

Obstetric Nephrology: Renal Hemodynamic and Metabolic Physiology in Normal Pregnancy

Ayodele Odutayo and Michelle Hladunewich

Summary

Glomerular hyperfiltration, altered tubular function, and shifts in electrolyte-fluid balance are among the hallmark renal physiologic changes that characterize a healthy pregnancy. These adjustments are not only critical to maternal and fetal well being, but also provide the clinical context for identifying gestational aberrations in renal function and electrolyte composition. Systemic vasodilation characterizes early gestation and produces increments in renal plasma flow and GFR, the latter of which is maintained into the postpartum period. In addition, renal tubular changes allow for the accumulation of nutrients and electrolytes necessary for fetal growth such that wasting of proteins, glucose, and amino acids in urine is limited in pregnancy and total body stores of electrolytes increase throughout gestation. Substantial insight into the mechanisms underlying these complex adjustments can be gleaned from the available animal and human literature, but our understanding in many areas remains incomplete. This article reviews the available literature on renal adaptation to normal pregnancy, including renal function, tubular function, and electrolyte-fluid balance, along with the clinical ramifications of these adjustments, the limitations of the existing literature, and suggestions for future studies.

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Introduction

Maternal accommodation to normal pregnancy begins shortly after conception with significant hemodynamic and urinary tract alterations noted as early as 6 weeks gestation. Maternal systemic vascular resistance falls significantly, leading to a decrease in mean arterial pressure that reaches a nadir between 18 and 24 weeks gestation (1,2). The resulting decreased afterload contributes to the increase in cardiac output characteristic of healthy human pregnancy. In parallel, increments in renal hemodynamic function are notable, and renal vascular and tubular responsiveness to circulating hormones is altered (2). In addition, dilation of the urinary collecting system—calices, renal pelvis, and ureters—can be appreciated with ultrasonography (3,4). These adjustments are not only critical to fetal and maternal well being, but also provide the clinical context for detecting gestational aberrations in renal function and electrolyte balance. Nevertheless, our understanding of the physiologic changes that accompany healthy human pregnancy is far from complete and further research into these physiologic processes is necessary to facilitate the management of complicated pregnancies.

This article reviews the literature on renal accommodation to normal pregnancy, including renal function, tubular function, and electrolyte-fluid balance (Figure 1). The clinical ramifications of these changes will be discussed along with limitations of the existing literature and suggestions for future studies.

Renal Function

Glomerular hyperfiltration is the most notable physiologic adaptation to normal pregnancy, which

clinically presents as a decrease in the serum creatinine. Both elegant micropuncture studies in animal models and careful human physiologic assessments have provided insights into the key factors that contribute to the increments in GFR. GFR is represented by the following equation:

$$GFR = K_f \times (\Delta P - \pi_{GC})$$

where ΔP is the transcapillary hydraulic pressure difference or the pressure generated across the glomerulus; π_{GC} is the mean glomerular intracapillary oncotic pressure, the force that opposes the formation of glomerular filtration; and K_f is the product of the surface area available for filtration and the hydraulic permeability, which is the permeability to ultrafiltrate across the three layers of the glomerulus (5).

Through elegant micropuncture studies in pregnant rodent models, Baylis examined each of the aforementioned determinants of GFR. In the 12-day pregnant rat, the investigators demonstrated a 34% increase in single glomerular plasma flow and a comparable 30% increase in the single nephron GFR, changes that were proportional to whole kidney GFR and renal plasma flow (RPF) measurements (6). In addition, the investigators noted that elevations in single nephron GFR were achieved without significant contributions from the other determinants of GFR. In particular, ΔP remained unchanged throughout pregnancy due to proportional dilation of the afferent and efferent arterioles, suggesting that the glomerular hyperfiltration that characterizes normal pregnancy in rats is solely

Divisions of Nephrology and Obstetric Medicine, Department of Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada

Correspondence:

Dr. Michelle Hladunewich, Divisions of Nephrology, Critical Care, and Obstetric Medicine, Department of Medicine, Sunnybrook Health Sciences Center, A139, 2075 Bayview Avenue, Toronto, ON M4N 3M5, Canada. Email: michelle.hladunewich@sunnybrook.ca

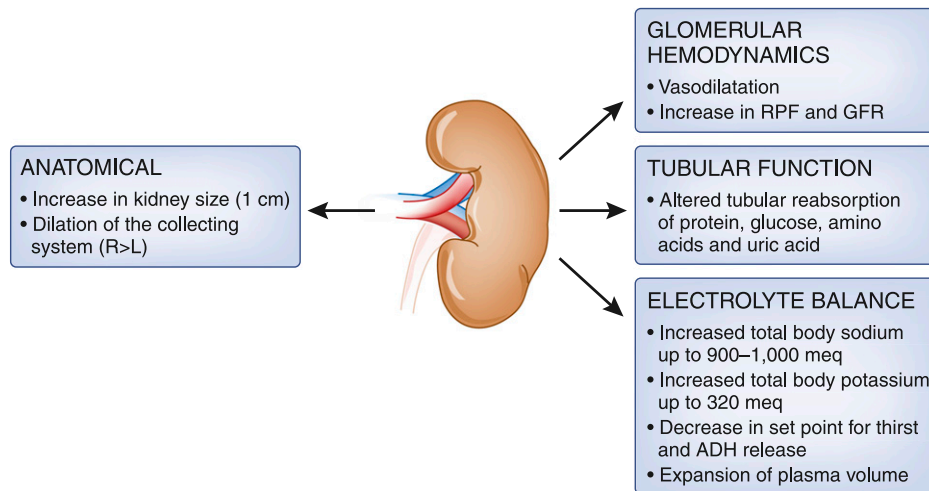


Figure 1. | Summary of renal hemodynamic and metabolic adaptations to normal human pregnancy. RPF, renal plasma flow; ADH, anti-diuretic hormone.

attributable to increased RPF secondary, at least in part, to plasma volume expansion (7). Of interest, the adjustments in GFR and RPF were preserved even after a five-sixth reduction in nephron mass (8). In an animal model of anti-glomerular basement membrane antibody-induced GN with resultant intraglomerular hypertension, a similar vasodilation was noted during pregnancy without any increase in intraglomerular pressure (ΔP) (9). Therefore, the physiologic adjustments that characterize normal pregnancy in rats may result in renoprotection during gestation and prevent progressive renal damage.

Relaxin and nitric oxide (NO) have been implicated as key factors in mediating the renal vasodilation and glomerular hyperfiltration that is characteristic of normal pregnancy in both animals and humans. *In vivo*, relaxin administration to male and nonpregnant female rats produced physiologic changes that mimicked normal pregnancy, with decrements in systemic vascular resistance along with significant increases in effective RPF and, hence, GFR (10–12). A corresponding study involving elimination of relaxin, via administration of relaxin-specific monoclonal antibodies or ovariectomy, prevented the characteristic renal hemodynamic changes in midterm pregnant rats (13). The proposed mechanism of relaxin involves an increase in vascular gelatinase activity, which upregulates NO-dependent vasodilation via the endothelin-B NO pathway (14). In pregnant rats, investigators have convincingly demonstrated increments in endogenous production of NO (15), and through acute or chronic inhibition of NO synthase, investigators have demonstrated abolishment of the glomerular hyperfiltration in pregnancy (16,17). Hence, NO is necessary for the hemodynamic adaptation in renal function during pregnancy, and relaxin may represent a pregnancy-specific mechanism for augmenting the effects of NO.

Both relaxin and NO may also factor in the development of glomerular hyperfiltration in human pregnancy, but the existing data are less conclusive. In a study involving healthy male and female volunteers, short-term administration of

recombinant relaxin produced increments in RPF, irrespective of sex, but no changes were noted in GFR, possibly due to the duration of relaxin exposure in study participants (18). In another study that looked at relaxin levels in the third trimester and early postpartum period, no correlation was found with any of the measures of renal hemodynamics, but this study cannot exclude a role for relaxin in early gestational renal hemodynamic adaptation (19). With respect to NO, serum levels of NO and urine metabolites have been documented to be elevated in healthy human pregnancy compared with the nonpregnant state; some studies have shown that they increase progressively throughout pregnancy, returning to baseline by 9–12 weeks postpartum (20,21). However, these findings have not been consistent (22), likely due to varied methodologies for controlling dietary intake. Nonetheless, in a study involving nonpregnant, early pregnant, and late-pregnant women, NO was inhibited with N(G)-monomethyl-L-arginine and significantly decreased hand blood flow was noted in both pregnant groups compared with nonpregnant controls (23). Similarly, the NO synthase Glu298Asp polymorphism has been associated with differences in endothelium-dependent dilation at 12 weeks gestation (24) and the concentration of L-homoarginine, another substrate for NO, has been shown to be positively correlated with flow-mediated vasodilation ($r=0.362$; $P=0.006$) (25).

Despite the robust literature in animal models and the possibility of similar hormonal alterations being responsible for the vasodilatory renal hemodynamic modifications in animals and humans, the notion that GFR is entirely RPF dependent is not necessarily true in humans. In contrast to the animal models (26), pregnancy in women with kidney disease can result in deterioration of renal function. Furthermore, the determinants of GFR cannot be directly examined in humans. Thus, our current knowledge of GFR and RPF in normal pregnancy is derived from a handful of serial studies with small sample sizes in which varying methodologies could produce remarkable differences in the estimates of renal hemodynamics.

There is variation among studies in the positioning of patients: semi-supine, recumbent, sitting, and left lateral decubitus (2,27–29). Some investigators have reported that the interplay of the supine position and the size of the gravid uterus may lead to compression of the inferior vena cava, resulting in decrements in cardiac output, RPF, and GFR (30). However, other investigators have failed to demonstrate any effect of patient position on renal hemodynamics in late pregnancy (28,31). Serial studies have also differed in the process for ensuring complete bladder emptying during urinary inulin and p-aminohippurate clearances. Whereas some investigators used bladder catheterization (28), others instructed patients to spontaneously void (2,29). Given the potential for urodynamic changes due to the gravid uterus, the risk of urinary retention, inadequate emptying, and incomplete urine collections is elevated in pregnancy and this can lead to errors in clearance methodology. Lastly, correction for body surface area (BSA) is inconsistently performed across studies, with some investigators using the BSA corresponding to the participant's stage of pregnancy as opposed to prepregnancy BSA (28). Through the former approach, renal function may be underestimated because the increments in BSA that characterize pregnancy do not necessarily represent a true increase in muscle or renal functional mass.

Nonetheless, in three independent studies, De Alvarez, Dunlop, and Bucht measured GFR and RPF in 22, 25, and 32 healthy pregnant women, respectively (29,32,33). The authors demonstrated that increments in RPF surpass that of GFR early in pregnancy (60%–80% versus 40%–60%) until RPF falls rapidly in the third trimester. As such, decrements in filtration fraction (FF) are noted until the third trimester, at which point FF increases. In contrast, two equally elegant studies by Sims *et al.* and Chapman *et al.* involving 13 women suggest that the decrement in FF (RPF>GFR) is limited to the first 12 weeks in pregnancy after which FF progressively increases (GFR>RPF) until it peaks at term (2,28).

To obtain an overall assessment of renal hemodynamics in normal human pregnancy, we synthesized the findings from these studies and included articles that focused on the postpartum period (Figure 2, Table 1, and Supplemental

Material). In addition, we specifically focused on the change in GFR and RPF from prepregnancy values or compared with nongravid patients undergoing the same protocol. The synthesis demonstrates increments in both RPF and GFR above nongravid levels, with the former slightly surpassing the latter (41% and 37%, respectively). However, GFR remains elevated until postpartum week 1 before returning to prepregnancy levels, whereas RPF gradually falls throughout pregnancy. Accordingly, FF decreases slightly (–1.89%) in early pregnancy, but consistently increases between gestational weeks 21 and 40, ultimately to 29% above nongravid levels by 31–40 weeks of gestation. At 2 weeks postpartum, FF remains elevated (32%) above its prepregnancy level. All values normalize between weeks 6 and 8 postpartum. It is noteworthy that the trajectory of GFR, RPF, and FF presented in this review differs from earlier reports by Davison and Dunlop, which noted a more sustained Δ RPF than Δ GFR (34). We attribute this discordance to the studies included in each of the syntheses, as our current review includes four original articles that were not included in the early literature (2,27,33,35).

In the first and second trimesters, it has been suggested that the rise in GFR is solely a product of increments in RPF (36). However, given the second trimester decrease in RPF, other changes must account for the maintenance of GFR by this stage of pregnancy. Without the ability to directly measure the determinants of GFR, one can only speculate that modest increments in either Δ P or K_f are required, because decrements in oncotic pressure have been excluded as the principal mechanism. One study demonstrated that π_A and π_{GC} decreased by only 1.1 and 1.5 mmHg, respectively, in the second trimester, a change insufficient to maintain the GFR elevation (27).

In the third trimester, the contributions of other determinants of GFR have been better elucidated. Using mathematical modeling of neutral dextran sieving coefficients to assess determinants of GFR, investigators concluded that elevated GFR at 36 weeks gestation was primarily due to a combination of increased RPF, decreased π_A (–4.6 mmHg), and increased K_f (36). These findings were further confirmed in a later study after augmentation of the GFR and RPF with an amino acid infusion (37). There are also

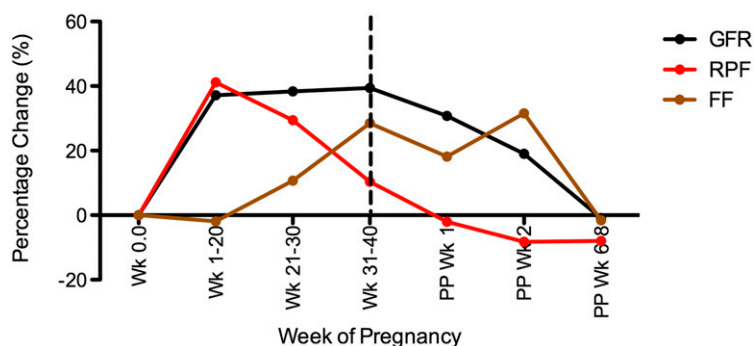


Figure 2. | Percentage increment in GFR, RPF, and FF as measured by inulin or iothalamate and p-aminohippurate clearance methodology, respectively, at different time points during gestation. The FF was calculated from individual patient data for GFR and RPF where available (2,27–29,32,33,35). Where data were provided only in graphical form (2,32), WebPlotDigitizer software (Mishawaka, IN; <http://arohatgi.info/WebPlotDigitizer/>) was used to extract raw data. RPF, renal plasma flow; FF, filtration fraction.

Table 1. Percentage increment in GFR, renal plasma flow, and filtration fraction as measured by inulin or iothalamate and p-aminohippurate clearance methodology, respectively, at different time points during gestation

Gestational Age (wk)	GFR (%)	Renal Plasma Flow (%)	Filtration Fraction (%)
1–20	37.13	41.18	–1.89
21–30	38.38	29.44	10.68
31–40	39.46	10.37	29.26
Postpartum wk 1	30.76	–2.05	18.15
Postpartum wk 2	19.05	–8.21	31.58
Postpartum wk 6–8	–0.91	–7.94	–1.59

very limited uncontrolled data from autopsy cases (38) and, more recently, controversial data from 12 third-trimester biopsies (39) to suggest that glomerular diameter may be greater than that measured in nonpregnant participants. Lastly, in the postpartum period, we utilized physiologic techniques to measure GFR, RPF, and oncotic pressure and computed a value for the two-kidney K_f in 22 women 2 weeks after delivery and demonstrated that RPF returned to baseline values and oncotic pressure increased above control values. As such, the maintenance of an elevated GFR at 20% above control values required either an isolated 16% increment in ΔP , a 50% increment in K_f , or some lesser contribution of each (35).

Taken together, gestational hyperfiltration in human pregnancy is not entirely dependent on increments in RPF and changes in ΔP cannot be excluded as a potential contributor. Whether this predisposes some women to intraglomerular hypertension, which may factor into the clinical deterioration noted as pregnancy progresses in many women with underlying kidney disease, is unknown. Further carefully designed physiologic investigations assessing glomerular hemodynamics in both normal pregnancy and in women with underlying renal disease are necessary to facilitate our understanding of the hemodynamics of normal pregnancy and the pathogenesis of renal disease in pregnancy.

Tubular Function

Most obstetric guidelines define significant protein excretion as ≥ 300 mg in a 24-hour period (40), double the upper limit of normal in healthy adults. However, this upper limit in normal pregnancy is based on relatively small studies in which urine protein or albumin excretion was measured serially throughout pregnancy. In one of the largest studies to date, Higby *et al.* studied 270 patients to determine the 24-hour excretion values of urinary total protein and albumin in normal pregnancy (41). The authors reported a mean 24-hour protein excretion of 116.9 mg (upper 95% confidence interval, 259.4 mg) and a corresponding 24-hour albumin excretion of 11.8 mg (upper 95% confidence interval, 28.7 mg) with no participants exhibiting microalbuminuria (>30 mg/L). Similarly in a serial study of protein/creatinine ratios in healthy singleton and twin pregnancies, protein excretion increased gradually throughout pregnancy and was noted to be more

pronounced in the twin pregnancies, albeit not impressively, with an increase of 150 mg/g in singleton pregnancies and 220 mg/g in twin pregnancies at 34–38 weeks gestation (42).

Other studies measuring only the urine albumin/creatinine ratio (ACR) have also not provided evidence for a significant “glomerular leak” in healthy pregnancies that perhaps could be attributed to hyperfiltration. In a sizable study examining 193 consecutive healthy pregnancies, there was an incremental rise in the ACR with length of gestation, but only 6 women were noted to have an ACR >15 mg/g (43). Urinary protein excretion is further increased during labor, but the ACR during this time point still remained within the normoalbuminuria range (44). Furthermore, another study did demonstrate that the protein/creatinine ratio exceeded the ACR more than might be expected (45). Thus, excretion of an alternate proteinaceous material may be responsible for the small augmentation in total proteinuria noted during healthy pregnancy and the method of choice for measurement of proteinuria may factor into this sometimes confusing clinical literature (46). As such, significant proteinuria or albuminuria should not simply be attributed to the hyperfiltration that accompanies the gravid state.

Recent studies critical to the understanding of the pathogenesis of pre-eclampsia have described the release of soluble antiangiogenic factors from an ischemic placenta that are injurious to the vascular endothelium, and this intricate balance of angiogenic and antiangiogenic factors may provide further insights with respect to protein excretion even in healthy pregnancy. Excess soluble fms-like tyrosine kinase 1 binds placental growth factor and vascular endothelial growth factor (VEGF), preventing their interaction with receptors located on the vascular endothelial cells (47). The resultant maternal endothelial dysfunction is best demonstrated at the level of the glomerulus in which GFR depression and proteinuria are a direct result of glomerular endotheliosis (48). In the glomerulus, VEGF is expressed by the podocytes and interacts with its receptors on the endothelium. An elegant animal experiment demonstrated that heterozygous knockout mice for podocyte-specific VEGF develop endotheliosis with GFR depression and proteinuria reminiscent of the human condition (49). Even in healthy pregnancies, these antiangiogenic factors are elevated at the end of pregnancy (50), and endotheliosis, albeit to a lesser extent, was noted in the aforementioned study in which healthy pregnant women were biopsied in the third trimester of pregnancy (39). These novel insights into the complex balance of angiogenic and antiangiogenic factors might explain the slightly higher levels of urine protein toward the end of pregnancy and in labor noted in some of the aforementioned studies. Furthermore, the effect of these factors in women who already have renal disease remains largely unexplored, but may explain the significant worsening of proteinuria noted in some renal diseases, such as diabetic nephropathy and IgA nephropathy, as pregnancy enters the later stages (51–53).

In the nonpregnant state, healthy kidneys efficiently reabsorb glucose ($>90\%$) and glycosuria is a clinical indicator of a filtered load that exceeds the maximal tubular reabsorption capacity. Despite the increased GFR that accompanies pregnancy, studies that utilized a continuous intravenous

glucose challenge with inulin clearance techniques did not document a difference in GFR between women who displayed glycosuria and those who did not, suggesting instead that the maximal tubular reabsorption capacity was significantly decreased in pregnant women who displayed glycosuria (54–56). The precise incidence, however, of glycosuria in pregnancy is unclear, with extensive variability noted between women and even in the same woman at different times during pregnancy (56,57). The largest study to date, a retrospective chart assessment of 17,647 pregnancies with normal carbohydrate screening, noted an incidence of only 1.6% on routine clinical screening (58). Furthermore, no relationship of glycosuria to clinical diabetes has been demonstrated, because the majority of women who demonstrate glycosuria have normal glucose tolerance, and even obviously diabetic pregnant women do not consistently demonstrate glycosuria.

A similarly confusing pattern has emerged for increased urinary excretion of amino acids and water-soluble vitamins (57,59). The few studies designed to determine mechanisms were inconclusive and noted patterns of excretion were not related to the biologic function or chemical structure of the compound (59). However, it is likely that alterations in both GFR and tubular reabsorption would be needed to account for the magnitude of some of the excretion rates noted. Finally, serum uric acid has been documented to be decreased in the first trimester, nadir in the second trimester, and then gradually increase as pregnancy progresses and high renal clearance is thought to be necessary to clear the increased production that accompanies fetal and/or placental growth (60,61). As such, uric acid has been noted to be elevated in pregnancies complicated by pre-eclampsia (62) and is often used to assist with the diagnosis of pre-eclampsia. However, it is not clear if the noted increase in serum uric acid during pregnancies complicated by pre-eclampsia is solely due to decreased renal clearance secondary to glomerular endotheliosis or increased production caused by trophoblast breakdown.

Electrolyte Balance

In contrast to tubular function, our knowledge of the factors that govern gestational changes in serum electrolytes is somewhat more definitive (Table 2). Total body sodium increases on an average by 3–4 mEq/d, ultimately producing a net balance of 900–1000 mEq, and total body potassium also increases by up to 320 mEq by the end of gestation (63).

Underlying this preferential retention of sodium is a complex interplay of natriuretic and antinatriuretic factors,

namely GFR, atrial natriuretic peptide, and progesterone for sodium wasting as well as aldosterone and deoxycorticosterone for sodium conservation. The early pregnancy increment in GFR leads to a net increase of 20,000–30,000 mEq/d in sodium filtration. This natriuresis is further augmented by atrial natriuretic peptide, which increases significantly by week 12 of pregnancy (2) and was demonstrated to augment the fractional excretion of sodium when infused in late pregnancy (64). In addition, progesterone attenuates sodium reabsorption by competitively inhibiting aldosterone at the tubular mineralocorticoid receptor (65). Other factors that may promote natriuresis include decrements in serum albumin concentration and increments in prostaglandins and melanocyte stimulating hormone (66).

These changes are counteracted by the antinatriuretic effects of aldosterone and deoxycorticosterone, which begin to rise gradually in early pregnancy and then drastically increase in the third trimester. Aldosterone is particularly responsive to slight changes in volume during pregnancy because volume expansion has been shown to suppress its production (67). In contrast, deoxycorticosterone, which is produced through extra-adrenal hydroxylation of progesterone (68), is not suppressible with a dexamethasone infusion (69). Therefore, aldosterone may play a more important role in sodium homeostasis, whereas deoxycorticosterone may play a more integral role in promoting sodium retention. Finally, considering the remarkable GFR-mediated increment in sodium filtration, glomerulotubular changes are needed to ensure sodium reabsorption in the proximal and distal tubules to avoid excessive renal solute losses (70). Some authors have suggested that this may be mediated by increments in the number of renal Na⁺/K⁺ ATPase (71), but this is controversial (72).

In the context of mineralocorticoid-induced retention of sodium, it is surprising that total body potassium also increases. The basis for potassium retention in pregnancy has been probed by Ehrlich and Lindheimer, who administered mineralocorticoids to 14 women in the third trimester and confirmed that potassium balance was still preserved despite significant sodium retention (73). Furthermore, when the authors administered mineralocorticoids to two male patients, the kaliuresis that ensued could be abolished by an additional infusion of progesterone (73). As such, elevated progesterone levels have been implicated in the dissociation of the antinatriuretic and kaliuretic effects of mineralocorticoids.

It is noteworthy that despite the net increase in body stores of sodium and potassium, serum levels of both electrolytes decrease during pregnancy by 4 and 0.25 mEq/L,

Table 2. Major physiologic changes associated with sodium and potassium balance in healthy human pregnancy

Physiologic Change	Effect During Pregnancy	Change During Pregnancy
GFR	Natriuretic	Increase in early pregnancy and sustained until delivery
Atrial natriuretic peptide	Natriuretic	Increase at 12 wk; still elevated at 36 wk
Progesterone	Natriuretic/antikaliuretic	Increase after luteinizing hormone surge during ovulation; peak at 4 wk before delivery
Aldosterone	Antinatriuretic/kaliuretic	Increased by 6 wk gestation and sustained until delivery
Deoxycorticosterone	Antinatriuretic	Increase in first trimester; peak in third trimester
Na ⁺ /K ⁺ transporters	Antinatriuretic	Increased in pregnancy

respectively (74,75). Currently, the mechanism underlying the decrement in serum sodium is best understood (75,76). In an animal study, plasma arginine vasopressin (AVP) levels were measured at varying levels of blood tonicity and the threshold for AVP secretion was demonstrated to be lower by 11 mOsmol in gravid compared with control rats (77). Corresponding studies involving healthy pregnant women administered hypertonic saline infusions also demonstrated lowering of the osmotic threshold for AVP release and thirst (78,79). These adjustments in osmoregulation therefore result in the preferential retention of water without sodium, which ultimately manifests as a decrement in serum sodium. With respect to potassium, some authors suspect that the decrement may result from hemodilution (76), but this has not been confirmed.

Taken together, pregnancy is characterized by increments in total body electrolyte stores, albeit with decrements in serum levels. Thus, clinicians must recognize that increments in serum electrolytes that still fall within the range of normal may constitute meaningful aberrations in electrolyte balance. Furthermore, conditions prone to either electrolyte retention or loss may be exacerbated during pregnancy. To facilitate identification of abnormalities in serum electrolytes, a recent report by Larsson *et al.* details biochemical reference values for normal pregnancy (80).

Conclusion

The physiologic adaptation that the kidneys undergo to transition through gestation is complex and our knowledge of these physiologic processes remains incomplete. Furthermore, the pregnant population is changing, with more women attempting pregnancy at advanced maternal ages with significant comorbidities and reproductive technologies resulting in frequent multiple gestations. Understanding the basic physiology will provide insights into the pathophysiology of renal disease in pregnancy. Hence, this is an area of research that should not be abandoned.

Disclosures

None.

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