Renal Physiology of Pregnancy

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1 Introduction

The term "physiologic" does not adequately describe the state of a woman during pregnancy. There are several shifts in biochemistry, psychology, and physiology. Every component of kidney physiology is modified by pregnancy. It is a physiological marvel that these alterations can be orchestrated. Significant volume expansion and vasodilation characterize kidney and systemic hemodynamics. Renal plasma flow (RPF) and glomerular filtration rate (GFR) rise by as much as 80% relative to pre-pregnancy values. Healthcare providers, to best serve their pregnant patients, need a thorough understanding of all how pregnancy changes their bodies [1–3].

Changes in glomerular filtration rate, tubular function, electrolyte and acid/base management, and other processes are all driven by the kidneys to ensure the health of both mother and child throughout pregnancy (Table 1).

Increased renal blood flow and glomerular filtration rate occur early in pregnancy due to systemic vasodilation, which is mediated by a change in the quantity of and a reaction to numerous hormones. Alterations in total body storage of electrolytes are brought on by the activation of the renin-angiotensin-aldosterone axis, which occurs in response to vasodilation, and by changes in renal tubular processing [4].

Hemodynamic shifts and fluid and electrolyte balance must be precisely orchestrated to develop and maintain a healthy pregnancy for both mother and child.

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Table 1 Physiologic changes in pregnancy

Increased
• Blood volume
• Cardiac output
• Levels of nitric oxide and relaxin
• Relative resistance to vasoconstrictors
• GFR by 50%
• Urine protein excretion
Decreased
• Systemic vascular resistance
• Systemic blood pressure
• Serum creatinine

Abbreviations: *GFR* Glomerular filtration rate

2 Basic Physiology of the Kidney

Kidney function is based on the nephron, which has three different subunits: Blood vessels, including the afferent arteriole (before the glomerulus) and the efferent arteriole(after the glomerulus), and the tubules (from the proximal tubule to the more distal collecting tubule), are responsible for the selective reabsorption and secretion of several molecules (electrolytes, proteins, and glucose) (after the glomerulus). Some molecules, like glucose and amino acids, are actively exchanged for others via the sodium/potassium pump. In contrast, others, like urea and hydrogen ions, are secreted by other portions of the tubules to maintain homeostasis and ultimately contribute to the generation of urine. In a typical pregnancy, the nephron's filtration, reabsorption, and secretion mechanisms all change [1–5].

3 Hemodynamic Alterations in the Kidneys

Vasodilation and increased volume are two hallmarks of pregnancy, both resulting from a complex interplay between several hormones (Table 2). By the end of the second trimester, the average blood pressure of a pregnant woman has dropped by around 10 mmHg to 105/60 mmHg. Several factors contribute to this, such as shifts in hormone levels and modifications to the renin-angiotensin-aldosterone system (RAAS). Maternal hormones may influence pregnancy-related alterations in maternal hemodynamics. During the mid-luteal phase of menstruation, there is a decrease in vascular resistance and an increase in cardiac output, which leads to a drop in mean arterial pressure compared to the mid-follicular phase [6, 7]. Although progesterone can raise RPF and GFR, it cannot explain the dramatic rise observed during pregnancy. The corpus luteum, decidua, and placenta secrete relaxin, a vasodilating hormone. Increasing vascular gelatinase activity via the endothelium endothelin B receptor-nitric oxide pathway plays a role in mouse kidney physiology during pregnancy. As measured by Ogueh and coworkers, the levels of relaxin

Table 2 Typical laboratory values during pregnancy (Adopted from reference [6])

Variable	Average values in pregnancy
Plasma osmolality	270 mOsm/kg
Serum sodium	135 mEq/L
Serum potassium	3.8 mEq/L
Serum bicarbonate	18–20 mEq/L
Serum creatinine	0.5 mg/dL
Blood urea nitrogen	9.0 mg/dL
Uric acid	2–3 mg/dL

increased steadily during pregnancy and then declined after delivery. At least in late pregnancy and the postpartum period, clinical connections between relaxin levels and hemodynamic measures have not been shown [5–7].

RAAS is upregulated during a healthy pregnancy. The ovaries and the decidua are two extrarenal sources that secrete renin. When a pregnant woman's body generates estrogen, it stimulates the liver to make more angiotensinogen, increasing the production of angiotensin II (ANG II). Despite this, it is well documented that systolic blood pressure often drops during pregnancy. The refractoriness could explain the vasodilated condition during pregnancy to ANG II that develops at this time. The presence of additional chemicals, such as progesterone and vascular endothelial growth factor-mediated prostacyclins, and/or the monomeric form of angiotensin 1 (AT1) receptors might account for this insensitivity [2, 3]. Return of ANG II sensitivity, decreased aldosterone production, heterodimeric AT1 receptors, and the presence of autoantibodies to AT1 all indicate that the RAAS is dysregulated in pregnancy (AT1-AA). At week 8 of a healthy pregnancy, aldosterone levels begin to climb, and by the end of the third trimester, they have increased by a factor of three to six over the upper range of normal (80 to 100 ng/dL). Overall, blood volume increases by 30%–50%, or 1.1–1.6 L, compared to women who are not pregnant [6, 8, 9].

4 Changes in GFR

Renal vascular dilatation results from systemic vasodilation that occurs during pregnancy. This causes a rise in the GFR and the ERPF (RPF). By the third month of pregnancy, the glomerular filtration rate (GFR) has increased by 40–50%, reaching a maximum of 180 mL/min. This plateau lasts until around week 36 of pregnancy. Changes in blood levels of analytes and changes in the clearance of drugs eliminated by the kidneys can result from even a modest increase in GFR. Four weeks into pregnancy, creatinine clearance has increased by 25%, and by 9 weeks, it has increased by 45%. While GFR rises and glomerular membrane charge selectivity shifts, protein and albumin are excreted more significantly in the urine [10–13].

5 Measurement of GFR

Estimating GFR is essential for the management of pregnant patients. In pregnancy, like in nephrology, there is still much room for improvement regarding GFR estimates. Like its known propensity to underestimate when GFR is more than 60 mL/min, the Modification of Diet in Renal Disease (MDRD) equation overestimates GFR in pregnant women with and without preeclampsia. In research comparing both equations to 24-h urine collections in preeclamptic patients, the CKD Epidemiology Collaboration equation was shown to underestimate GFR to a comparable degree as the MDRD equation. Comparing MDRD and cystatin-C-based equations, both produce mean GFR values greater than 120 mL/min. However, cystatin C produced higher first and second-trimester GFRs, followed by a fall in GFR in the third trimester. This contradicts evidence from early studies showing that GFR increases steadily until the term. Postpartum, GFR was shown to decrease using the MDRD equation but increase using the cystatin C equation. Recent prospective research comparing cystatin-C-based GFR estimations with inulin clearances at three time points in 12 pregnant individuals revealed no association. The best method for determining GFR in expectant mothers is still a 24-h urine collection to calculate creatinine clearance. [6, 8–15].

6 Mechanism of Increased GFR

The GFR rises by around 50% from its pre-pregnancy value during pregnancy. It needs to be better understood what processes are responsible for this growth. Keep in mind that GFR is expressed in several different ways and that different parts of it change at different stages of pregnancy.

$$\mathrm{GFR} = \left(\Delta P - \pi_{\mathrm{GC}}\right) \times K_{\mathrm{f}}$$

where (ΔP) is the oncotic pressure at the glomerulus and (π_{GC}) is the net hydraulic pressure in the glomerulus. Although direct measurement of transcapillary hydraulic pressure in humans is impossible, this parameter can be studied in animal models utilizing micropuncture. The π_{GC} value is calculated by averaging the afferent (π_A) and efferent (π_E) oncotic pressures. Oncotic pressure (P) at the entrance to the afferent arteriole (A) is expressed as a fraction 1 minus FF, where FF is the percent of plasma filtered by the glomerulus.

$$\pi_{\mathrm{E}} = \pi_{\mathrm{A}} / \left(1 - \mathrm{FF}\right)$$

The FF value is calculated by dividing the GFR by the RPF.

$$\mathrm{FF} = \mathrm{GFR} / \mathrm{RPF}$$

The capacity to ultrafiltrate through the three layers of the glomerulus is measured by the glomerular ultrafiltration coefficient, Kf, which is the product of the surface area accessible for filtration and the hydraulic permeability (*k*). The permeability estimate is calculated using the data obtained from the autopsy and the computer simulation.

During pregnancy, there is a significant reduction in oncotic pressure due to the increase in plasma volume, which helps to increase GFR [6]. Modifications to the filter surface area and the hydraulic permeability may also cause slight shifts in Kf. WhetherpP rises during human pregnancy is still a matter of debate. Baylis found no difference in hydrostatic or oncotic pressure in his early tests of the 12-day pregnant rat, and he credited the increase in GFR to higher RPF [16]. Pregnant women's glomerular size selectivity appeared to change, and oncotic pressure was lower, although increased P was not [17]. They reasoned that the elevated RPF was the primary cause of the improved GFR. Since RPF constantly decreases approaching the term, this explanation cannot account for the fact that GFR continues to rise later in pregnancy. An evaluation of the dynamics of glomerular filtration in postpartum humans revealed that the persistent increase in GFR after delivery was caused by either an increase in *P* of up to 16%, an increase in Kf of around 50%, or a combination of these two factors [18]. It is impossible to rule out the likelihood that P does vary, according to Odutayo and Hlaudunewich, because both estimated and observed changes in Kf and GC are relatively small [18].

7 Alterations in Tubular Function

Changes in tubular waste and nutrition processing occur during pregnancy. Increases in GFR and reductions in proximal tubular reabsorption contribute to increased uric acid excretion. At around 22–24 weeks of pregnancy, serum uric acid levels drop to their lowest point, between 2.0 and 3.0 mg/dL, and then gradually return to normal levels by term. It is believed that higher clearance is required to deal with the extra output from the placenta and baby during pregnancy.

After being freely filtered at the glomerulus, glucose is reabsorbed almost entirely in the proximal tubule and just a little in the collecting tubule. When glucose is excreted in the urine, it is usually because the amount filtered out is more than what the kidneys can absorb. The reabsorption of glucose is less efficient, and glucose excretion is more variable during pregnancy. Earlier research hypothesized that glucosuria with normoglycemia or physiologic glucosuria resulted when an elevated GFR and the resulting elevated filtered load of glucose exceeded the ability of the proximal tubule to reabsorb glucose. Research involving glucose infusion and simultaneous assessments of glucose excretion and inulin clearance in 29 pregnant women showed that this effect was independent of glucosuria. Those without glucosuria regained their average reabsorption ability 8–12 weeks after giving birth, but those who had had glucosuria to varied degrees during pregnancy retained a residual impairment in reabsorption capacity. Pregnancy may also reduce

reabsorption efficiency at the distal end of the nephron. The fractional reabsorption of amino acids and b-microglobulin is diminished, leading to higher excretion, similar to what happens with uric acid and glucose [5–20].

Total urine protein and albumin excretion rise throughout a healthy pregnancy, peaking around week 20. Most of the protein in urine is of the Tamm-Horsfall type, with some albumin and other circulating proteins present in trace amounts. Although the time of the increase in proteinuria during pregnancy falls outside the window of the peak increase in GFR, this is generally explained as a result of the increase in GFR. In late pregnancy, there is an increase in albuminuria, although not at abnormally high levels [20]. Increases in circulating soluble antiangiogenic factors, which are present in abnormally high amounts in preeclampsia and disturb the slit diaphragm, are also observed late in normal pregnancy and may account for late-term increases in proteinuria [21]. Third-trimester selective changes in glomerular charge or the presence of additional protein substances are another possible explanation [21, 22].

Protein levels in urine, more significant than 300 mg every 24 h, are considered abnormal in pregnant women [23]. This estimate was based on a limited sample size, and subsequent research has demonstrated that average protein excretion is far lower than 200 mg/24 h [24, 25]. The 24-h urine collection remains the gold standard for quantifying proteinuria in pregnant patients, despite the widespread adoption of urine protein/creatinine for quantification of proteinuria in nonpregnant patients and its usefulness as a screening tool for the presence or absence of proteinuria. Since pregnant women's dilated urinary tracts may hold more pee than usual, a high proportion of scheduled urine samples are lost due to timing and retention issues [25].

Control of fluid and electrolyte balance by the kidneys.

During pregnancy, the body has a decreased threshold for triggering osmoreceptors associated with antidiuretic hormone (ADH) and thirst. Serum sodium levels typically drop by around 5 mEq/L, and plasma osmolality approaches 270 mOsm/kg. The hormone b-human chorionic gonadotropin may have a role in this shift, as it is elevated during the luteal phase of the menstrual cycle [26]. Vasodilation, arterial underfilling, and ADH release have all been linked to decreased serum sodium. Relaxin levels are elevated in pregnant women, and in animals, relaxin has been found to promote ADH secretion and water consumption [27]. An increase in aldosterone and its antinatriuretic effects coincides with mild hyponatremia.

Additionally, deoxycorticosterone increases the activity of sodium pumps across several membranes, which aids in salt retention. The natriuretic effects of elevated GFR, atrial natriuretic peptide, and progesterone levels counteract these effects. However, the net balance between these effects is the preferred retention of water over salt and decreased osmolality, even though the total sodium increase during pregnancy is predicted to be 900–1000 mEq. By the time pregnancy is through, the body's total supply of potassium has increased by around 320 mEq. This happens because progesterone has anti-kaliuretic actions, which counteract the effects of aldosterone's salt retention. During pregnancy, the amount of potassium excreted remains constant, whereas the amount reabsorbed by the tubules adjusts to the

changing filtered load. Progesterone was not discovered to play a role in the acute control of potassium or sodium excretion in the pioneering investigation by Brown and colleagues [28].

Notably, a placental enzyme called vasopressin causes a rise in the metabolic clearance of ADH beginning about week ten and continuing through the middle of pregnancy. Enzyme activity reaches its highest point in the third trimester, remains elevated during labor and delivery, and then drops to undetectable levels within the first 2–4 weeks after giving birth. However, increased production in pregnancy often maintains average plasma ADH concentrations. Polydipsia, polyuria, high-normal blood sodium, and abnormally low urine osmolality are all symptoms of transitory diabetes insipidus (DI), which affects a small percentage of women. Compared to women without DI, these ladies can have higher vasopressinase activity. Desmopressin (DDAVP), resistant to degradation by vasopressinase, can be used to treat this condition. While many pregnant women report urinating often, genuine polyuria (0.3 L/day) is unusual [29].

8 Conclusion

During pregnancy, the kidneys are subjected to extreme stress. Hence a nephrologist needs to be familiar with the kidneys' typical responses to this situation. Numerous physiological changes occur throughout pregnancy. The kidneys play crucial roles in various pregnancy-related processes, including salt, potassium, water retention, blood pressure regulation, and many more. These shifts are governed by mechanisms that are complex and only partially understood. Our current knowledge of kidney development in the mother is mainly based on studies conducted in the 1970s and 1980s. As women live longer, they have more children later in life, and as a result, more women are experiencing complications during pregnancy. To better recognize pathology in our ever-changing patient population, it is crucial to have a firm grasp of typical physiologic changes [29].

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