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Kidney Physiology in Pregnancy

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ABSTRACT
A remarkable orchestration of physiologic changes occurs throughout pregnancy. The kidneys are major contributors to the changes in the environment for the pregnant woman and foetus as a result of the changing hormonal milieu of pregnancy. Practically every facet of kidney function is affected by the functional effects of pregnancy on renal physiology. As serum creatinine, urea, and uric acid concentrations fall, the glomerular filtration rate rises by 50%. Lower osmolality and serum sodium levels are the result of reduced antidiuretic hormone and thirst thresholds. Despite an increase in intravascular capacity of 30% to 50% by the second trimester, blood pressure decreases by about 10 mmHg. The renin-aldosterone-angiostensin system is activated as a result of the decrease in systemic vascular resistance, which is multifactorial and partly due to hyposensitivity to vasoactive hormones. A rise in serum aldosterone causes a net sodium gain of about 1000 mg. The pregnant woman is protected from hypokalemia by a concurrent increase in progesterone. Up to 80% of women experience physiologic hydronephrosis, and the kidneys lengthen and enlarge. Understanding these significant changes in kidney physiology during pregnancy will be provided by this review, which is essential in providing care for pregnant patients.

Keywords: Women, Kidneys, and Renal Physiology

1. INTRODUCTION

Almost every area of renal physiology is impacted by pregnancy. A feat of physiology is accomplished through the orchestration of the changes that take place. Vasodilation and substantial volume expansion are features of kidney and systemic hemodynamics. In comparison to non-pregnant levels, renal plasma flow (RPF) and glomerular filtration rate (GFR) both rise by 50% and by 80%, respectively. 1 Proteinuria, glucosuria, a decrease in serum osmolality, and a decrease in blood sodium levels are all mildly increased as a result of altered tubular activity and processing of water and electrolytes. Because of the fluid retention during pregnancy, physiologic hydronephrosis is frequent and the kidneys grow bigger. There are illustrations of typical laboratory modifications. In this article, significant alterations in kidney physiology that occur during pregnancy will be reviewed.

Body Modifications

Pregnancy-related alterations to the body are well-known. [2,3] Pregnant women with hydronephrosis experience it in 43% to 100% of cases, and the prevalence increases with each passing trimester.[4]Serial quantitative studies by ultrasonography show that the maximum incidence of hydronephrosis is reached at 28 weeks, with a 63% overall incidence

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of hydronephrosis. 5 Pregnant women with asymptomatic bacteriuria have a 40% higher risk of developing pyelonephritis than nonpregnant women due to the dilated collecting system, which can store 200 to 300 mL of urine and cause urinary stasis. [3] Additionally, the kidneys' length rises by 1 to 1.5 cm during pregnancy before shrinking over the following six months after delivery.[6] Christensen and colleagues used computed ultrasonography to show expansion in kidney volume in 24 healthy women without signs of pelvic stenosis, even though this growth was previously mistakenly attributed to hydronephrosis. [7] While various magnetic resonance techniques can be utilised when ultrasound is nondiagnostic and can help determine the degree of obstruction and whether it is intrinsic or extrinsic in character, ultrasound is still the imaging modality of choice for evaluating hydronephrosis in pregnancy. [7,8] On average, pregnancy might result in a 30% increase in kidney volume. [9] Rather than any changes in the number of nephrons, the growth is due to increasing kidney vascular and interstitial volume. [10,11]Under mechanical compressive forces on the ureters and maybe as a result of progesterone's effects, the renal pelvis and calyceal systems enlarge. Progesterone can lower contraction pressure, peristalsis, and ureteral tone. However, mechanical compression of the ureters itself provides the best etiologic support for hydronephrosis. [12] Up to 86% of pregnant women have hydronephrosis on the right side. [13] This is caused by the right ureter entering the pelvis at an angle whereas the left ureter travels parallel to the ovarian vein and at a less acute angle. Hormonal effects were unable to account for this disparity. According to studies, progesterone injection to non-pregnant women does not result in hydronephrosis, and there is no connection between progesterone or oestrogen levels and the degree of calyceal dilatation. [12,14] When the ureter enters the conduit above the pelvic brim in women who have pelvic kidney or ureteral diversion, hydronephrosis is not seen. The higher prevalence of hydronephrosis in primigravidas also lends support to the idea that mechanical compression causes hydronephrosis during pregnancy. The ureter constricted between the iliopsoas and a gravid uterus at the level of the sacral promontory can be identified using magnetic resonance imaging. [15,16]

Hemodynamic changes in the kidneys

Vasodilation and volume expansion are characteristics of pregnancy, which are brought on by the careful synchronisation of several hormones. One of the first pregnancy-related changes is a drop in blood pressure, which by the second trimester had averaged 105/60 mmHg, or about 10 mmHg. Numerous factors, including as changes in the renin-angiotensin-aldosterone system (RAAS) and other hormonal swings, are probably to blame. Pregnancy-related hemodynamic alterations may be influenced by maternal hormones. The midluteal phase of menstruation has lower mean arterial pressure than the midfollicular phase, which is accompanied by a drop in vascular resistance and an increase in cardiac output.[17] Although progesterone can cause an increase in RPF and GFR, it cannot explain the extent of the rise experienced during pregnancy. The placenta, decidua, and corpus luteum all release the vasodilating hormone known as relaxin. Through an increase in vascular gelatinase activity, which works through the endothelium endothelin B receptor-nitric oxide pathway, it is linked to the physiology of the kidneys during pregnancy in rodents. [18] According to Ogueh and colleagues, relaxin steadily increased during pregnancy and then decreased after delivery. However, at least in late gestation and postpartum, clinical connections between relaxin levels and hemodynamic measures have not been shown. [19,20] Raas is typically upregulated during pregnancy. Ovaries and decidua are two extrarenal organs that release renin. The liver creates more angiotensinogen as a result of the placenta's production of

oestrogen, which also results in more angiotensin II being produced (ANG II). Despite this, it is known that systolic blood pressure falls during pregnancy, most likely for a variety of reasons. Pregnancy-related refractoriness to ANG II may account for the vasodilated condition. The monomeric form of angiotensin 1 (AT1) receptors and/or the presence of other drugs like progesterone and vascular endothelial growth factor-mediated prostacyclins may also contribute to this insensitivity. Preeclampsia causes RAAS dysregulation, which results in heterodimeric AT1 receptors, a return of ANG II sensitivity, reduced aldosterone, and the presence of AT1 autoantibodies (AT1-AA). In a healthy pregnancy, aldosterone levels begin to rise at gestational week 8 and continue to grow throughout the third trimester, increasing 3- to 6-fold the upper limit of normal (80-100 ng/dL). In comparison to non-pregnant women, the outcome is a net gain of 1.1 to 1.6L and a 30% to 50% increase in blood volume.

GFR variations

The remarkable increase in GFR is one of the initial renal alterations. Davison and Noble used 24-hour urine collections throughout the menstrual cycle, conception, and up to 16 weeks of pregnancy in an elegant research of 11 healthy women to describe serial assessments of creatinine clearance. They showed that increases in GFR during pregnancy happened as a continuation of previous changes, and that creatinine clearance increased throughout the luteal phase of the typical menstrual cycle. In the study's 9 successful pregnancies, the creatinine clearance rose 20% at 4 weeks postmenstrual time, 25% as early as week 4, and 45% by week 9. The GFR increased less and was not sustained in the two women who had spontaneous, simple abortions. Amazingly, these modifications took place 3 weeks before the abortion became clinically obvious. In a group of 10 pregnant women, Chapman and colleagues discovered early increases in GFR and kidney blood flow caused by inulin and paminohippurate clearances in conjunction with systemic and kidney vasodilation. A number of studies point to an approximate 40%–50% overall progressive rise in GFR with peak increases sustained at term in uncomplicated pregnancies. It has been demonstrated that hyperfiltration persists at levels 20% above normal at postpartum week 228 and goes away one month later.

GFR measurement

In order to properly care for a pregnant patient, it's imperative to be able to estimate GFR. Similar to general nephrology, accurate calculation of GFR is still a topic of ongoing research in pregnancy. Pregnant women with and without preeclampsia have lower GFRs according to the Modification or Diet in Renal Disease (MDRD) equation, which is consistent with its recognised propensity to underestimate when GFR is higher than 60 mL/minute. According to a study comparing both equations to 24-hour urine samples in preeclamptic patients, the CKD Epidemiology Collaboration equation appears to underestimate GFR to a comparable extent as the MDRD equation. Despite evidence from other studies that GFR increases consistently until term, cystatin C produced increased first and second trimester GFRs followed by a decline in GFR in the third trimester in a retrospective investigation. The cystatin C equation demonstrated that GFR increased postpartum, in contrast to the MDRD equation, which showed a decline. A recent prospective study comparing cystatin-Cbased GFR estimations to inulin clearances at three time periods in 12 pregnant individuals revealed no association. [33] Therefore, the preferred method for determining GFR in pregnant women remains 24-hour urine collection for creatinine clearance computation.

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GFR-Increasing Mechanisms

In comparison to levels prior to pregnancy, the GFR rises by 50% during pregnancy. Incomplete knowledge exists regarding the precise mechanisms causing this growth. It is crucial to keep in mind how GFR is expressed and to recognise the elements that change throughout pregnancy. GFR 14 DP2pGC3Kf, where the glomerulus's net hydraulic pressure is (DP) and its oncotic pressure is (pGC). Humans cannot directly quantify transcapillary hydraulic pressure, but animal models can by employing micropuncture procedures. The average of the afferent and efferent oncotic pressures is known as pGC (pE). When the filtration fraction (FF), or the portion of plasma filtered along the glomerulus, is subtracted from the oncotic pressure (pE), which enters the afferent arteriole, by 1, the result is:

pE 1/4 pA=12FF

The GFR divided by the RPF gives rise to the phrase "FF":

FF 1/4 GFR = RPF

The ability to ultrafiltrate through the glomerulus' three layers determines the hydraulic permeability (k), which is the product of the surface area available for filtration and the glomerular ultrafiltration coefficient (Kf). Modeling and autopsy samples are used to estimate permeability. Because of the expansion of the plasma volume during pregnancy, oncotic pressure is markedly reduced, which results in a rise in GFR. Modest modifications in the hydraulic permeability and filter surface area may also have a small impact on Kf. There is considerable disagreement over whether DP rises during human pregnancy. Baylis found no change in the hydrostatic or oncotic pressure in early investigations on the 12-day pregnant rat and linked rising GFR to rising RPF. In a study, Roberts and colleagues found that pregnant women's glomerular size selectivity appeared to be altered and that their oncotic pressure was reduced, but they were unable to detect any indication of a rise in DP. They came to the conclusion that rising RPF is mostly to blame for the elevated GFR. This reasoning cannot explain why RPF constantly decreases as pregnancy progresses but GFR remains elevated later in the pregnancy. An investigation of the glomerular filtration dynamics in a human postpartum study revealed that a persistent increase in GFR postpartum is caused by either a rise in DP up to 16%, an increase in Kf of around 50%, or a combination of smaller increments of DP and Kf. Odutayo and Hlaudunewich claim that it is impossible to rule out the possibility that DP changes because estimated increases in Kf and measured changes in pGC are both low.

Modifications in Tubular Function

The way the tubular system handles nutrition and wastes changes during pregnancy. Increases in GFR, declines in proximal tubular reabsorption, or a combination of both lead to an increase in uric acid excretion. Early in pregnancy, serum uric acid levels decrease, reaching a nadir of 2 to 3.0 mg/dL by 22 to 24 weeks, before gradually increasing to normal by term. The greater clearance is believed to be required to accommodate the increased output from the placenta and foetus. Freely filtered at the glomerulus, glucose is almost entirely reabsorbed in the proximal tubule and a minor quantity in the collecting tubule. Typically, the presence of glucose in the urine indicates that the amount of glucose filtered out has been more than the tubular reabsorptive capacity. In pregnancy, glucose reabsorption is less efficient and excretion is more variable. Older research hypothesised that increasing GFR, along with a rise in the amount of glucose filtered, exceeded the proximal tubule's ability to reabsorb glucose, resulting in glucosuria with normoglycemia or a physiologic glucosuria. In a study including 29 pregnant women, glucose infusion along with

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simultaneous measures of glucose excretion and inulin clearance showed that pregnant women had decreased glucose reabsorption independent of the presence of glucosuria. In contrast to women with varied degrees of glucosuria throughout pregnancy, who were no longer glucosuric, women with glucosuria reverted to an effective condition of reabsorption 8 to 12 weeks after giving birth. Pregnancy may also result in less efficient distal nephron reabsorption. Similar to how uric acid and glucose are handled, there is a decreased fractional reabsorption of amino acids and b-microglobulin, leading to an increase in excretion of these compounds.Total urine protein and albumin excretion rise throughout a healthy pregnancy, with this increase being most pronounced after 20 weeks. With a minor amount of albumin and other circulating proteins, urine primarily contains Tamm-Horsfall proteins. Although the timing does not coincide with the peak increase in GFR, the rise in proteinuria during pregnancy is frequently linked to the increase in GFR. Despite having levels that do not go above the upper limit of normal, there is evidence that albuminuria increases in late pregnancy. Circulating soluble antiangiogenic factors, which disrupt the slit diaphragm in preeclampsia and are elevated late in normal pregnancy, are also enhanced and may be the cause of late-term elevations in proteinuria.Selective changes in glomerular charge or the presence of more protein material, both of which are observed in the third trimester, are additional potential contributing factors. Protein levels of 300 mg/24 hours or higher, which is double the typical limit for non-pregnant women, are considered abnormal proteinuria in pregnant women. Further research has demonstrated that mean amounts of protein excretion typically do not surpass 200 mg/24 hours, despite the fact that this value was generated from a rather small sample.The 24-hour urine collection is still the gold standard for quantifying pregnant women with proteinuria, even if the use of urine protein/creatinine for quantifying proteinuria in non-pregnant patients has grown more common and can be used to screen for presence or absence of proteinuria. Unfortunately, because of timing and retention issues brought on by dilated systems that can hold high quantities, a significant portion of timed urine collections in pregnant women are incomplete.

Water and electrolyte handling by the kidneys

During pregnancy, the threshold for activating antidiuretic hormone (ADH) and thirst osmoreceptors is decreased. The serum sodium levels decrease by an average of 4 to 5 mEq/L, and plasma osmolality is close to 270 mOsm/kg. Increased b-human chorionic gonadotropin, a trend also observed to a lesser extent in menstrual women during the luteal cycle, may be the mechanism underlying this alteration. the occurrence of vasodilation, arterial underfilling, and subsequent ADH release are thought to be connected to the decline in serum sodium. Because relaxin levels rise during human pregnancy and it has been demonstrated in animal research to stimulate ADH secretion and water intake, it may be involved in this process. Aldosterone and its antinatriuretic effects increase concurrently with mild hyponatremia. Deoxycorticosterone also encourages sodium retention and upregulation of sodium pumps across different membranes. The natriuretic forces of elevated GFR, rising levels of atrial natriuretic peptide and progesterone counteract these forces. Although the Clinical Summary states that the expected total sodium increase during pregnancy is between 900 and 1000 mEq, the net balance between these effects is preferential retention of water over salt and lower osmolality. By the conclusion of gestation, the body's total potassium stores have risen by about 320 mEq. Because of progesterone's antikaliuretic properties, this happens despite the salt retention caused by aldosterone. Throughout pregnancy, potassium excretion is maintained constant thanks to changes in tubular

reabsorption that adjust to changes in filtered load. Progesterone was not discovered to play a role in the acute control of sodium or potassium excretion in a previous investigation by Brown and colleagues.It is important to note that a placental enzyme called vasopressinase, which is created at week 10 and throughout midpregnancy, causes an increase in the metabolic clearance of ADH. Enzyme activity peaks throughout the third trimester, remains high during labour and delivery, and then declines to undetectable levels between two and four weeks after birth. However, due to increased secretion, plasma ADH concentrations are often maintained normal during pregnancy. A few women experience polyuria as a result of temporary diabetes insipidus (DI), which is characterised by polydipsia, polyuria, high-than-normal blood sodium, and unnaturally low urine osmolality. These women might have more vasopressinase activity than women without DI. Desmopressin (DDAVP), which is not broken down by vasopressinase, can be used to manage it. Although frequent urine is frequently observed in pregnant women, genuine polyuria (.3 L/day) is uncommon.

2. CONCLUSION

It is crucial for the practising nephrologist to comprehend the typical renal adaptations to pregnancy because the kidneys experience extraordinary demands during pregnancy. Lower levels of blood creatinine, urea, and uric acid are the result of early GFR increase, which peaks at 40% to 50% of pre-pregnancy values. Although there is a net gain in salt and potassium, the retention of water is larger, with gains of up to 1.6 L. Progesterone's actions and RAAS changes cause a decrease in systemic vascular resistance, which lowers blood pressure and increases RPF. A successful pregnancy for both the mother and the unborn child depends on the careful orchestration of hemodynamic alterations and fluid and electrolyte balance.

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