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Renal function in normal and disordered pregnancy

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Abstract

Purpose of review—Renal dysfunction during pregnancy is a common and serious complication. Understanding normal physiology during pregnancy provides a context to further describe changes in pregnancy that lead to renal dysfunction and may provide clues to better management.

Recent findings—Hormonal changes during pregnancy allow for increased blood flow to the kidneys and altered autoregulation such that glomerular filtration rate (GFR) increases significantly through reductions in net glomerular oncotic pressure and increased renal size. The mechanisms for maintenance of increased GFR change through the trimesters of pregnancy, continuing into the postpartum period. Important causes of pregnancy-specific renal dysfunction have been further studied, but much needs to be learned. Pre-eclampsia is due to abnormal placentation, with shifts in angiogenic proteins and the renin–angiotensin–aldosterone system leading to endothelial injury and clinical manifestations of hypertension and organ dysfunction. Other thrombotic microangiopathies occurring during pregnancy have been better defined as well, with new work focusing on the contribution of the complement system to these disorders.

Summary—Advances have been made in understanding the physiology of the kidney in normal pregnancy. Diseases that affect the kidney during pregnancy alter this physiology in various ways that inform clinicians on pathogenesis and may lead to improved therapeutic approaches and better outcomes of pregnancy.

Keywords

filtration; pre-eclampsia; pregnancy; thrombotic microangiopathy

INTRODUCTION

Pregnancy induces and requires major changes in the structure and function of the kidney. This results in kidney growth, as well as high blood flows and supernormal kidney function throughout pregnancy. Understanding these changes is essential, not only to recognize normal values and mechanisms, but also to allow evaluation of changes in renal function in the many disorders that can occur during this period.

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Conflicts of interest

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This article reviews physiological changes in normal pregnancy pertinent to common causes of renal dysfunction. We then focus on the pathophysiology of pregnancy-related kidney disease. Some related issues, such as gestational hypertension, pregnancy in chronic kidney disease, dialysis or after transplantation are not reviewed.

RENAL CHANGES IN NORMAL PREGNANCY

Substantial structural, functional and hemodynamic changes take place during normal pregnancy. These have been extensively studied, but are not yet fully elucidated.

Because of changes in the vascular and interstitial spaces [1], the kidneys normally increase in size by up to 30% [2], with a 1–1.5cm increase in length [3]. Hydronephrosis, mainly secondary to ureteric mechanical obstruction, is common during pregnancy and may further enlarge the kidneys. The right ureter is more commonly affected because of the angle at which it crosses the iliac and ovarian vessels at its entry to the pelvis [4].

Starting even before conception, renal function changes in response to hormonal variations during the menstrual cycle [5,6]. Compared with the mid-follicular phase, mean arterial pressure and systemic vascular resistance are lower in the midluteal phase, resulting in increased cardiac output, renal plasma flow (RPF) and glomerular filtration rate (GFR) [5–7]. These changes continue through much of pregnancy (see Fig. 1). Increases in GFR by 20% and 45% were noted at 4 and 9 weeks gestation, respectively [7]. At term, GFR was found to be 40% higher compared with nonpregnant women, and then declined to normal, nonpregnant levels 1 month after delivery [8]. The relationship between RPF and GFR changes as pregnancy advances. In early pregnancy RPF exceeds GFR and, as such, filtration fraction is slightly lower than in nonpregnant controls. This changes some time between week 12 and the third trimester, in which RPF falls toward nonpregnant levels, whereas GFR continues to be elevated, resulting in an increased filtration fraction. All these values normalize 4–6 weeks after delivery [6,9–15].

It is useful at this stage to remember that:

$$\text{GFR} = K_f \times (\Delta P - \pi_{GC}) \quad (1)$$

where ΔP is the hydraulic pressure gradient between the glomerular capillary and Bowman's capsule, π_{GC} is the mean oncotic pressure in the glomerular capillary and K_f is the glomerular ultrafiltration coefficient, the product of the surface area available for filtration and the permeability of the filtration membrane.

π_{GC} can be calculated from the afferent (π_A) and efferent (π_E) oncotic pressures:

$$\pi_{GC} = \frac{\pi_A + \pi_E}{2} \quad (2)$$

As filtration takes place, the concentrations of proteins, which are not filtered, increase, resulting in higher oncotic pressure at the efferent side of the glomerular capillary. Thus, π_E is a function of π_A and the filtration fraction:

$$\pi_E = \frac{\pi_A}{(1 - \text{filtration fraction})} \quad (3)$$

And

$$\text{Filtration fraction} = \frac{\text{GFR}}{\text{RPF}} \quad (4)$$

Thus, for GFR to increase, one or more of the following has to take place: $\uparrow K_f$, $\uparrow P$ or $\downarrow \pi_{GC}$. In addition, increased RPF increases GFR even without any changes to P or K_f . As RPF increases, a lower fraction is filtered out initially, resulting in less concentration of plasma proteins, and less opposing force to filtration, decreasing π_{GC} [16,17].

Increased P and K_f , as well as reduced π_{GC} have all been described to contribute, at different stages and to different degrees, to the high GFR seen throughout normal pregnancy. In a 12-days pregnant rat model, increased GFR during pregnancy correlated with increased RPF [18], secondary to vascular volume expansion, with no changes in hydraulic or oncotic pressures. Tubuloglomerular feedback, which would normally counteract the rise in GFR, was reset to allow for higher GFR [19]. Increased RPF as the cause for increased GFR was also suggested in a human study that correlated GFR to RPF, with only minor contributions from lowered π_{GC} [20]. However, when GFR continues to be elevated despite reduced RPF (later in pregnancy), changes in K_f are suggested to affect the increased GFR [20]. Glomerular enlargement noted on renal biopsies from pregnant women [21] and from autopsy studies [22] may contribute to the suggested increase in K_f . At term, elevations of GFR, up to 41%, were found to be mainly mediated by reduced π_{GC} [15]. At this point, RPF was normal and π_{GC} was most likely decreased because of hemodilution of plasma proteins through the substantial plasma volume expansion that occurs in pregnancy. Finally, 2 weeks after delivery, an observed 20% increase in GFR was attributed to increases in either K_f or P by 50 and 16% respectively, or by smaller changes in both [14].

Several hormones and multiple mechanisms have been implicated in the aforementioned changes. Early on, luteal phase progesterone may play a role in increasing the RPF and GFR, and this role may continue during pregnancy [5]. Increased renin is produced by extra-renal sources, namely, the ovaries and decidua, angiotensinogen production by the liver increases under the influence of estrogen, and aldosterone levels are higher during normal pregnancy [5,6]. Vasodilation, however, takes place during pregnancy despite the revved up rennin–angiotensin–aldosterone system (RAAS) due to several factors. Progesterone and vascular endothelial growth factor (VEGF)-mediated prostacyclins increase refractoriness to angiotensin II [23]. In addition, angiotensin II type I (AT1) receptors are less responsive during normal pregnancy as they exist in a monomeric state [24].

Relaxin, produced by the corpus luteum, decidua and placenta, increases RPF, GFR and solute clearance by afferent and efferent vasodilation in rats [25,26]. This is mediated through upregulation of nitric oxide-dependent vasodilation [27]. In human studies, however, inconsistencies were noted. Relaxin increased RPF but not GFR in healthy

volunteers [28]. Moreover, in a recent study comparing relaxin levels between women with pre-eclampsia and normal pregnancies, no difference in relaxin levels was found between the two groups, and no clear correlation was found between relaxin levels and GFR, mean arterial pressure, RPF or renal vascular resistance in late pregnancy [29].

Sodium retention and volume expansion are, at least in part, mediated by the increased RAAS activity. Some of the stimulus for this increased activity could primarily be because of systemic vasodilation, leading to a relatively lower volume and pressure state [5–7]. This leads to retention of about 900 to 1000mEq of sodium and about 6–8 l increased total body water, of which 4–6 l is located in the extracellular compartment [30,31].

RENAL DYSFUNCTION DURING PREGNANCY

It is helpful to use the classic approach categorizing causes of reduced kidney function into prerenal, intrinsic renal and postrenal causes. Causes incriminated in nonpregnant states should be considered. However, certain causes are either unique to or more common during pregnancy. Table 1 lists the differential diagnosis of renal dysfunction in pregnancy based on physiology and timing.

Fluid losses secondary to excessive vomiting, as in hyperemesis gravidarum, or blood loss from pregnancy-related complications such as antenatal bleeding, can cause prerenal dysfunction. Bilateral hydronephrosis, albeit rare, is a possible cause of postrenal dysfunction. Acute cortical necrosis can result from several obstetric complications including septic abortion or abruptio placentae. Intrinsic renal disease specific to pregnancy is seen with pre-eclampsia, eclampsia and the syndrome of hemolysis, elevated liver enzymes and low platelets (HELLP). Many other forms of thrombotic microangiopathies (see below), can be triggered or contributed to by pregnancy. The remainder of this review focuses on pre-eclampsia and other thrombotic microangiopathies.

THE PRE-ECLAMPSIA SPECTRUM

Pre-eclampsia, eclampsia, HELLP syndrome, and acute fatty liver of pregnancy (AFLP) may share the same underlying pathophysiology. In addition, there is substantial overlap in their presentations. Defined as hypertension in the second half of pregnancy with proteinuria (>300 mg/day) [32], pre-eclampsia occurs in 3–5% [33,34] of all pregnancies, and accounts for significant morbidity and mortality in both mother and infant. Mild-to-severe microangiopathy affects the brain, liver, kidneys and placenta to varying degrees, leading to pre-eclampsia, eclampsia or HELLP [35]. Significant decline in renal function develops, but patients seldomly manifest azotemia [36]. Severe pre-eclampsia accounts for about 40% of acute kidney injury during pregnancy in the developed world [37].

Histologically, there is glomerular endothelial cell swelling and detachment, subendothelial fibrinoid deposits, occlusion of glomerular capillaries, reduced density and size of endothelial fenestrae, and thickening of the glomerular basement membrane [36,38]. These changes, typical of thrombotic microangiopathy, impair the glomerular capillary hydraulic permeability and reduce filtration surface area, resulting in a diminished GFR. Despite hypertension and increased renal vascular resistance, no difference was found in RPF

between women with pre-eclampsia and normal pregnancy, or in afferent oncotic pressure (π_A) in one study. However, π_{GC} was slightly lower than in pregnant controls owing to the increased filtration fraction in the latter group [36] (see Fig. 2).

Cardiac output has been variably reported in pre-eclampsia, increasing in many but decreasing in some studies. Peripheral vascular resistance (PVR), however, invariably is increased when compared with normal pregnancy, resulting in high blood pressure. This is in contrast to what happens in gestational hypertension, wherein cardiac output seems to drive hypertension whereas PVR remains as low as in normotensive pregnancies [39–42].

Our understanding of how pre-eclampsia develops continues to advance. Placentation is defective in women with pre-eclampsia, with failure of invasion of cytotrophoblasts to the deep uterine muscular layers. Spiral arteries fail to transform from high resistance vessels to the normal large capacitance vessels seen in pregnancy [43,44]. Resultant hypoperfusion causes release of angiogenic factors, altering maternal endothelial function and precipitating pre-eclampsia [45,46]. Other contributory factors implicated in the development of pre-eclampsia include RAAS involvement (detailed below), immune mechanisms [47,48] and release of oxidative stress products in the placenta [49–51].

Significant work has gone into elucidating the role of RAAS in pre-eclampsia. A full fetal-side placental RAAS was identified, but its role has not been well explored. However, the maternal placental RAAS has been implicated in the development of pre-eclampsia [52]. Placental ischemia may contribute to increased local renin production, akin to activation in renovascular disease [53,54]. In contrast to normal pregnancy, angiotensin II and norepinephrine sensitivity is increased, resulting in vasoconstriction and volume retention, high blood pressure, endotheliosis and proteinuria [55,56]. This happens despite paradoxically lower levels of plasma renin activity (PRA) and aldosterone noted in pre-eclamptic women [57,58]. The increased sensitivity to angiotensin II results from upregulation and heterodimerization of AT1 receptors to bradykinin B2 receptors [59], and the presence of agonistic antibodies to the AT1 receptors [60,61].

Imbalances between angiogenic and antiangiogenic factors have been implicated in the pathogenesis of pre-eclampsia [62–64]. Increased levels of soluble Fms-like tyrosine kinase-1 (sFlt1, the soluble form of VEGF receptor 1) and soluble endoglin (sEng), both secreted by the placenta, reduce the levels of free VEGF, placental growth factor (PlGF) and other factors, contributing to endothelial dysfunction, reduced vasodilatation and proteinuria [64–66].

Links between these angiogenic factors and RAAS were suggested by several studies. Higher urinary sFlt1 and total VEGF levels were noted in diabetic patients with proteinuria. These correlated positively with the level of angiotensin II, and were nicely blocked by losartan [67]. AT1 autoantibodies and angiotensin II activated AT1 receptor induced sFlt production in vitro [68]. This relationship, however, did not hold true in a rat model with increased renin and AT1-agonistic autoantibody (AA), wherein there was no increase in sFlt levels [69]. In addition, no correlation was found between AT1-AAs and sFlt in some

human studies [70,71], except for one human study, wherein the level of AT1-AA correlated with the severity of the disease and with sFlt levels [72].

Advances have been made in using the levels of angiogenic factors to predict development of pre-eclampsia or its severity, and to help differentiate pre-eclampsia from other forms of hypertension or chronic kidney disease (CKD). Development of automated methods to measure these markers, and standardization for use in clinical practice is under way [73■].

THE NON-PREGNANCY-SPECIFIC THROMBOTIC MICROANGIOPATHIES

Although not as common as pre-eclampsia, other thrombotic microangiopathies cause significant morbidity and mortality during pregnancy [74,75] and have diagnostic similarities to pre-eclampsia. Diseases in this category are hemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP) and primary and secondary antiphospholipid syndromes.

Small vessel thrombosis is followed variably by platelet consumption with or without a consumptive coagulopathy, hemolysis of red blood cells, endothelial damage and end-organ damage. Renal involvement is more common in HUS, CNS involvement in TTP and liver involvement in HELLP syndrome. Beyond thrombosis, histological findings in the kidney include endothelial cell swelling, protein deposits in the subendothelial layer and double contouring of the basement membrane [76].

HUS is caused by excessive complement activation. In its typical form, this can be triggered by verotoxin. In the atypical form (a-HUS), an acquired or inherited imbalance between factors involved in activation and regulation of the complement system can be identified in most cases. Factors H, I and membrane cofactor protein are the main inhibitors of the complement alternative system. Lack of suppression of these inhibitory factors secondary to inactivating mutations in their respective genes [77,78■], or secondary to acquired factor H antibodies [74], can result in excessive complement activation. Complement activation can alternatively result from activating mutations in factor B or C3 coding genes [79,80]. Resultant excessive activation of C3 convertase leads to endothelial damage [81].

TTP on the other hand can be secondary to low levels of a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member-13 (ADAMTS-13), which can be due to acquired inhibitory antibodies or to constitutional deficiency. ADAMTS-13 cleaves multimers of von Willibrand factor (vWF), reducing the ability of clots to form. Deficiency in ADAMTS-13 thus results in increased clotting activity and platelet consumption, leading to TTP [24,82].

Not all cases of HUS or TTP are clearly secondary to the abnormalities described above. However, identification of these factors in an individual patient has important implications for the management. ADAMTS-13 deficiency has better outcomes after plasmapheresis to remove inhibitory antibodies. There may also be a role for using rituximab in these cases [83,84]. Plasmapheresis is also used in complement-mediated a-HUS. Eculizumab, a monoclonal humanized antibody, blocks the common terminal complement activation, and is an effective treatment for a-HUS [85■,86■,87,88].

Pre-eclampsia, HELLP and AFLP all have features of thrombotic microangiopathy, but they are generally self-limited and improve rapidly with the end of pregnancy. However, recent studies suggest underlying issues with complement regulation in many cases, which may eventually change some of our diagnostic and therapeutic approaches to these disorders. This is well covered in a recent review [86■].

CONCLUSION

Normal pregnancy is associated with a number of harmonized changes that affect the renal structure and hemodynamics. Our understanding of these changes is still incomplete, and ongoing research is required in this area. Many disorders can lead to renal dysfunction during pregnancy, challenging the outcomes for mother and child. Better understanding of these disorders, including their markers and predictors, as well as better treatment options hopefully can soon improve our practice.

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KEY POINTS

- Pregnancy is associated with hormonal changes that directly and indirectly alter renal function.
- Increased GFR in pregnancy is mainly influenced by reduced average oncotic pressure and increased ultrafiltration capacity.
- Renal dysfunction is a common complication of pregnancy.
- Pre-eclampsia is a disease of placental insufficiency, leading to alterations in angiogenic proteins and resetting the RAAS.
- Thrombotic microangiopathies are increasingly differentiated as defects in immune, genetic or complement status with key effects on therapy.

FIGURE 1.

Renal hemodynamic changes of pregnancy. Black arrows depict changes in comparison to the nonpregnant state. CO, cardiac output; TPR, total peripheral resistance; RPF, renal plasma flow; π_{GC} , glomerular oncotic pressure; P_{GC} , glomerular capillary pressure; K_f , transcapillary ultrafiltration coefficient; GFR, glomerular filtration rate.

FIGURE 2.

Renal hemodynamic changes of pre-eclampsia. Black arrows reflect changes compared to normal pregnancy. RPF, renal plasma flow; π_{GC} , glomerular oncotic pressure; P_{GC} , glomerular capillary pressure; K_f , transcapillary ultrafiltration coefficient; GFR, glomerular filtration rate; RAAS, renin–angiotensin–aldosterone system.

Table 1

Differential of renal dysfunction in pregnancy based on physiology and timing

Prerenal	Intrinsic renal	Postrenal
Early		
Hyperemesis gravidarum	CKD progression Autoimmune disease, GN Complications of hemorrhage, sepsis, UTI, stones Familial HUS? TTP Anticardiolipin antibody syndrome	Rare
Late		
Bleeding	CKD progression	Obstruction from stones
AFLP	Severe pre-eclampsia/ HELLP AFLP HUS/TTP Autoimmune GN, postinfectious GN Pyelonephritis	Obstruction from uterus
Postpartum		
Bleeding	HUS	Retained clots
Medication side-effects	Severe pre-eclampsia CKD progression ATN from sepsis or hemorrhage	

AFLP, acute fatty liver of pregnancy; ATN, acute tubular necrosis; CKD, chronic kidney disease; GN, glomerulonephritis; HELLP, hemolysis, elevated liver enzymes and low platelets; HUS, hemolytic uremic syndrome; TTP, thrombotic thrombocytopenic purpura; UTI, urinary tract infection.