $P_{\text{osmol}}$ ($\sim 10$ mosmol/kg) $P_{\text{AVP}}$ in near-term Sprague-Dawley rats averaged 2 pg/ml, levels similar to those in virgin controls. Furthermore, even though body tonicity was decreased significantly in the pregnant animals, basal $U_{\text{osmol}}$ was similar and > 1400 mosmol/kg in both groups, and during oral water loading both suppressed their $P_{\text{AVP}}$ to undetectable levels and manifested similarly dilute urines. By injecting saline of varying tonicity (200–1200 mosmol/kg) these authors created a range of blood tonicities that permitted analysis of the effects of different levels of $P_{\text{osmol}}$ on antidiuretic hormone secretion. Figure 2 reveals that there are highly significant correlations between $P_{\text{osmol}}$ and $P_{\text{AVP}}$ in both gravid and control rats, and that antidiuretic hormone levels increase as soon as tonicity does in both pregnant and non-pregnant animals. The levels do not remain constant until $P_{\text{osmol}}$ reaches the basal values in virgins, increasing thereafter: a scenario anticipated if there were both non-osmotic secretion at the lower tonicities during gestation and similar AVP secretory thresholds in the pregnant and non-pregnant states. Inspection of the figure also reveals that when $P_{\text{osmol}}$ values are similar, vasopressin concentrations are higher in the pregnant compared with the virgin rats. The highly significant regressions of $P_{\text{AVP}}$ on $P_{\text{osmol}}$ define the apparent osmotic thresholds for AVP release (the abscissal intercepts), which is > 10 mosmol/kg lower in pregnant animals. However, the slope of the regression line for pregnant animals, a measure of the “sensitivity” of the hormonal response to increasing tonicity, was unaltered (Fig. 2).

These data in rodents—the rapid dilution of the urine and suppression of hormone release when hydration

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**Fig. 1.** Plasma urea ($P_{\text{urea}}$), sodium ($P_{\text{Na}}$) and osmolality ($P_{\text{osmol}}$) measured weekly starting before conception and during the first trimester in nine healthy women who had normal pregnancy outcomes. MP: menstrual period; LMP: last menstrual period. Shaded area is ±1sd. From Ref. 5 with permission.
decreased tonicity below basal levels, coupled with increments in AVP levels with each 1–2% rise in $P_{\text{osmol}}$ above baseline measurements with a regression line of $P_{\text{AVP}}/P_{\text{osmol}}$ intercepting the abscissa 10 mosmol/kg below that for virgins—convincingly demonstrated that the osmotic threshold for antidiuretic hormone secretion is decreased in rat gestation. Recently, Koehler et al. (13) have confirmed and extended these findings by noting that the osmotic threshold for AVP secretion returns to non-pregnant levels by the 6th day of lactation.

Was the gestational resetting of the hormone secretory threshold the only explanation of the osmoregulatory changes? Studies performed on homozygous Brattleboro rats with congenital hypothyamic diabetes insipidus suggested the answer to be no (12, 14). These animals are unable to produce circulating AVP and yet their $P_{\text{osmol}}$ also decreases over 10 mosmol/kg during gestation. One explanation is that hypertonicity stimulates oxytocin (13), which at high levels has antidiuretic action (15). However, the pregnant Brattleboro animals decrease their $P_{\text{osmol}}$ while maintaining urines as dilute as those measured in the non-pregnant state (12, 14). A more logical explanation was that the osmotic threshold for thirst also is altered in pregnancy. In fact, decreases in thresholds for both drinking and AVP release appear necessary to produce the new steady state with minimal changes in water turnover. Otherwise, $P_{\text{osmol}}$ would remain at non-pregnant levels despite considerable hormone release if pregnant animals were not stimulated to drink at lower levels of body tonicity. On the other hand, if only the thirst threshold decreased, AVP release would cease after a small decrease in osmolality, the animal would enter a diuretic state and considerable polydipsia would be necessary to maintain even a modest decrement in body tonicity. How do such observations in rodent gestation relate to the changes in osmoregulation observed in human pregnancy?

**Studies in human pregnancy**

Several groups have measured vasopressin levels in pregnant women, during either cross-sectional and/or serial studies, and in some of these reports $P_{\text{AVP}}$ was related to body tonicity either in the basal state or following overnight water deprivation (8, 16–18). Most author fail to provide the evidence necessary to determine if their assay was reliable. On the other hand, Davison et al., after developing methodology to inactivate rapidly vasopressinase upon blood drawing (19), evaluated systematically the functional aspects of the osmoregulatory system, including relating $P_{\text{osmol}}$ to $P_{\text{AVP}}$ and/or thirst during fluid restriction, water
loading and stepwise increments of body tonicity evoked by hypertonic saline, during pregnancy (19, 20). They also measured the MCR of AVP (10), comparing the results to those of the MCR of 1-deamino-8-o-AVP (dDAVP), a vasopressin analogue resistant to degradation by vasopressinase (21).

In their initial study, Davison et al. (19) reported that eight women studied in late pregnancy and 8–10 weeks postpartum had basal $P_{\text{osmol}}$ values that were 9 mosmol/kg lower during than after pregnancy, yet $P_{\text{AVP}}$ was measureable and similar to their non-pregnant values. Following fluid restriction, tonicity, $U_{\text{osmol}}$ and hormone levels rose similarly during the third trimester and postpartum, while water loading reduced $P_{\text{osmol}}$ significantly and $P_{\text{AVP}}$ became undetectable during both test periods. The slow infusion of hypertonic saline resulted in a gradual rise of body tonicity, again achieving similar increments before and after delivery, and by applying regression analysis to AVP–osmolality relationships the authors demonstrated that the osmotic thresholds for thirst and AVP release were significantly lower in human gestation.

Next, the time course of these threshold changes was explored in a serial study of normotensive women tested first during the luteal phase of the menstrual cycle before conception, then between gestational weeks 5 and 8 and between weeks 10 and 12 (the periods when body tonicity is decreasing towards and reaching its nadir (see Fig. 1), once more during weeks 28–33 and then 3 months postpartum (Fig. 3 and Table 1) (20). Basal $P_{\text{osmol}}$ and vasopressin levels were similar at each test period, whether in early or late gestation or in the non-pregnant state. Osmotic thresholds for hormone release and drinking already were decreased significantly 5–8 weeks after the missed menstrual period, that for thirst appearing to have declined more rapidly than the threshold for AVP release (Table 1); consistent with this, urinary volumes increased slightly but significantly during this period, without a concomitant increment in solute excretion. Also, the thirst thresholds, although lower in gestation, were always 2–5 mosmol/kg above those for hormone secretion, which is an explanation of why urines are concentrated in the basal state in both pregnant and non-pregnant subjects. Unexpected, however, was a marked decrement in the slope of the regression of $P_{\text{AVP}}/P_{\text{osmol}}$, but not thirst/ $P_{\text{osmol}}$, in late pregnancy (see below).

An ancillary experiment performed during the serial investigation concerned the integrity of oropharyngeal–neuroendocrine reflexes in pregnancy. Water ingestion will decrease AVP release via a potent CNS-mediated reflex mechanism even when increased body tonicity is sustained by ingesting or infusing hypertonic saline (22). We observed this reflex to be sustained during gestation with a potency similar to that observed in the non-pregnant state (23). Nausea, a common symptom of early pregnancy, is a potent non-osmotic stimulus of AVP secretion, known to override the suppressive influence of hypotonicity in non-pregnant subjects (24). In this respect, DeVane (17) has reported that $P_{\text{AVP}}$ is not stimulated by nausea in pregnant women, further claiming that hormone levels are
decreased before midtrimester, a phenomenon that protects grávidas from undesirable stimulation of the uterus. Our studies failed to confirm these observations because, as noted, basal $P_{\text{AVP}}$ is unaltered in gestation and, in addition, first-trimester nausea was associated with exaggerated hormone release, a stimulus that was capable of overriding the AVP-suppressive oropharyngeal reflex evoked by drinking (23).

The studies of osmoregulation in both rodents and pregnant women, reviewed above, appear conclusive and permit the following formulation: the osmotic thresholds for both thirst and AVP secretion each decrease ~10 mosmol/kg during the very first weeks of human gestation. Lowering of the thirst threshold stimulates water intake and dilution body fluids. However, AVP is not suppressed at the usual level of tonicity; the hormone still circulates and the ingested water is retained. Plasma osmolality declines to a level slightly below the new osmotic thirst threshold (the latter situated a few mosmol/kg above that for hormone release) where a new steady state, with little change in water turnover, is established.

Non-osmotic vasopressin release in pregnancy

The influence of nausea and the oropharyngeal reflex on non-osmotic AVP release in pregnancy were discussed above. Here, we review ongoing controversy regarding the roles of volume and blood pressure, two potent non-osmotic modulators of vasopressin secretion. Pregnancy is accompanied by a substantial increase in blood volume (25, 26) and this alteration, theoretically, should suppress AVP release (11). However, Schrier et al. (27–29) have hypothesized that, owing to the marked vasodilation that also accompanies gestation, expansion of the intravascular space is suboptimal and “effective” volume actually is decreased. According to their view, hormonal changes in pregnant women are similar to those in patients with two serious disorders: cirrhosis and congestive heart failure. In the latter diseases absolute extracellular volume is expanded, and AVP circulates despite hypotonicity and hyponatremia. It is postulated that decrements in “effective” volume create and maintain the hypotonic state through non-osmotic AVP release and stimulate the renin–aldosterone–catechol systems, resulting in high circulating levels of angiotensin II, aldosterone and norepinephrine. In support of the first suggestion is that their urine is relatively concentrated and $P_{\text{AVP}}$ measurable in the face of substantial hyponatremia and hypotonicity; furthermore, patients with cirrhosis and heart failure excrete water loads poorly (28). Reports describing serial hemodynamic and hormonal alterations in pregnant baboons (30), activation of the renin–aldosterone system starting early in human gestation (31) and increased vascular sensitivity of grávidas to angiotensin conversion enzyme inhibition (32) support the concept of decreased “effective” volume in human pregnancy. In fact, some insinuate that non-osmotic factors are the primary cause of the lower $P_{\text{Na}}$ and $P_{\text{osmol}}$ during human gestation (28, 29).

We addressed the role of volume in a rodent model and in human studies (33–35), first by hypothesizing that if “effective” volume was indeed decreased in gestation, pregnant rats should secrete AVP in an exaggerated manner when subjected to further volume deficits (33). For example, in non-pregnant animals $P_{\text{AVP}}$ does not increase until volume deficits reach ~7%, but then additional decrements are associated with exponential rises in hormone levels (11, 36). If an animal’s volume is suboptimal, one should detect a rise in hormone level with smaller percentage deficits and perhaps a greater secretory response to further depletion. This was not the case because, despite a substantial increase in blood volume at 14 days that nearly doubled near term (day 21), the threshold in pregnant rats was still a decrement of ~7% and the exponential rise thereafter was virtually identical to the virgin controls (33). Thus, AVP levels increased in the pregnant animals when intravascular volumes, though below values normal for pregnancy, were still considerably greater than in non-pregnant rats. Similar results

### Table 1. Osmotic thresholds for vasopressin release and thirst in study depicted in Fig. 3.

<table>
<thead>
<tr>
<th>Period</th>
<th>$P_{\text{osmol}}$ (mosmol/kg)</th>
<th>Slope</th>
<th>$r$</th>
<th>$P_{\text{osmol}}$ (mosmol/kg)</th>
<th>Slope</th>
<th>$r$</th>
<th>24-h Volume (litres)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preconception</td>
<td>$285^b$</td>
<td>0.61</td>
<td>0.87</td>
<td>$290^b$</td>
<td>0.52</td>
<td>0.97</td>
<td>1.5 ± 0.4</td>
</tr>
<tr>
<td>5–8 weeks</td>
<td>278</td>
<td>0.59</td>
<td>0.89</td>
<td>280</td>
<td>0.49</td>
<td>0.97</td>
<td>1.9 ± 0.2d</td>
</tr>
<tr>
<td>10–12 weeks</td>
<td>276</td>
<td>0.53</td>
<td>0.93</td>
<td>280</td>
<td>0.45</td>
<td>0.97</td>
<td>1.5 ± 0.4</td>
</tr>
<tr>
<td>27–33 weeks</td>
<td>276</td>
<td>0.23c</td>
<td>0.89</td>
<td>279</td>
<td>0.47</td>
<td>0.97</td>
<td>1.6 ± 0.6</td>
</tr>
<tr>
<td>Postpartum</td>
<td>$286^b$</td>
<td>0.60</td>
<td>0.90</td>
<td>290</td>
<td>0.45</td>
<td>0.97</td>
<td>1.5 ± 0.4</td>
</tr>
</tbody>
</table>

*Values are means ± SD. Osmotic thresholds are the abscissal intercept of the mean regression line. The $r$ value for vasopressin is the mean $r$ (correlation coefficients of individual infusions ranged from 0.79 to 0.99). From Ref. 20 with permission.

$^b$p < 0.001: non-pregnant versus pregnant.

$^c$p < 0.001, 27–33 weeks versus others.

$^d$p < 0.05. 5–8 weeks versus others.
have been reported recently by Koehler et al. (37), who noted further that the threshold (% depletion to evoke non-osmotic secretion) actually rose during lactation. The results of both studies suggest that the volume-sensing AVP secretory mechanism(s) is reset during pregnancy so that the increased intravascular volume is recognized as normal.

Our postulate that pregnancy is not a state of decreased “effective” volume and that the pregnant women act as if she is normovolemic in response to AVP secretion, the hypotonicity being due to resetting of osmotic thirst and to AVP secretory thresholds, was pursued further. Pregnant rats were “expanded” from their first day of sperm positivity, some by daily injections of desoxycorticosterone acetate (DOCA) and others by ingesting high-sodium diets (34). Significant decrements in plasma renin activity and aldosterone occurred, indicating expansion of their “effective” volumes. Still, \( P_{\text{osmol}} \) and \( P_{\text{Na}} \) decreased below the values of similarly treated controls. Further evidence against a suboptimally filled intravascular volume, albeit indirect, is found in studies where blood pressure maintenance is stressed by hemorrhage or blockade of the vasopressin, renin–angiotensin and sympathetic nervous systems (25, 38, 39).

There is a paucity of data concerning the influence of volume on AVP release in human gestation, but they too support the notion that a decreased “effective” intravascular space is no responsible for decrements in the osmotic thresholds. Davison et al. (35), studied effects of acute central volume expansion induced by immersion on osmoregulation during gestation, hypothesizing that if underfilling of the intravascular space was responsible for the decreased thresholds, “refilling” it would move the thresholds back toward normal. Figure 4 summarizes relationships between \( P_{\text{AVP}} \) and \( P_{\text{osmol}} \) during hypertonic saline infusion tests performed on seven volunteers studied serially in the initial and last trimesters and 10–12 weeks postpartum. Each woman was tested twice during each period, once while undergoing head-out water immersion. The regression lines in the figure demonstrate that acute central volume expansion had no effect on the osmotic thresholds for hormone release at any period, but did decrease the sensitivity of the system (the slope). The latter change actually was greatest in the third trimester, which in fact would support an “overfilled” intravascular compartment.

To ascertain the role of decreased blood pressure in rodent gestation, gravid rats were treated chronically with DOCA and norepinephrine to ensure expansion and maintain blood pressure slightly but significantly above similarly treated controls (34). The pregnant animals became hypotonic, their \( P_{\text{osmol}} \) values decreasing significantly below those of the virgin animals. Again, we have observations suggesting that factors other than hemodynamic stimuli mediate the changes in AVP release and \( P_{\text{osmol}} \) in pregnancy.

**Metabolic clearances of AVP and DDAVP during pregnancy**

The hypothesis that MCRs of AVP might be increased in human gestation was based on several observations. In 1984 we described the clinical course of three women who developed diabetes insipidus in late gestation or the immediate puerperium, a period when circulating vasopressinase is at or near its highest level, the disease remitting rapidly postpartum (40). Second, in the serial study describing the time course of the threshold changes, the slope of the regression line relating \( P_{\text{AVP}} \) to \( P_{\text{osmol}} \) was decreased markedly in the third trimester (high enzyme levels) compared to early gestation (vasopressinase barely detectable) or to the non-pregnant state. This change in slope might represent a reduction in the secretory response to osmotic stimuli (i.e. a blunting of the “sensitivity” of the system owing, for example, to the volume expansion that occurs during pregnancy), but against this interpretation was the fact that the sensitivity of the thirst response to osmotic stimuli had not been altered, the slope remaining similar to those described in the first trimester, as well as before and after gestation (Table 1). In addition, the relationship of \( P_{\text{AVP}} \) to \( P_{\text{osmol}} \) remains unchanged throughout pregnancy in the rat (a species that does not produce circulating vasopressinase), despite marked increases in volume during late gestation, the slope remaining similar to that in virgin animals (41). Such observations led us to explore the MCR of AVP in human pregnancy.

Davison et al. (10) measured the MCR of AVP by a constant infusion method in five women, starting prior to conception and ending 12 weeks postpartum. The
rate of hormone delivery was adjusted in a manner that achieved three different steady-state plasma concentrations of vasopressin during each test, and ensured that the AVP levels would be comparable at every stage of the study. Figure 5 demonstrates that the MCR, similar in early pregnancy to that recorded before and after the pregnancy, rose strikingly between gestational weeks 8 and 22, values after mid-gestation averaging three- to four-fold those recorded prior to conception, early in gestation, and three months postpartum. Hormone disposal was not influenced by alterations of $P_{AVP}$ within the physiological range, and because basal $P_{AVP}$ was similar at every stage of the study, we concluded that production rates also must be increased by midgestation.

Why does the MCR rise so high in human pregnancy? Increments in blood flow to kidney, liver and the developing placenta, all important sites of AVP inactivation, cannot account for an increase of such magnitude. Trophoblast mass increases 1000-fold between gestational weeks 6 an 24, a time when circulating vasopressinase rises from barely detectable to extremely high levels, leading us to speculate that the aminopeptidase enzyme may be responsible for these changes in MCR. Thus, experiments were designed to compare the MCRs of AVP with that of the vasopressinase-resistant analogue dDAVP during late pregnancy and postpartum (21). Six normotensive women were studied serially, disposal rates for both AVP and dDAVP measured by infusion techniques at four different time periods in relation to pregnancy. The initial tests were in the third trimester when placental mass and vasopressinase levels are at or near maximal values. Subjects were retested 24–48 h postpartum when the placenta is present no longer but the aminopeptidase enzyme, because of its long half-life, is circulating still at a very high level. Studies were repeated 5–6 weeks postpartum, when enzyme levels are rapidly approaching the undetectable range, and again 6 weeks later, the period designated to represent the non-pregnant state. Results (Fig. 6) revealed that pregnancy does not appear to alter the MCR of dDAVP at a time when there is a striking increment in the AVP disposal rate. Of interest is the fact that the MCR of AVP was still quite elevated 24–48 h postpartum, as were the vasopressinase levels, the hormone disposal rate decreasing to non-pregnant levels as the aminopeptidase enzyme disappeared from the blood. Such data suggest that most of the fourfold rise in AVP disposal during pregnancy is due to in vivo degradation by circulating vasopressinase, the placenta accounting for, at most, 30% of the rise.

Relevance of altered osmoregulation and AVP metabolism to human pregnancy

The osmoregulatory changes observed in rats and humans do not occur in all species. For example, $P_{osmol}$ does not decrease while hormonal disposal rates remain unaltered in pregnant sheep (which produce no detectable vasopressinase) (42–44). Thus, questions arise as to the clinical relevance of all these changes. One answer may relate to the physiological hypervolemia of normal gestation, because some believe that the increase in intravascular volume optimizes fetal development. Hypoosmolality would facilitate such expansion because the ingestion and retention of less solute is required per liter of extracellular water retained. This is
advantageous especially when sodium is scarce. More striking, however, are the clinical implications resulting from the fourfold rise in the MCR. This increase is relevant especially in the management of patients with AVP-deficient states and may be responsible for one form of a syndrome termed transient diabetes insipidus of pregnancy.

**Diabetes insipidus in pregnancy**

The various diseases responsible for diabetes insipidus (DI) in pregnancy are reviewed elsewhere (45–47). Patients now are treated rarely with synthetic forms of AVP. If they are, the gestational rise in the hormone disposal rate obviously will increase replacement requirements, but currently virtually all women with known central DI are managed with dDAVP, the MCR of which is unaltered by pregnancy. Still, there are anecdotal claims that dDAVP requirements have had to be increased by midterm, but these are probably instances where the symptoms associated with the decrease in the threshold for thirst have been misinterpreted as dDAVP “escape”, and in the few cases investigated appropriately the preconception replacement dose has proved sufficient during pregnancy (47).

**Transient DI of pregnancy**

As alluded to previously, there is a polyuric polydipsic disorder that presents during the second half of gestation and remits postpartum. This syndrome, noted periodically in the early literature, was characterized further by Barron et al. (40), who described three women whose polyuria was resistant to pharmacological doses of synthetic AVP in the immediate puerperium but whose disease remitted soon after including their ability to concentrate with overnight dehydration as well as with pitressin. Circulating AVP was sought for and measurable in one woman, and the disease was labelled transient “vasopressin-resistant” DI of pregnancy and not nephrogenic DI, because the authors were aware that the AVP detected might have represented immunoassayable fragments, i.e. something was destroying the hormone. This led to the prediction of, search for and study of women in whom transient DI might reflect massive in vivo AVP destruction owing to extremely elevated levels or exaggerated effects of vasopressinase (it was also one reason why we first focused on hormonal MCRs in normal gravidas in search of an explanation for the altered slope of the regression of $P_{AVP}$ on $U_{osm}$ in the third trimester). Figure 7 summarizes the signal study by Dürr et al. (9) in which a patient who became hypernatremic with massive polyuria failed to concentrate her urine despite pharmacological doses of AVP, but her $U_{osmol}$ rose above 800 mosmol/kg when dDAVP was administered. These authors also used two methods to demonstrate that $P_{AVP}$ after the last and highest incremental dose of AVP (which, surprisingly, in relation to the magnitude of the dose, only measured 240 pg/ml) was not intact hormone but represented inactive fragments, now of sufficient magnitude to interfere with an extremely specific radioimmunoassay (in essence, most of the final incremental dose of AVP, 25 μg, had been inactivated in less than 30 min). They also demonstrated abnormally high levels of circulating vasopressinase in the patient (as had Barron et al. in one of their cases) and suggested this to be the cause of the disorder, but an alteration in the enzyme’s kinetics is another possibility. Other examples of this transient
Osmoregulation and vasopressin in pregnancy

Fig. 7. Study during postpartum day 6 in a patient who developed diabetes insipidus late in pregnancy and who remained polyuric in the puerperium. She was unable to concentrate her urine during fluid restriction (NPO), and plasma AVP (P AVP) was undetectable despite a P Na of 153 mEq/l. Her urine remained dilute despite the stepwise administration of a large dose of AVP, but urinary osmolality increased to 800 mosmol/kg after receiving 1-deamino-8-arginyl AVP (dDAVP). Plasma AVP measured after the last dose of AVP was 240 ng/l (when values in the thousands were anticipated), but the authors elegantly demonstrated that the radioimmunoactive material was not bioactive but probably fragments. Finally, plasma vasopressinase 12 days postpartum was tenfold higher than in women at term. From Ref. 9 with permission.

disease have now been cited (reviewed in Refs. 46–48), and, of interest, most of these gravidae also have preeclampsia or display liver and/or coagulation abnormalities, or both.

There is another form of transient DI in pregnancy. Some women have subclinical forms of central DI. The disease presents during gestation, brought to the fore with the increase in the MCR of AVP that normally occurs in pregnancy. Cases described by Baylis (49), Hughes (50) and Iwasaki (51) and their respective colleagues, as well as the transient postpartum polyuria noted in women with Sheehan’s syndrome, may fit this category (52, 53). Finally, there are instances where female carriers of the X-linked disorder nephrogenic diabetes insipidus have developed hormone-resistant polyuria during pregnancy, the reasons for which appear obscure (Drs Bichet and Robertson, personal communications).

The cause(s) of altered osmoregulation during gestation

Finally, we explore the mechanism responsible for the osmoregulatory changes in pregnancy, and here data are meager. During pregnancy there are increases in the levels of several hormones whose action potentially could alter AVP release. We have been unable to identify roles for estrogen, progesterone, prolactin, endogenous opioids or the renin–angiotensin system (12, 41, 47, 54). Data from our laboratory suggest that if a humeral agent is causative it will emanate from the fetal placental unit. This is because pseudopregnancy in the rat, a state mimicking the hormonal milieu of gestation in the absence of a fetus or placenta, is not accompanied by decrements of P osmol (41). In this respect, observations by Davison (20, 35) and Weisiger (55) and their colleagues are of interest.

Davison et al. (20, 35) demonstrated that human chorionic gonadotropin (hCG) administered during the luteal phase of the menstrual cycle decreased the osmotic thresholds for thirst and vasopressin release to those of pregnant women. They also described a patient with hydatiform disease who manifested decreased thresholds, hypoosmolality and hyponatremia, P Na, P osmol and the AVP and thirst thresholds only normalizing when serum hCG became undetectable 3 months after removal of the mole (20).

Weisiger et al. (55) administered synthetic human relaxin (an ovarian hormone) to rats and observed decreases in the osmotic threshold for AVP release but not in the slope describing P AVP/P osmol. More recently they noted that serum relaxin levels are increased during gestation, presumably due to stimulation of the ovaries by hCG (56, 57), the peak occurring by gestational week 5. In this respect Davison et al. (20) were unable to reproduce their findings when hCG was administered to male volunteers. Thus, as in 1994, observations relating to both hCG (20, 35) and relaxin (55, 58, 59) remain intriguing but require further study.

References
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