Section 1 Physiology

Chapter 1

Renal Physiology

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Introduction

Remarkable and unique changes enable the kidneys to adjust to the increased metabolic demands of pregnancy. Renal adaption occurs following conception, is maximal prior to major increases in uteroplacental blood flow and is maintained until at least late gestation. Adjustment of systemic and renal homeostasis enables enhanced glomerular filtration, volume expansion, modified electrolyte and acid base balance and augmented erythropoietin and active vitamin D synthesis. These alterations are likely to contribute to successful pregnancy outcomes. Current understandings of underlying mechanisms of gestational transformations are outlined in what follows, and potential pathophysiological pathways of pregnancy-associated deterioration in renal function are discussed.

Gestational Changes in the Renal Tract

Increases in renal blood flow and interstitial space result in volume expansion of the kidneys up to 70 percent, equating to approximately 1 cm in length [1]. Dilatation of the renal tract (calyces, renal pelvis and ureter) is evident in 90 percent of women by the third trimester [1], and is more prominent on the right. This effect is proposed to be the consequence of the ureter passing over the right iliac artery. However, renal tract dilatation is also recognized in transplanted kidneys, implying that circulating factors are contributory. Urological complications are discussed in more detail in Chapter 15.

Renal Function in Pregnancy

Renal Blood Flow

Ovulation is followed by an increase in renal plasma flow, as measured by para-aminohippurate clearance. After conception, there are further increases in effective renal plasma flow, reaching rates 50–85 percent greater than nonpregnant values [2].

Longitudinal assessments of effective renal plasma flow in healthy women during pregnancy and postpartum consistently report augmented flow. There is discrepancy at later gestation, however, with some reports of up to 20 percent reduced flow toward term [3, 4], and others of sustained blood flow [5]. Positional changes in late pregnancy may influence renal hemodynamics [5], but this is not confirmed by all studies [3].

Glomerular Filtration

In parallel with changes in renal blood flow, prior to conception there is a 20 percent increase in glomerular filtration during the luteal phase of the menstrual cycle compared with the week of menstruation [6], and a 7 percent increase compared with the follicular phase [7].

Assessments of inulin and 24-hour creatinine clearance in healthy pregnant women report increases in glomerular filtration as early as four weeks postconception [6], peaking at 40–65 percent postpartum values [3, 4] in the second trimester. In the last trimester, glomerular filtration, assessed by 24-hour creatinine clearance, appears to fall to nonpregnant values [8]. In a study of serial 24-hour creatinine clearance in early pregnancy, a 45 percent increase was present by nine weeks' gestation. Two women who subsequently had miscarriages had a less marked increase in creatinine clearance compared to women with uncomplicated pregnancies, evident three weeks prior to fetal loss, suggesting that adequate early renal adaptation appears to be important for successful pregnancy. Furthermore, in women with severe chronic kidney disease (CKD), a decline, rather than an improvement, in renal function with pregnancy is associated with lower birth weight [6].

Increments in glomerular filtration are less than renal plasma flow, suggesting that adjustments in

regulation of glomerular filtration occur. Dextran sieving studies in healthy pregnant women, which enable assessment of relative filtration of different sizes of neutral molecules, suggest that there is a reduction in porosity to small molecules in early pregnancy that is more pronounced in later pregnancy [9]. Changes in breadth of glomerular pore size during pregnancy, as compared with postpartum, have also been reported, calculated by modeling from dextran clearances [10]. It is likely that there are dynamic changes throughout pregnancy in the magnitude of the filtration fraction and its constituents, with similar gestational changes in the glomerular filtration barrier permeability, but understanding remains limited.

Mechanisms of Gestational Change in Glomerular Filtration

The kidney has one of the largest pregnancy redistributions of blood flow compared with other nonreproductive organs. Yet, despite extensive recognition of this adaptation to pregnancy, there are few studies of pregnant women exploring potential mechanisms. In nonpregnant individuals, plasma volume expansion leads to increased glomerular filtration, and is likely in part to contribute to increased renal blood flow in pregnancy (see "Volume Regulation in Pregnancy" section later in this chapter). It is unlikely to exclusively mediate this, however, as maximal plasma volume expansion occurs at later gestation than the highest glomerular filtration rates.

Further augmentation of glomerular filtration can be achieved by protein loading, by amino acid infusion or by a high-protein meal. One study of 14 healthy pregnant women reported increments in glomerular filtration of 18, 10 and 12 percent following an amino acid infusion in early and late pregnancy and postpartum, respectively, compared with a control infusion of compound sodium lactate solution [11]. The authors propose this effect reflects recruitment of "dormant" nephrons, thus enabling assessment of "renal reserve." Rat studies of amino acid infusions in pregnant and nonpregnant animals confirm that there is a further increase in glomerular filtration in pregnant animals of the same magnitude as in the nonpregnant state, thus confirming that renal vasodilatory responses in pregnancy remain intact. Hence, mechanisms of autoregulation of glomerular filtration appear to remain intact and "renal reserve" is maintained regardless of gestational adaptation.

Women with renal transplants also have renal adaptation during pregnancy comparable to healthy controls, despite preexisting compensatory renal hypertrophy, although the response is reduced. Interestingly, donor gender or age did not influence gestation-induced renal adaptation in a cohort of 20 renal transplant recipients [12].

Some authors propose that there is a reduction in threshold for autoregulation that may be protective against periods of hypoperfusion secondary to gestational hypotension, but this has not been formally assessed. Furthermore, the proportion of "renal reserve" recruitment in pregnancy is unclear. The contribution of limited reserve in women with CKD to renal function in pregnancy is explored in Chapters 2 and 5.

Glomerular Hemodynamic Studies

Single glomerular micropuncture studies measuring hydrostatic and oncotic pressure in Munich-Wistar rats have confirmed that there are no differences between pregnant and nonpregnant states despite an increased whole kidney glomerular filtration rate [13]. Although probable, the same mechanism for increased glomerular filtration in human pregnancy cannot be assumed as experimental changes in renal blood flow in rats appear to elicit a much wider response in glomerular filtration than is observed in humans. This is likely to be the consequence of filtration equilibrium occurring more proximally in the glomerular capillaries of rats than humans, and thus increments in plasma flow are able to continue to increase glomerular filtration. However, there is evidence from glomerular dynamic modeling studies in healthy pregnant women that changes in glomerular filtration are predominantly driven by augmented effective renal plasma flow [9], with some contribution from reduced plasma oncotic pressure [10]. Equal vasodilation of both afferent and efferent arterioles must be responsible, allowing increased renal plasma flow to augment ultrafiltration without increments in transglomerular hydrostatic pressure.

Hyperfiltration states (e.g. essential hypertension, type 1 diabetes) are considered to result in glomerular hypertension. The augmented filtration fraction necessary to maintain total glomerular filtration is associated with glomerular injury and secondary focal segmental glomerulosclerosis. Glomerular

normotension is likely to explain why sequential pregnancies in women with normal kidney function are not associated with progressive renal injury, nor is there evidence of glomerular injury in multigravid rats.

Relaxin Studies

The presence of an intact corpus luteum plays an important, but not critical role in hemodynamic renal adaptation in pregnancy. The ovarian hormone relaxin rises minimally in the luteal phase then exponentially in early pregnancy, and has been demonstrated to mediate gestational changes. A study of nine women with pregnancies conceived by ovum donation, with undetectable serum relaxin, reported a reduction in plasma osmolality and an increase in creatinine clearance in the first trimester, but change from baseline was significantly less than in healthy controls with detectable relaxin [14].

Further mechanistic evidence is provided by rat models, which are summarized next [15]:

- Exogenous relaxin administration to chronically instrumented conscious nonpregnant, ovarectomized female and male rats results in renal hemodynamic changes comparable to those in pregnant animals.
- Anti-relaxin antibody administration to pregnant rats abrogates any gestational increase in renal blood flow or glomerular filtration.
- Relaxin infusion in nonpregnant rats reduces renal vasoconstrictor response to angiotensin II *in vitro*.

The relationship between relaxin concentration and renal adaption in humans is less clear. Healthy volunteers were administered intravenous human synthetic relaxin over six hours, but, despite a rapid rise in renal blood flow of up to 60 percent, there were no differences before and after treatment in glomerular filtration [16]. The absence of an association between relaxin administration and increased glomerular filtration may be temporal, as larger studies of chronic relaxin therapy over several weeks for heart failure and systemic sclerosis reported significant changes in creatinine clearance that were dose dependent. However, the influence of relaxin on the magnitude of gestational-associated change in filtration fraction is unknown.

The mechanism of relaxin-induced changes in renal blood flow has also been explored in rat models and appears to be mediated by the potent endothelial-derived vasodilator nitric oxide. Evidence is provided by the following studies [15]:

- Blockade of nitric oxide synthase with L-arginine analogs in chronically instrumented pregnant rats abrogated gestation-associated increases in renal blood flow and glomerular filtration, both with acute and chronic administration, and prevented renal adaptation if given in early pregnancy.
- L-arginine analogs blocked relaxin-induced increases in renal vasodilation and hyperfiltration and blunted myogenic reactivity in pregnant rats.
- Endothelial removal in rat renal arteries prevented relaxin-induced vasodilation.

The mechanism of induction of nitric oxide synthesis is unclear. There was no increase in endothelial nitric oxide synthase (eNOS) isoforms in mid-trimester pregnant rats compared with nonpregnant controls. One study reported reduced eNOS expression in pregnant animals, but higher renal inducible (iNOS) and neuronal (nNOS) expression than in nonpregnant animals, and increased protein abundance of the specific nNOS beta isoform in mid-trimester rats has been confirmed by others [15].

Endothelin B (ET_B) receptor activation appears to be contributory to gestation-associated renal adaptation. Evidence comes from the following studies [15]:

- ET_B receptor antagonists administered to pregnant rats prevented a gestational increase in renal vasodilation and hyperfiltration.
- ET_B receptor-deficient rats do not exhibit gestational renal adaptation.
- ET_B receptor antagonists abrogate renal adaptation in relaxin-treated nonpregnant rats.

It is unclear whether the renal effects of ET_B receptor activation are a consequence of increased expression, or another unknown mechanism. Similarly, the pathway by which relaxin elicits ET_B receptor activity has not been elucidated, as relaxin does not appear to stimulate ET_B receptor synthesis *in vitro*.

Matrix metalloproteinase-2 (MMP-2) has been proposed to be a potential downstream mediator of renal vasodilation in pregnancy by hydrolysis of big ET to ET_{1-32}, which interacts with ET_B receptors and is summarized in what follows [15]:

- MMP synthesis is increased in uterine fibroblasts in the presence of relaxin.
- MMP-2 is upregulated in small renal arteries of both midterm pregnant rats and nonpregnant rats with relaxin-induced renal vasodilation.

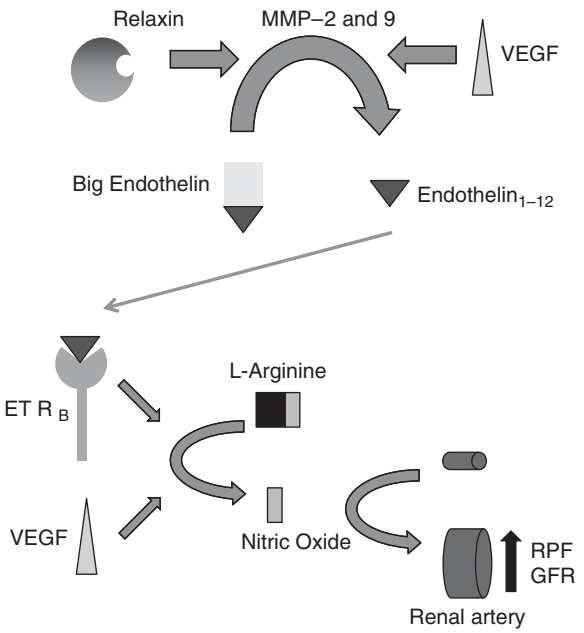


Figure 1.1 Mechanisms of glomerular hyperfiltration in pregnancy

- Inhibition of MMP-2 in pregnant rats or relaxin-treated rats reduced renal adaptation and enhanced renal artery myogenic reactivity.
- MMP-2 activity is increased in ET_B receptor-deficient rats, and therefore may act upstream of MMP-2 activation.

MMP-9 has been shown to be upregulated in small renal arteries isolated from short-term (four to six hours) relaxin-treated nonpregnant rats, but in this model MMP-2 expression was unchanged. Following administration of specific neutralizing antibodies MMP-9 was found to mediate relaxin-associated reduction in myogenic activity, but not MMP-2. However, if the rats were treated with relaxin for several days, MMP-2 activity was increased and the MMP-2 neutralizing antibody inhibited the blunting of myogenic activity. Thus length of exposure to relaxin in order to activate different mediator pathways is likely important.

McGuane and colleagues have recently reported the novel association between angiogenesis and relaxin-mediated vasodilation [17]. Nonpregnant rats were treated with a vascular endothelial growth factor (VEGR) receptor tyrosine kinase inhibitor (SU5416) before and during a five-day period of relaxin administration. Expected increases in renal plasma flow and GFR were abolished. *In vitro* studies support the role of angiogenic factors mediating relaxin-induced vasodilation. Pretreatment of small rat and mice renal arteries and human subcutaneous arteries with SU5416, placental growth factor (PlGF) or VEGF-neutralizing antibodies inhibited the vasodilator effects of relaxin, with evidence of upregulated MMP-2 activity [17].

Relaxin stimulates VEGF synthesis in endometrial cell lines and both VEGF and PlGF have been shown to upregulate MMP-9 in human aortic smooth muscle cells. Together these findings suggest that angiogenic factors may be important mediators of relaxin-induced vasodilation that have effects both upstream and downstream from vascular MMP activity.

A summary of the factors contributing to renal vasodilation and hyperfiltration with gestation is outlined in Figure 1.1.

Progesterone Studies

Evidence from pseudo-pregnancy in rats confirms that the feto-placental unit is not essential for renal adaptation to pregnancy. Furthermore, gestational increase in glomerular filtration occurs before maximal placental progesterone synthesis. However, removal of the placenta during mid-pregnancy abrogates changes in renal blood flow and glomerular filtration [18]. Progesterone, but not estrogen, administered to nonpregnant women results in up to 15 percent increase in inulin clearance and creatinine clearance, but only affected effective renal plasma flow, not glomerular filtration, when given acutely to men.

Other Glomerular Changes in Pregnancy

Glomerular Volume

A controversial study including renal biopsy specimens from 12 healthy pregnant women demonstrated increased glomerular volume. There was also evidence of glomerular endotheliosis despite the absence of proteinuria and hypertension, which had previously been proposed to be a hallmark of preeclampsia (although the severity of changes seen was less marked as compared to biopsies from women with preeclampsia) [19]. An autopsy series also confirmed that glomerular size is greater in in pregnancy compared with nonpregnant individuals, but that there were no differences in glomerular cellularity [20].

Glomerular Proteinuria

Total urinary protein excretion rises with gestation. The most widely recognized upper limit of "normal" is 300 mg/24 hours, derived from the upper 95 percent confidence interval (259.4 mg) from a study of 270 healthy pregnant women [21]. Older studies examined differences in protein filtration during pregnancy. Increased urine concentration of several plasma constituents is described (e.g. α-1 antitrypsin, transferrin, beta-lipoprotein, complement fractions β1-A-C, IgD and α-macroglobulin), whereas some urinary plasma proteins are reduced (e.g. thyroxine-binding prealbumin, IgG and IgA) and others are unchanged (e.g. hemopexin, haptoglobin and IgM) compared to nonpregnant women subjects, suggesting dynamic gestational changes in glomerular permeability.

There is a gestational increase in urinary albumin excretion with variable rates of resolution reported between 12 weeks and 12 months postpartum [9, 22, 23, 24]. Given the substantial increase in glomerular filtration and the molecular size of albumin, it might be anticipated that higher levels of albuminuria would be present. Tubular reuptake may reduce total urinary albumin concentrations, but gestation-associated increase in transferrin, a comparable-sized molecule to albumin, is considerably greater [25]. Selective tubular reuptake could be contributory, although it has been proposed that increased glomerular basement membrane negative charge could repel anionic plasma proteins, thus reducing their filtration and urinary excretion.

Vascular endothelial growth factor is responsible for the maintenance of podocyte and glomerular basement membrane integrity in nonpregnant individuals, and angiogenic balance is likely to play an important role in glomerular protein excretion during pregnancy, but direct relationships between glomerular structure and function and local or circulating angiogenic factors in healthy pregnancy are yet to be confirmed.

Tubular Changes in Pregnancy

Tubular Proteinuria

Renal tubules reabsorb most filtered proteins, but also catabolize proteins with excretion of constituent peptides and directly secrete proteins into urine. Filtered low-molecular proteins should be almost completely reabsorbed by the proximal tubule, but urinary levels of alpha-1 microglobulin, beta 2 microglobulin, retinol-binding protein and clara cell protein have been found to be increased in the second and third trimesters in healthy individuals in the absence of increased plasma concentrations [26]. This has led to the proposal that proximal tubular reabsorption capacity is either compromised during pregnancy or at capacity due to increased filtration.

Other changes in urinary protein composition with gestation include increased urinary excretion of tubular enzymes [25], which are of similar molecular weight to urinary lysosomal enzymes, suggesting further gestational changes in tubular function rather than increased filtration of circulating plasma enzymes.

Glycosuria

Glycosuria is more frequently recognized in pregnant than nonpregnant individuals despite no changes in serum glucose concentrations. Augmented glomerular filtration of glucose is likely to overwhelm proximal tubular reuptake [27], hence glucose is more readily detectable in the urine of pregnant women.

Uric Acid

Serum uric acid concentrations fall by approximately 25 percent in healthy pregnancy compared with nonpregnant controls, then increase toward term. Uric acid passes freely through the glomerulus, predominantly reabsorbed in the proximal tubule with reuptake of 90 percent of the filtered load along the nephron. Pregnancy is associated with altered handling of uric acid with lower plasma concentrations in early pregnancy associated with reduced tubular resorption [28]. Reuptake appears to be restored in later pregnancy, or increased plasma concentrations may be the consequence of a fall in glomerular filtration toward term.

Historically uric acid concentration was used as predictor of preeclampsia, as it was observed to rise before the onset of hypertension and proteinuria and was associated with reduced renal clearance. However, subsequently the ability of uric acid to differentiate between different hypertensive disorders has been disproven, and a meta-analysis of 41 studies including 3,913 women confirmed uric acid concentrations to be only a weak predictor of eclampsia and severe hypertension and not associated with intrauterine death [29]. Furthermore, discrimination between preeclampsia and preexisting renal disease is not possible. Assessment of uric acid concentration

is no longer recommended to predict or diagnose hypertensive disorders of pregnancy.

Volume Regulation in Pregnancy

During pregnancy there is a net volume expansion of 6–8 liters, which includes 4–6 liters in the interstitium, and a 50 percent increase in plasma volume. There is a concomitant reduction in plasma osmolality of 10mOsm/kg, which is apparent in early pregnancy and persists until delivery. Postpartum there is substantial natriuresis to restore nonpregnant osmolality and extracellular volume [30]. Several reports suggest that inadequate volume expansion is associated with poor fetal growth, which is evident as early as weeks 5 and 10 [31].

Despite the reduction in osmolality, there is also progressive retention of approximately 900 mmol of sodium. Dynamic homeostatic mechanisms must be reset throughout gestation in order to accommodate changes in additional volume and reduced plasma osmolality. However, women given diuretics or salt restriction retain an appropriate neurohumoral antinatriuretic response [32].

It is unclear whether systemic vasodilatation leading to relative "underfill" is the primary stimulant for sodium and water retention or conversely if renal sodium reuptake is the initial event leading to plasma volume expansion. A study of women in the first trimester confirmed that both vasodilation and plasma volume expansion are already initiated by six weeks' gestation [33].

The following influences on volume and plasma osmolality have been described during pregnancy:

Vasodilation

Pregnancy-induced systemic vasodilation is predominantly mediated by nitric oxide and results in venous pooling, thus reducing effective circulating blood volume. "Underfill volume" sensing will be triggered, including renin-angiotensin-aldosterone system (RAAS) activity, atrial natriuretic peptide (ANP) suppression and antidiuretic hormone (ADH) release, leading to volume expansion throughout gestation.

Relaxin

Relaxin appears to play an important role in osmoregulatory gestational changes. Increments in circulating relaxin are temporally related to early plasma volume expansion [34]. A fall in plasma osmolality is blunted in women who conceived by ovum donation [14]. The presence of ovaries appeared to be critical to the development of plasma volume expansion and reduced plasma osmolality. Furthermore, relaxin-neutralizing antibodies infused in pregnant rats abolished gestational changes in plasma osmolality, and administration of exogenous relaxin to rats following ovarectomy was associated with a decrease in plasma osmolality [15].

Renin-Angiotensin-Aldosterone System (RAAS) Activation

In early pregnancy, plasma activity, total concentration and substrate or renin is enhanced in comparison with nonpregnant controls, resulting in increased plasma angiotensin II and aldosterone concentrations. Plasma aldosterone in pregnant women has been reported to be up to fourfold higher than in nonpregnant individuals [2]. RAAS activation occurs in spite of concurrent plasma volume expansion and increased renal blood flow. There is marked blunted vasopressor response to angiotensin II, while antinatriuretic activity is probably enhanced [35].

Although a resetting of activation of RAAS occurs, augmentation of activity is observed following usual triggers including sodium restriction, and reduced venous return due to supine or upright posture demonstrating highly sophisticated adaptation. Underlying mechanisms leading to enhanced renin synthesis are unclear. Increased circulating prostaglandins have been proposed to initiate vasodilation leading to relative volume depletion and stimulation of RAAS activity. In rat models, renin and aldosterone concentrations revert rapidly to prepregnant values after delivery, suggesting that nonpregnant sensing thresholds are quickly reestablished.

Atrial Natriuretic Peptide (ANP)

Atrial natriuretic peptide (ANP) concentrations are not increased in early pregnancy despite volume expansion. Elevated levels are found at later gestations corresponding to dilatation of the atrium. Resetting of plasma volume expansion stimulus for release must occur, and this is supported by meta-analysis [36]. ANP remains elevated postpartum with up to 148 percent increases in concentration compared with nonpregnant women [36], consistent with the period of natriuresis, and consistent with the finding of increased urinary cGMP postpartum, a mediator of ANP activity.

Some authors propose that there is a blunted response to ANP in pregnancy, which, although described in rats, has not been confirmed in humans. There is evidence of enhanced cGMP metabolism by phosphodiesterase-5 in the inner medullary collecting duct in gravid rat models, and inhibition of phosphodiesterase-5 abolished gestation associated refractoriness to ANP in pregnant rats. Whether this pathway is relevant in humans remains to be established.

Antidiuretic Hormone (ADH)/Vasopressin

In nonpregnant individuals, substantial ADH release would be elicited by a fall in plasma osmolality of 10mOsm/kg, inhibiting thirst and enhancing water excretion, but ADH does not appear to be triggered at the same threshold in pregnancy. Several human studies have demonstrated higher circulating ADH concentrations in pregnant women at the same plasma osmolality as nonpregnant controls, particularly in the first trimester, and these findings have been supported by rat models. One study of ADH concentrations reported no difference between pregnant and nonpregnant rats despite a reduction in plasma osmolality of 8mOsm/kg. Collecting duct aquaporin 2 expression was increased and appeared to be mediated by V2 vasopressin receptors [37].

Human chorionic gonadotrophin (hCG) may be contributory in early pregnancy adaptations in ADH. Six nonpregnant females were given hypertonic saline during the luteal phase of the menstrual cycle. Additional administration of hCG resulted in a reduction in plasma osmolality, ADH and thirst, which was not evident in control males [38].

ADH concentrations fall in later pregnancy compared with early pregnancy and ADH clearance increases three- to fourfold in the second and third trimesters. A placenta-derived vasopressinase has been identified, but its contribution to ADH mediated change is unclear.

Gestational volume expansion would also be expected to suppress ADH release, but does not occur in rat models This trigger may be "overridden" by systemic vasodilation leading to perceived underfilling of the vasculature, or due to resetting of the threshold for ADH release.

Tubuloglomerular Feedback

Tubuloglomerular feedback has been studied in chronically instrumented rats. In nonpregnant animals, plasma volume expansion is detected as increased tubular fluid volume delivery to the macular densa, leading to afferent arteriolar vasoconstriction and reduced glomerular filtration, thus regulating tubular fluid volume. In pregnant rats this response was not activated until higher rates of renal blood flow were present compared to nonpregnant controls [39], confirming a "resetting" of the threshold of volume expansion to suppress tubuloglomerular feedback. However, a response to increased renal plasma volumes was still observed, thus autoregulation is maintained in order to tolerate higher plasma volumes.

Electrolyte Homeostasis in Pregnancy

Volume expansion leads to net dilution of electrolytes during pregnancy. However, there is a net gain in total sodium, potassium and calcium achieved by the following mechanisms:

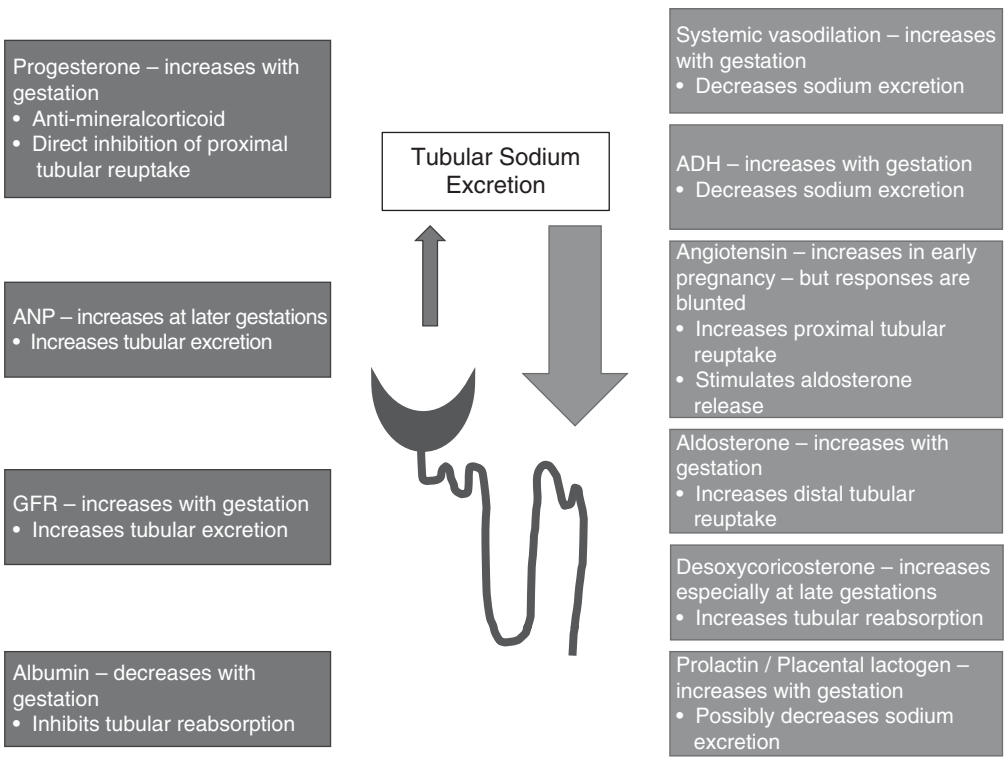
Sodium

Plasma sodium concentration falls by 4–5mmol/L during pregnancy. Filtered sodium load increases due to the elevated glomerular filtration rate, but reabsorption by the tubules is enhanced resulting in a net gain in sodium. Multiple contributory factors have been proposed and are outlined in Figure 1.2.

Aldosterone responsive epithelial Na channel (ENaC) activity in late pregnancy appears to be instrumental in sodium retention. ENaC channel mRNA expression in the renal collecting tubule has been demonstrated to increase in the presence of estrogen *in vitro*. Inhibition of renal ENaC in late pregnant rats blunted sodium retention and plasma volume expansion, and late gestation increase in blood pressure [40]. However, aldosterone responsive sodium chloride co-transporter (NCC) mRNA expression appears to be unchanged in pregnant rats compared to virgin controls [41] and an explanation for this discrepancy is unclear.

Potassium

There is a reduction in urinary potassium excretion during pregnancy leading to retention of approximately 350mmol of potassium despite elevated aldosterone concentrations and increased urinary bicarbonate excretion. Mineralocorticoids administered to healthy pregnant women in the third trimester had little effect on potassium excretion and the authors proposed this is due to the anti-



ANP: Atrial Natriuretic Peptide; GFR: Glomerular filtration

Figure 1.2 Influences on sodium excretion during pregnancy

mineralocorticoid effect of progesterone [42]. More recently, H+/K+ ATPase types 1 and 2 mRNA have been demonstrated to be increased in the cortex and medulla of late pregnant rats compared with virgin controls, which could explain the mechanism of potassium retention independent of aldosterone. [43] Precise gestational changes in potassium handing within the nephron are poorly understood.

Calcium

Calcium excretion increases during pregnancy by two- to threefold, and is proposed to be the consequence of increased glomerular filtration coupled with reduced reuptake in the thick ascending limb of the loop of Henle. Elevated plasma 1,25-dihydroxy-Vitamin D3 concentrations are observed in pregnancy, leading to increased intestinal absorption of calcium and suppression of parathyroid hormone (PTH) concentrations. PTH-induced tubular calcium reuptake is subsequently blunted. Calciuria is discussed in more detail in Chapter 18.

Acid-Base Homeostasis in Pregnancy

During pregnancy there is a net increase in hydrogen ion synthesis due to increased basal metabolic rate and calorific intake. Plasma pH is higher than healthy nonpregnant individuals during pregnancy, however, due to respiratory alkalemia driven by an elevated respiratory rate. A mild compensatory metabolic acidemia is also evident, with concentrations between 18 and 22mmol/l in healthy pregnant women. There is no evidence of gestational changes in renal bicarbonate reabsorption or hydrogen ion excretion in healthy pregnancy.

Assessment of Renal Function in Pregnancy

Creatinine production during pregnancy is unchanged during pregnancy, hence serum creatinine concentrations fall due to increased renal clearance. Gestation-specific reference ranges for creatinine concentration are not well defined. Accurate assessment

Table 1.1 Comparison for methods of assessment of glomerular filtration in pregnancy

Method of Assessment	Gold Standard Comparison	Overestimate/Underestimate
24-hour creatinine clearance	Inulin clearance	Significant correlation
Timed creatinine clearance	24-hour creatinine clearance Inulin clearance	Significant correlation
Cockcroft Gault	Inulin clearance Creatinine clearance	Underestimates Overestimates using current weight and underestimates using prepregnancy weight
Modified Diet in Renal Disease Formula	Inulin clearance 24-hour creatinine clearance	Underestimates
Chronic Kidney Disease – EPI	24-hour creatinine clearance	Underestimates
Cystatin-C	24-hour creatinine clearance	Underestimates

of glomerular filtration rate in pregnancy is challenging, and comparisons of estimates with formal infusion clearances are presented in Table 1.1.

Glomerular Filtration Rate (GFR) Estimation Formulae

Formulae to estimate glomerular filtration rate (GFR) have been studied during pregnancy. Comparing the modified diet and renal disease (MDRD) formula with inulin clearance [44] and the chronic kidney disease-EPI formula with creatinine clearance[45] both underestimate filtration by approximately 20 percent. These formulae should not be used during pregnancy. Similarly, formulae that include weight or body surface area underperform, as they are dynamic during pregnancy and do not reflect kidney size. For example, a study of the Cockcroft-Gault formula overestimated glomerular filtration by approximately 40mls/min compared with inulin clearance.[44]

Twenty-Four-Hour Creatinine Clearance

Twenty-four-hour creatinine clearance is the best assessment of glomerular filtration in clinical practice. Although there is the recognized limitation of variable proximal tubular creatinine secretion, independent changes in urinary creatinine excretion compared with serum creatinine concentration with gestation are not reported [6], thus alterations in tubular secretion are unlikely. However, pooling of urine in dilated ureters and incomplete bladder emptying may impair accurate timed collections resulting in falsely low clearance. Some authors propose that women should lie in the left lateral position prior to micturition for an hour in order to minimize this confounder, although this is unlikely to be practical for most women. Moreover, studies comparing 24-hour creatinine clearance with inulin clearance have not identified significant differences between measurements [4, 46].

Cystatin C

Cystatin is proposed to be a more accurate indicator of glomerular filtration at the higher end of the normal range than creatinine. Cystatin is freely filtered at the glomerulus, actively reabsorbed and catabolized by tubular cells. Several studies of cystatin in pregnancy identify limitations as a useful marker of glomerular filtration. Concentrations are shown to rise in the second trimester rather than the anticipated fall with increasing glomerular filtration. Cystatin is an anionic 13kDa molecule; thus it would be expected that increased filtration occurs as a consequence of the postulated reduced negative charge of the basement membrane with gestation. An explanation for this paradoxical finding is unclear.

Several reports support the role of cystatin as a diagnostic marker of preeclampsia with correlation reported between serum concentrations and 24-hour creatinine clearance [47]. Elevated concentrations are described in women with chronic hypertension, but the role of cystatin as a predictive or diagnostic marker of superimposed preeclampsia in women with CKD has not been explored.

Mechanisms of Pregnancy-Associated Progression in Renal Disease

The pathophysiology of pregnancy-associated progression of renal disease in women with more severe CKD is unclear. Micropuncture studies in healthy rats with five or more pregnancies confirmed no differences in glomerular or whole kidney hemodynamics compared with nonpregnant controls. In rat models of CKD due to anti-glomerular basement membrane glomerulonephritis, raised glomerular capillary pressure was observed in nonpregnant females, but pregnancy resulted in no further change in glomerular pressure [48]. There was a tendency for an increase in overall glomerular filtration, single nephron glomerular filtration and renal blood flow in pregnant rats with glomerulonephritis. However, in this model there were no differences in glomerular filtration between rats with experimental glomerulonephritis and controls, hence the severity of kidney disease may not be sufficient to be associated with an accelerated decline in function.

Baylis and Wilson assessed glomerular hyperfiltration in uninephrectomized rats with high dietary protein feeding following five repetitive pregnancies [49]. Again there was evidence of raised glomerular pressure and also elevated single nephron glomerular filtration and glomerular plasma flow rate in the nonpregnant operated animals compared with controls, but single nephron GFR and glomerular plasma flow rates were lower in repetitively pregnant rats compared with nonpregnant animals. There was still a significant but variable increase in single nephron glomerular filtration in response to amino acid infusion suggestive of preserved renal reserve.

Finally, pregnancy-associated glomerular hemodynamic changes were assessed in the spontaneously hypertensive rat. Despite marked glomerular hypertension compared with normotensive controls, there were no differences in glomerular pressure between mid-gestation pregnant and nonpregnant animals, nor any evidence of reduced glomerular filtration after repeated pregnancies [50]. Interestingly there was no increase at mid-gestation in renal vascular resistance, nor was there an increase in renal blood flow in response to an amino acid infusion in both moderately and severely hypertensive animals suggestive of a loss of renal vasodilatory response potentially due to structural adaptations.

Other proposed mechanisms of pregnancy-associated acceleration in renal disease include subacute thrombotic microangiopathy, podocyte loss, angiogenic imbalance and preexisting endothelial dysfunction; however, none has been studied in detail. A potential protective anti-fibrotic role of relaxin, described in nonpregnant patients with CKD, has not been explored in pregnancy.

Conclusion

Remarkable physiological adaptation to pregnancy occurs in the renal vasculature, glomerulus and tubules. Understanding the underlying mechanism of augmented glomerular filtration without hyperfiltration injury is evolving, and could be invaluable to inform development of therapeutic strategies for nonpregnant patients with CKD. However, pathophysiology of pregnancy-associated progression of renal impairment remains elusive, and requires further study in order to prevent this condition and the catastrophic consequences for new mothers, their infants and their families.

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