Current Hypertension Reports (2020) 22: 91
https://doi.org/10.1007/s11906-020-01099-1

PREECLAMPSIA (VD GAROVIC, SECTION EDITOR)

Preeclampsia and Kidney Disease: Deciphering Cause and Effect

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Published online: 14 September 2020
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Abstract

Purpose of Review Preeclampsia and chronic kidney disease have a complex, bidirectional relationship. Women with kidney disease, with even mild reductions in glomerular filtrate rate, have an increased risk of developing preeclampsia. Preeclampsia, in turn, has been implicated in the subsequent development of albuminuria, chronic kidney disease, and end-stage kidney disease. We will discuss observational evidence and mechanisms linking the two disease processes.

Recent Findings Preeclampsia is characterized by an imbalance in angiogenic factors that causes systemic endothelial dysfunction. Chronic kidney disease may predispose to the development of preeclampsia due to comorbid conditions, such as hypertension, but is also associated with impaired glycocalyx integrity and alterations in the complement and renin-angiotensin-aldosterone systems. Preeclampsia may lead to kidney disease by causing acute kidney injury, endothelial damage, and podocyte loss.

Summary Preeclampsia may be an important sex-specific risk factor for chronic kidney disease. Understanding how chronic kidney disease increases the risk of preeclampsia from a mechanistic standpoint may open the door to future biomarkers and therapeutics for all women.

Keywords Preeclampsia · Hypertensive disorders of pregnancy · Chronic kidney disease · End-stage kidney disease

Introduction

There have been significant advances in our understanding of the pathogenesis of preeclampsia over the last two decades. Preeclampsia is a systemic disorder characterized by endothelial dysfunction that impacts multiple organ systems, including the kidney, where the most common presentation is new-onset proteinuria. The impact of preeclampsia on kidney histology has been well documented, with postpartum biopsies demonstrating classic pathologic features, including glomerular endotheliosis and vascular injury [1, 2]. While proteinuria typically resolves within months of delivery, there is an expanding body of evidence suggesting that there is a future risk of kidney disease after preeclampsia. Preeclampsia has been associated with an increased risk of albuminuria [3, 4], chronic kidney disease (CKD) [5], and end-stage kidney disease (ESKD) [5–8]. As women tend to be older and have more comorbidities at the time conception in the more recent era [9], the incidence of preeclampsia has been increasing [10], which makes preeclampsia a potentially important sex-specific risk factor for CKD.

Confounding the "cause and effect" relationship of preeclampsia and kidney disease is the fact that kidney disease itself is a significant risk factor for preeclampsia. Kidney donation [11•], stage 1 CKD [12], and a previous episode of resolved acute kidney injury [13] have all been associated with an increased risk of preeclampsia, suggesting that even mild kidney dysfunction can be significant. Women with kidney disease often have concomitant hypertension, which is also a risk factor for superimposed preeclampsia [14]. Whether undiagnosed kidney disease is present at the time of conception, leading to both an increased risk of preeclampsia and an increased risk of significant kidney disease in the future, is still unclear [7, 15].

In this review, we will review the current definitions of preeclampsia and discuss the pathogenesis of preeclampsia, focusing on specific connections to the kidney. We will also review the observational evidence supporting the bidirectional

This article is part of the Topical Collection on *Preeclampsia*

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relationship between kidney disease and preeclampsia, discuss mechanisms linking the two disease processes, and consider future directions.

Definitions of Preeclampsia

Preeclampsia is characterized by widespread endothelial dysfunction that can affect multiple organ systems. Preeclampsia is one of 4 major hypertensive disorders of pregnancy, which include preeclampsia/eclampsia, chronic hypertension, chronic hypertension with superimposed preeclampsia and gestational hypertension. The American College of Obstetrics and Gynecology (ACOG) released a report in 2013, updating the definitions of these 4 conditions [16]. Preeclampsia is defined as the presence of blood pressure elevation > 140 mmHg and/or 90 mmHg after 20 weeks' gestation with either proteinuria (defined as 300 mg of protein in 24 h or a protein/creatinine ratio of 0.3 g/g creatinine (Cr)) or, in the absence of proteinuria, other severe features (Table 1). Severe features can include thrombocytopenia, acute kidney injury (defined as serum Cr of 1.1 mg/dl or greater or a doubling of serum Cr), abnormal liver function tests, pulmonary edema, or neurologic abnormalities, such as seizures or visual symptoms. The International Society for Hypertension in Pregnancy (ISSHP), another major society, also updated their diagnostic criteria in 2018 (Table 1) [17]. Similar to the ACOG guidelines, proteinuria is no longer required for the diagnosis of preeclampsia if other severe features are present. The ISSHP also includes evidence of ureteroplacental insufficiency as a severe feature.

The removal of proteinuria as an absolute requirement for the diagnosis of preeclampsia is in part an acknowledgment of the heterogeneity of the condition [18]. Hemolysis elevated liver enzymes and low platelets (HELLP) syndrome, as an example, can present without significant proteinuria, though is a severe manifestation of the disease [19]. Furthermore, the degree of proteinuria has not been shown to consistently correlate with maternal or fetal outcomes, and thus heavy proteinuria (> 5 g in 24 h), is no longer a severe feature in the ACOG guidelines [20, 21]. The lack of correlation could simply be a timing issue. If a woman presents early in the course of preeclampsia, she may have minimal proteinuria, as compared to a woman who presents later in the course with heavy proteinuria; the underlying pathophysiology has not changed in the two women. For this reason, both ACOG and ISSHP discourage the term "mild" to describe preeclampsia, as what may be mild at presentation may become severe with time. Spot urine protein-to-creatinine measurements have been shown to have good correlation with 24-h urine protein measurements in preeclampsia [22], and allow for the rapid diagnosis and management of pregnant women.

Pathogenesis of Preeclampsia: the Role of the Placenta

The placenta is a central actor in the pathogenesis of preeclampsia. While preeclampsia is a condition unique to pregnancy, it can also occur in the setting of a molar pregnancy, suggesting that it is the trophoblastic tissue, and not the fetal tissue, that is necessary for the disease to develop [23]. In preeclamptic placentas, the cytotrophoblast fails to invade and remodel the spiral arteries, creating high resistance vessels and, ultimately, placental hypoxia [24]. Pathologic examination of the placentas from women with preeclampsia reveals multiple characteristic changes, including infarctions, narrowing of the arterioles, fibrin deposition, and thrombosis [25, 26]. Preeclampsia tends to resolve after the delivery of the placenta, which also points to its essential role, with the notable exception of postpartum preeclampsia, a rare but highly morbid condition [18, 27].

While the placenta is essential for the development of preeclampsia, there are several maternal risk factors that can increase the risk of preeclampsia. Older age at pregnancy, chronic hypertension, diabetes, autoimmune disease, obesity, and CKD are all risk factors for the development of preeclampsia [14, 28, 29]. Each individual woman who develops preeclampsia may have more or less contribution from placental and maternal risk factors, giving rise to the concept of a *maternal* and a *placental* phenotype of preeclampsia. For example, early, preterm preeclampsia (< 34 weeks' gestation) is characterized by more ureteroplacental dysfunction and intrauterine growth restriction than term preeclampsia (> 37 weeks) and, thus, could be considered *placental* preeclampsia [30]. This is a particularly useful paradigm for research purposes, including the study of biomarkers discussed further below. In practice, there is a significant amount of overlap in many clinical scenarios [31].

Abnormal placentation, due to a combination of maternal and placental factors, ultimately leads to placental ischemia, setting off a cascade of downstream events. The placenta will increase the production of soluble fms-like tyrosine kinase-1 (sFlt-1), a splice-variant of the vascular endothelial growth factor (VEGF) receptor Flt-1, that lacks the transmembrane and cytoplasmic domains. The soluble receptor, sFlt-1, will then bind pro-angiogenic factors, such as VEGF and placental growth factor (PlGF), tipping the balance toward an anti-angiogenic state. Women with preeclampsia, particularly preterm preeclampsia, have elevated sFlt-1/PlGF ratios, and this can be a useful test to rule out preeclampsia in the short term [32–34]. This angiogenic imbalance is associated with lower levels of nitric oxide and other vasodilatory factors, higher levels of cytokines such as TNF-α and interleukin (IL)-6, and systemic vasoconstriction [24, 32, 35]. IL-10, an immunomodulatory molecule that regulates the maternal-fetal

Table 1 Diagnostic criteria for preeclampsia according to American College of Obstetrics and Gynecology 2013 guidelines and the International Society for the Study of Hypertension in Pregnancy 2018

Disorder	Blood pressure	American College of Obstetrics and Gynecology 2013	International Society for the Study of Hypertension in Pregnancy 2018
Preeclampsia-eclampsia	SBP ≥ 140 mmHg or DBP ≥ 90 mmHg greater than 4 h apart on at least 2 occasions OR SBP ≥ 160 mmHg or DBP ≥ 110 mmHg on 2 occasions in a shorter time interval (min) After 20 weeks' gestation	Proteinuria (> 300 mg/24 h, protein/Cr ratio > 0.3 g/g Cr or 1+ dipstick) OR any of the following severe features*: SBP ≥ 160 mmHg or DBP ≥ 110 mmHg Platelets < 100,000/μl Elevated liver enzymes Severe epigastric pain Acute kidney injury (Cr > 1.1 mg/dl or baseline Cr × 2) Pulmonary edema New neurologic or visual disturbance	Proteinuria (> 1+ or 30 mg/dl on automated dipstick, followed by protein/Cr ratio > 0.3 g/g Cr) OR any of the following severe features†: Acute kidney injury (Cr > 1 mg/dl) Elevated liver enzymes Epigastric pain Neurologic disturbance Hematologic complications: -Platelets < 150,000/μl -Disseminated intravascular coagulation -Hemolysis Utero-placental dysfunction, including IUGR Any of the severe features above†, with the exception that IUGR can be part of chronic hypertension and therefore cannot be used as a diagnostic criterion for superimposed preeclampsia
Preeclampsia superimposed on chronic hypertension	Worsening blood pressure or need for additional antihypertensive therapy. After 20 weeks' gestation	Any of the severe features* listed above. In women with proteinuria predating pregnancy, a significant and sustained increase in proteinuria may indicate the presence of superimposed preeclampsia	

SBP systolic blood pressure, *DBP* diastolic blood pressure, *Cr* creatinine, *IUGR* intrauterine growth restriction

interface and the vasculature, is also dysregulated in the setting of preeclampsia [36].

While the placenta is a critical factor in the pathogenesis of preeclampsia, there are several pathways, both up and downstream, that are important to consider when evaluating the bidirectional relationship between kidney disease and preeclampsia. We will next review the observational evidence linking kidney disease and preeclampsia, and discuss potential pathogenic mechanisms.

Observational Evidence: Kidney Disease as a Risk Factor for Preeclampsia

CKD is a well-established risk factor for the development of preeclampsia [12, 37]. The risk of preeclampsia appears to be related to both the degree of glomerular filtration rate (GFR) reduction, as well as to the presence or absence of hypertension. Hypertension is a significant risk factor for preeclampsia, in women with and without kidney dysfunction. In pregnancies complicated by chronic hypertension, approximately 15–25% will develop superimposed preeclampsia [17, 38]. However, preeclampsia risk also appears to be related directly to GFR, which is particularly well-demonstrated in pregnancies of living kidney donors without significant hypertension [11, 39, 40]. A Norwegian birth registry study found that women were more likely to have preeclampsia after kidney donation (5.7%) as compared to before donation (2.6%, p = 0.026), though there was not an increased risk of adverse fetal outcomes [40]. None of the kidney donors with preeclampsia after delivery had a diagnosis of chronic hypertension. A study evaluating pregnancy outcomes after donation in Ontario, Canada, also demonstrated an increased risk of preeclampsia after kidney donation as compared to matched controls (11% vs. 5%, odds ratio (OR) 2.7, 95% confidence interval (CI) 1.2–5.0) [11•]. Similar to the Norwegian study, there was no increase in the risk of preterm birth, low birth weight, stillbirth or neonatal death in pregnancies after kidney donation. These findings suggest that most of the preeclampsia occurred at term and was without severe features, i.e., a "maternal" phenotype of preeclampsia. Women with single kidneys due to unilateral renal agenesis have also been shown to have an increased risk of preeclampsia or eclampsia (OR, 2.41; 95% CI, 1.23–4.72) [41]. A recent study found that a prior episode of resolved acute kidney injury may increase the risk of preeclampsia in future pregnancies [13]. Taken together, these observational studies suggest that a reduction in GFR, even if mild and/or transient, can increase the risk of preeclampsia. In women with a diagnosis of CKD, either due to systemic or kidney-limited disease, the risk of preeclampsia and adverse pregnancy outcomes can be even more striking, with the presence of preexisting hypertension and baseline proteinuria further modifying the risk. Preeclampsia can be a difficult diagnosis to make in women with established CKD

due to presence of preexisting hypertension and proteinuria, which will tend to progressively worsen over the course of pregnancy [42–44]. Therefore, a sudden and sustained increase in blood pressure and proteinuria are often used to diagnose preeclampsia superimposed on CKD. In a classic study of pregnancy outcomes in women with advanced kidney disease (defined as a Cr of at least 1.4 mg/dl or higher), nearly half of women developed hypertension and high-grade proteinuria by the third trimester and 59% had preterm delivery [45]. In the Torino-Cagliari Observational Study (TOCOS) of 504 pregnancies in women with CKD, the risk for new onset hypertension and doubling of proteinuria, indicative of superimposed preeclampsia, increased across CKD stages, from 8% in stage 1 CKD to approximately 50% in stage 3–5 CKD [37]. Among women with stage 1 CKD, the risk of adverse outcomes (preterm delivery, need for neonatal intensive care unit, small-for gestational age infant) increased in the presence of baseline hypertension and proteinuria > 1 g/24 h. A meta-analysis published in 2015 evaluated the maternal complications of pregnancy in women with CKD [46]. The authors reviewed 23 observational studies, with data on 506,340 pregnancies in women with CKD, excluding women with systemic lupus erythematosus, hereditary renal diseases, kidney transplants, ESKD, acute kidney injury, or a solitary kidney. They found that women with CKD had increased odds of developing preeclampsia (OR 10.36, 95% CI 6.28–17.09), premature delivery (OR 5.72, 95% CI 3.26–10.03), small for gestational age infants (OR 4.85, 95% CI 3.03–7.76) and stillbirth, fetal and neonatal death (OR 1.80, 95% CI 1.03–3.13). In a subgroup analysis, they found that women with macroproteinuria had an increased odds of developing preeclampsia compared to those without ($p = 0.01$).

Given the difficulty in diagnosing preeclampsia in CKD, there has been interest in the use of the biomarkers in women with CKD to differentiate true, "superimposed" preeclampsia from worsening hypertension or proteinuria in pregnancy from other causes (Table 2). In a longitudinal study of women with chronic hypertension and chronic kidney disease, a PlGF concentration below the 5th percentile, assessed between 20 and 36 weeks, had high diagnostic accuracy for superimposed preeclampsia requiring delivery in the following 2 weeks [49••]. sFlt-1 levels, though increased in women with superimposed preeclampsia, did not add diagnostic accuracy in this cohort. A recent biomarker analysis of 15 women with CKD and superimposed preeclampsia, as compared to several other control groups (gestational age- and CKD stage-matched pregnant controls, women with preeclampsia and no CKD, women with normotensive pregnancies and non-pregnant women with CKD), found that plasma hyaluronan and vascular cell adhesion molecule (VCAM) were elevated in the setting of superimposed preeclampsia in women with CKD and correlated with PlGF concentrations [51•]. Other markers, such as markers of complement activation and tubular injury (kidney injury molecular-1 and urinary lipocalin-2) were not discriminatory, though complement factor H was lower in women preeclampsia compared to women with normal pregnancy. These biomarkers may be useful in the clinical setting, and may also provide insight into the pathogenesis of preeclampsia in women with CKD, discussed further below.

Pathogenesis: Linking Kidney Disease to Preeclampsia

Despite the large body of evidence that kidney disease increases the risk of preeclampsia, the exact mechanism linking the two diseases is unclear (Fig. 1). CKD itself results in systemic endothelial dysfunction that could create an environment that both impairs placental and fetal development, as well as predispose to the development of preeclampsia [53]. One emerging area of interest in CKD is the glycocalyx, a polysaccharide layer that lines the endothelium and is a marker of endothelial integrity [54]. The glycocalyx is thought to protect the vessel wall and may prevent cardiovascular injury. In a study of patients with CKD, two components of the glycocalyx, syndecan-1 and hyaluronan, were found to increase across CKD stages and strongly correlated with markers of endothelial dysfunction, such as soluble VCAM-1 and sFlt-1 [54]. The authors also demonstrated a decreased glycocalyx thickness in 5/6 nephrectomized rats. A study by Dane et al. measured the glycocalyx by a noninvasive sidestream-darkfield imaging methodology in subjects with ESKD before and after transplant [55•]. They found that there was significant thinning of the glycocalyx in ESKD, but transplant was able to restore the integrity of the endothelium. There is also evidence that the glycocalyx is impaired in the setting of preeclampsia. A study by Weissgerber et al., using the same non-invasive sidestream-darkfield imaging, found that early onset preeclampsia is associated with impaired glycocalyx integrity [56•]. The finding of elevated levels of hyaluronan, a glycocalyx component, in women with superimposed preeclampsia in the setting of CKD cited previously [51•], support the theory that systemic endothelial dysfunction, and perhaps impaired glycocalyx integrity, contribute to preeclampsia risk in CKD.

The complement system has also been implicated in the pathogenesis of preeclampsia and in multiple kidney diseases, creating a potential pathogenic link [57]. Women with severe features of preeclampsia have been shown to have elevated levels of terminal complement pathway activation (C5b-9) in the urine [58•]. C5a levels have been associated with increased blood pressure, arterial stiffness, and trophoblast dysfunction [59]. Eculizumab, a complement C5a inhibitor, has been used in a few women with HELLP syndrome and may have prolonged gestation, though data is limited [60]. While a small study suggested that women with HELLP syndrome

may have an increased frequency of mutations in alternative complement pathway genes [61], clear pathologic germline mutations in complement genes have not been identified in all women with preeclampsia [62]. Given the significant phenotypic overlap, providers need to have a high index of suspicion for atypical hemolytic uremic syndrome (aHUS) in patients presenting with severe preeclampsia, particularly in the postpartum period when aHUS is most likely to present [63]. As our understanding of the complement pathway and the clinical relevance of gene variants of unknown significance increase, the role of complement in preeclampsia may become clearer, and also open the door to new therapeutic interventions for both conditions.

RAAS is also dysregulated in the setting of preeclampsia. In normal pregnancy, there are elevated levels of renin, angiotensin II, and aldosterone; however, pregnant women have a relative resistance to these vasoconstrictive factors. Pregnant women have a natural aldosterone inhibitor in the form of progesterone, which attenuates sodium reabsorption by competitively inhibiting the mineralocorticoid receptor in the kidney [64]. In preeclampsia, women paradoxically have lower renin, angiotensin II, and aldosterone levels than in normal pregnancy, but have an exaggerated response to angiotensin II [24, 65]. In a small cross-sectional study, women with CKD and a diagnosis of superimposed preeclampsia ($n = 11$), women with preeclampsia ($n = 9$), and women with CKD and no preeclampsia ($n = 8$) had various biomarkers, including RAAS components, assessed in the third trimester [50•]. They found that women with preeclampsia, either with no CKD or superimposed on CKD, had lower urinary levels of tetrahydroaldosterone, lower plasma renin, and lower PlGF than women with CKD, suggesting that RAAS disruption is

Table 2 Biomarkers for superimposed preeclampsia in chronic kidney disease

Biomarker subgroup	Biomarkers evaluated for preeclampsia	Abnormal or discriminatory markers in superimposed preeclampsia in women with CKD
Angiogenic	sFlt-1 PlGF	Rolfo et al. [47]: sFlt-1 significantly elevated and PlGF significantly decreased in women with superimposed preeclampsia as compared to women with CKD and normal pregnancy.
		Masuyama et al. [48]: sFlt-1 significantly elevated and PlGF significantly decreased in women with superimposed preeclampsia as compared to pregnant women with CKD and normal blood pressure and matched controls.
		Bramham et al. [49]: low PlGF (< 5 percentile) predicted delivery due to preeclampsia within 2 weeks. sFlt-1 elevated but not discriminatory in women with superimposed preeclampsia as compared to women with CKD without preeclampsia, preeclampsia, and healthy controls.
		Kurlak et al. [50]: lower PlGF levels in women with superimposed preeclampsia as compared to women with preeclampsia, CKD, and normotensive pregnancy.
Renin-angiotensin-aldosterone system	Plasma renin Plasma angiotensinogen Urine angiotensinogen Urine tetrahydroaldosterone	Wiles et al. [51]: urinary angiotensinogen-creatinine ratio higher and plasma renin lower in superimposed preeclampsia than CKD alone. No difference in plasma angiotensinogen.
		Kurlak et al. [50]: lower plasma renin and lower urine tetrahydroaldosterone in superimposed preeclampsia than in women with CKD, but similar levels to women with preeclampsia alone. Lower urinary angiotensinogen in women with superimposed preeclampsia than women with preeclampsia.
Complement pathway	C3a, C5a, C5b-9 Complement Factor H	Wiles et al. [51]: no significant differences in complement markers in superimposed preeclampsia.
Immunologic	Urinary IgM	Leanos-Miranda et al. [52]: higher urinary IgM in women with CKD who develop adverse pregnancy outcomes, including preeclampsia, as compared to women with CKD and no adverse pregnancy outcomes.
Endothelial	Serum hyaluronan VCAM	Wiles et al. [51]: serum hyaluronan and VCAM elevated in superimposed preeclampsia and correlated with PlGF, but not GFR.

CKD chronic kidney disease, *sFlt-1* soluble fms-like tyrosine kinase 1, *PlGF* placental growth factor, *C* complement, *IgM* immunoglobulin M, *VCAM* vascular cell adhesion protein, *GFR* glomerular filtration rate

similar in superimposed preeclampsia and preeclampsia alone. However, there were lower levels of urinary angiotensinogen in women with CKD and superimposed preeclampsia than in women preeclampsia alone. In the previously cited study of biomarkers in superimposed preeclampsia, the authors found that women with preeeclampsia superimposed on CKD had higher levels of urinary angiotensinogen than women with CKD alone; however, the levels of urinary angiotensinogen did not correlate with PlGF [51•]. These studies suggest that intrarenal production of angiotensinogen may be relevant in preeclampsia pathogenesis. Women with preeclampsia may also have agonistic autoantibodies against the angiotensin AT1 receptor [66]. These antibodies have been implicated in the initial failure of trophoblast invasion of preeclamptic placentas and can also stimulate sFlt-1 secretion, suggesting a possible pathogenic role in preeclampsia [67, 68], though they have not been studied specifically in the CKD population. The role of RAAS in preeclampsia pathogenesis in women with and without CKD is an active area of interest and the use of RAAS biomarkers requires future study.

Observational Evidence: Preeclampsia as a Risk Factor for Kidney Disease

There are now many observational studies linking preeclampsia to the future risk of kidney disease, from "milder" kidney dysfunction characterized by albuminuria [69–71] to more severe and rare disease, such as ESKD [6, 7]. A meta-analysis of 7 cohort studies, including 273 women with preeclampsia and 333 women with uncomplicated pregnancies, found that 31% of women with preeclampsia had microalbuminuria, as compared to 7% of women with uncomplicated pregnancies, an average of 7.1 years postpartum [3]. Women with severe preeclampsia had an ever higher risk of developing microalbuminuria, with an 8-fold increase over women with uncomplicated pregnancies. A history of hypertension in pregnancy was associated with an increased risk of microalbuminuria (OR 1.37, 95% CI 1.02–1.85) decades after an affected pregnancy in a secondary analysis of the Family Blood Pressure Program [4]. There are some studies that have not found an increased risk for microalbuminuria after preeclampsia, which could be related to issues of power and/or length of follow-up [72, 73]. Albuminuria is not just a marker of kidney dysfunction but is also associated with increased cardiovascular disease risk [74]. As preeclampsia is also associated with cardiovascular disease [75–77], albuminuria may be a useful marker to follow after delivery.

Preeclampsia has been associated with the development of CKD and ESKD in several studies, though with some exceptions. Vikse and colleagues, using the Norwegian birth registry, found that women with preeclampsia in their first pregnancy are at an increased risk of developing ESKD (relative risk 4.7, 95% CI 3.6–6.1), though the absolute risk was still quite low (14.5 per 100,000 person-years) [6]. A Taiwanese study found that hypertensive pregnancy disorders, in general, were associated with an increased risk of both CKD (hazard ratio (HR) 9.38, 95% CI 7.09–12.4) and ESKD (HR 12.4, 95% CI 8.5418.0), and that women with preeclampsia were at an even higher risk than those with gestational hypertension [5]. A study using the Prevention of Renal and Vascular End Stage Disease (PREVEND) cohort data, did not find a significantly increased risk of CKD or ESKD in women who reported a hypertensive disorder of pregnancy (HR 1.04, 95% CI 0.79–1.37). They did find a slightly steeper decline in eGFR over the course of follow-up in women with a hypertensive pregnancy as compared to those without (98 to 88 ml/min/1.73 m^2 as compared to 99 to 91 ml/min/1.73 m^2, p = 0.05), but this was likely not a clinically meaningful change. The authors were not able to separate preeclampsia from other hypertensive disorders of pregnancy, which is an important limitation of this study. A recent meta-analysis by Piccoli et al. found that preeclampsia is significantly associated with a risk of ESKD, but they found insufficient data for albuminuria and CKD [8]. They also reported that the number of women needed to follow after a preeclamptic pregnancy to detect one adverse event was 310 for ESKD, but only 4 for albuminuria.

We conducted a population-based study using the Olmsted County, MN, population and identified women with ESKD by using the US Renal Database System and also found an increased risk odds of developing ESKD after preeclampsia (OR 4.0, 95% CI 1.21–13.28), similar to the Norwegian and Taiwanese data [7]. Unique to our study was our ability to review pre-pregnancy medical records. We found that among 44 ESRD cases, 21% had evidence of kidney dysfunction prior to pregnancy that was often undiagnosed and only evident by serum Cr and protein measurements. This finding highlights the difficulty in proving the pathogenic link between preeclampsia and kidney disease.

Pathogenesis: Linking Preeclampsia to Kidney Disease

One of the most challenging factors in unraveling the relationship between preeclampsia and CKD is the role that undiagnosed, preexisting kidney disease plays in this observed relationship. Even mild, stage 1 CKD has been associated with an increased risk of preeclampsia [12]. As women may not routinely seek medical care prior to pregnancy, it is difficult to know whether conditions such as kidney disease or hypertension may have been present for some time prior to a first prenatal visit. Serum creatinine is not a routine screening test in the general population, nor in an otherwise uncomplicated pregnancy.

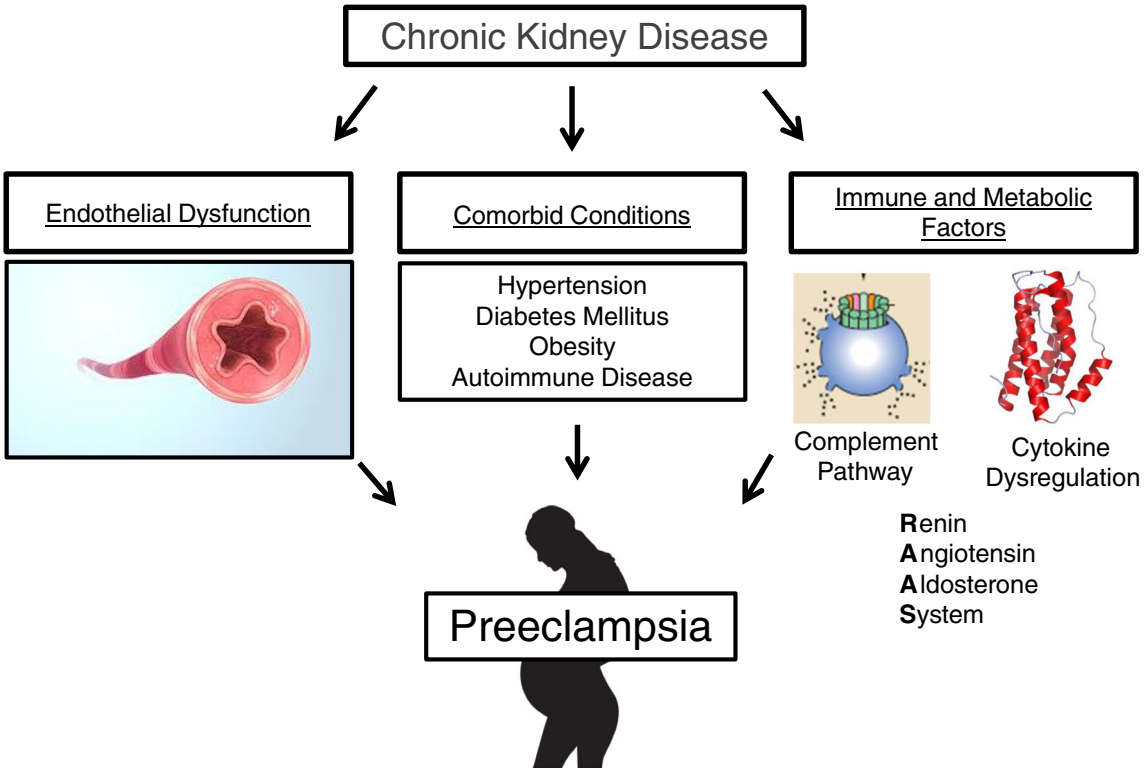

Fig. 1 Chronic kidney disease Increases the risk of preeclampsia by multiple mechanisms. Mechanisms discussed include endothelial dysfunction, comorbid conditions, and immune and metabolic factors, such as complement pathway abnormalities, the renin-angiotensin-aldosterone dysfunction, and abnormal cytokine profiles

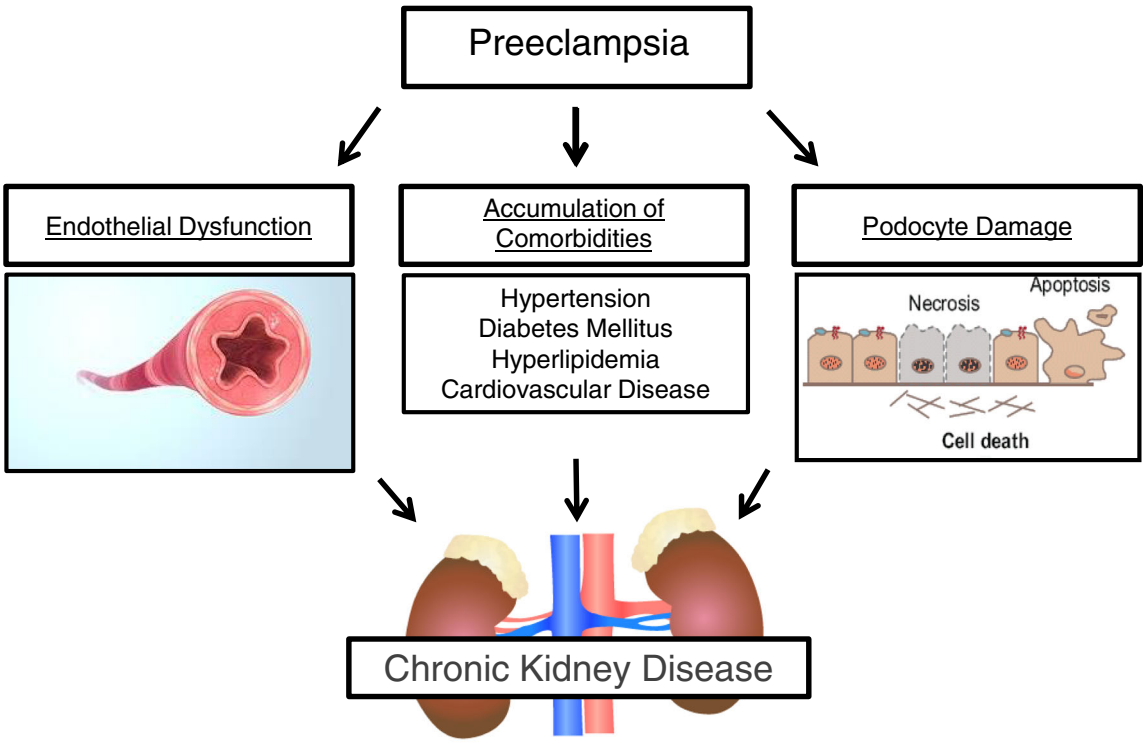

Fig. 2 Preeclampsia increases the risk of chronic kidney disease by multiple mechanisms. Mechanisms discussed include endothelial dysfunction, accelerated accumulation of comorbidities, and podocyte damage

It is likely that at least some of the observed risk of future kidney disease is due to prepregnancy kidney disease. Our study noted that 21% of women who went on to develop ESKD had some kidney dysfunction prior to pregnancy, which is remarkably similar to the percentage of women found to have underlying glomerular disease in biopsy series. In a study by Murakami et al., the authors performed postpartum renal biopsies in women with severe hypertension or proteinuria in pregnancy and found that 19 women (22.1%) had underlying kidney disease, most often IgA nephropathy [78]. In the study by Fisher et al., with 176 kidney biopsies of women with preeclampsia in the postpartum period, 31 out of 176 (17.6%) of women had glomerular disease identified on kidney biopsy [1]. Given that most of the studies linking preeclampsia to ESKD are registry-based, few women have prepregnancy testing of kidney function, even fewer have postpartum biopsies and proteinuria is not always followed to resolution, there is no good way to quantify the degree of confounding in the general population.

However, there are several plausible mechanisms linking preeclampsia to future CKD, irrespective of underlying kidney disease (Fig. 2). Kidney biopsy samples have clear evidence of endothelial damage, in the form glomerular endotheliosis and vascular injury [1]. As noted previously, early onset set preeclampsia is associated with damage to the glycocalyx, which may predispose to future kidney disease [56•]. Preeclampsia is one of the most common causes of acute kidney injury in pregnancy, and acute kidney injury is a known risk factor for the development of CKD [79, 80]. Preeclampsia may also indirectly increase the future risk of kidney disease by increasing the occurrence of hypertension, diabetes, and hyperlipidemia and other metabolic disturbances that predispose to CKD [81, 82].

Another potential pathway to future kidney disease after preeclampsia is through damage to the podocyte. In an autopsy study, Garovic et al. were able to identify a significant reduction in nephrin and synaptopodin staining in the kidney tissue of women who died from complications of preeclampsia as compared to pregnant women that died from other causes [83]. In a subsequent study of 15 women with preeclampsia and 15 women with normotensive pregnancies, podocin-positive podocytes were identified in all of the women with preeclampsia and none of the normotensive women [84]. A larger prospective study found that women who went on to develop preeclampsia all had podocyturia present in the second trimester, as compared to women who had normotensive pregnancies or gestational hypertension [85••]. While a Danish study did not find the same reduction in podocyte number in kidney tissue as the previous autopsy study, they did identify a significant increase in the proliferation index of podocytes, suggesting increased podocyte turnover [86]. Loss of urinary podocytes can persist in the postpartum period, as well, which could reflect ongoing, subclinical kidney injury and a future link to kidney disease [87]. Podocyturia is seen in patients with focal segmental glomerular sclerosis (FSGS) [88], which has been identified as a the most common pathologic pattern in kidney biopsies from women with persistent proteinuria after preeclamptic pregnancies [89]. In a review of 13 biopsies performed up to 10 months postpartum in women with varying degrees of proteinuria and no known history of kidney disease, FSGS was found in 8 of 13 kidney biopsies [89].

Conclusion

Our understanding of the pathogenesis of preeclampsia and the potential for long-term, systemic disease is constantly evolving. Multiple lines of evidence point to a future risk of kidney disease after a preeclamptic pregnancy. While underlying, subclinical kidney disease likely confounds this association in part, there are multiple potential pathways from preeclampsia to future CKD, such as the accelerated accumulation of comorbidities, direct endothelial injury, acute kidney injury, and podocyte damage. Understanding how CKD increases the risk of preeclampsia from a mechanistic standpoint may open the door to future biomarkers and therapeutics for all women, particularly in the complement and RAAS pathways. Heightened awareness of the association between preeclampsia and CKD among primary providers and obstetricians will hopefully help identify women with undiagnosed CKD who have preeclampsia as their first manifestation of disease. As albuminuria is a marker of endothelial integrity and is associated with preeclampsia, kidney disease risk, and cardiovascular disease, it may be an ideal longitudinal, prognostic marker for women with a history of preeclampsia, to identify a higher risk population. Given the growing body of evidence that preeclampsia is a sex-specific risk factor for CKD, there will hopefully be an emphasis on including an obstetrical history in the routine work-up of CKD.

Funding Dr. Kattah is supported by the Catalyst Award from the Department of Medicine, Mayo Clinic, Rochester, MN.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Fisher KA, Luger A, Spargo BH, Lindheimer MD. Hypertension in pregnancy: clinical-pathological correlations and remote prognosis. Medicine (Baltimore). 1981;60(4):267–76.
2. Nochy D, Birembaut P, Hinglais N, Freund M, Idatte JM, Jacquot C, et al. Renal lesions in the hypertensive syndromes of pregnancy: immunomorphological and ultrastructural studies in 114 cases. Clin Nephrol. 1980;13(4):155–62.
3. McDonald SD, Han Z, Walsh MW, Gerstein HC, Devereaux PJ. Kidney disease after preeclampsia: a systematic review and meta-analysis. Am J Kidney Dis. 2010;55(6):1026–39.
4. Kattah AG, Asad R, Scantlebury DC, Bailey KR, Wiste HJ, Hunt SC, et al. Hypertension in pregnancy is a risk factor for microalbuminuria later in life. J Clin Hypertens (Greenwich). 2013;15(9):617–23.
5. Wang IK, Muo CH, Chang YC, Liang CC, Chang CT, Lin SY, et al. Association between hypertensive disorders during pregnancy and end-stage renal disease: a population-based study. Cmaj. 2013;185(3):207–13.
6. Vikse BE, Irgens LM, Leivestad T, Skjaerven R, Iversen BM. Preeclampsia and the risk of end stage renal disease. N Engl J Med. 2008;359(8):800–9.
7. Kattah AG, Scantlebury DC, Agarwal S, Mielke MM, Rocca WA, Weaver AL, et al. Preeclampsia and ESRD: the role of shared risk factors. Am J Kidney Dis. 2017;69(4):498–505.
8. •• Covella B, Vinturache AE, Cabiddu G, Attini R, Gesualdo L, Versino E, et al. A systematic review and meta-analysis indicates long-term risk of chronic and end-stage kidney disease after pre-eclampsia. Kidney Int. 2019;96(3):711–27 **Recent meta-analysis of studies looking at the association between preeclampsia and kidney disease**.
9. Saftlas A, Wang W, Risch H, Woolson R, Hsu C, Bracken M. Prepregnancy body mass index and gestational weight gain as risk factors for preeclampsia and transient hypertension. Ann Epidemiol. 2000;10(7):475.
10. Wallis AB, Saftlas AF, Hsia J, Atrash HK. Secular trends in the rates of preeclampsia, eclampsia, and gestational hypertension, United States, 1987-2004. Am J Hypertens. 2008;21(5):521–6.
11. • Garg AX, Nevis IF, McArthur E, Sontrop JM, Koval JJ, Lam NN, et al. Gestational hypertension and preeclampsia in living kidney donors. N Engl J Med. 2015;372(2):124–33 **Study demonstrating that living kidney donors have an increased risk of preeclampsia after donation**.
12. Piccoli GB, Attini R, Vasario E, Conijn A, Biolcati M, D'Amico F, et al. Pregnancy and chronic kidney disease: a challenge in all CKD stages. Clin J Am Soc Nephrol. 2010;5(5):844–55.
13. Tangren JS, Powe CE, Ankers E, Ecker J, Bramham K, Hladunewich MA, et al. Pregnancy outcomes after clinical recovery from AKI. J Am Soc Nephrol 2016.
14. Sibai BM, Lindheimer M, Hauth J, Caritis S, VanDorsten P, Klebanoff M, et al. Risk factors for preeclampsia, abruptio placentae, and adverse neonatal outcomes among women with chronic hypertension. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. N Engl J Med. 1998;339(10):667–71.
15. Kattah AG, Garovic VD. From delivery to Dialysis: does pre-eclampsia count? Am J Kidney Dis. 2018;71(5):601–4.
16. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol. 2013;122(5):1122–31.
17. Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, et al. Hypertensive disorders of pregnancy: ISSHP classification, diagnosis, and management recommendations for international practice. Hypertension. 2018;72(1):24–43.
18. Sibai BM, Stella CL. Diagnosis and management of atypical pre-eclampsia-eclampsia. Am J Obstet Gynecol. 2009;200(5):481 e1–7.
19. Stella CL, Malik KM, Sibai BM. HELLP syndrome: an atypical presentation. Am J Obstet Gynecol. 2008;198(5):e6–8.
20. Schroeder BM. ACOG practice bulletin on diagnosing and managing preeclampsia and eclampsia. American College of Obstetricians and Gynecologists. Am Fam Physician. 2002;66(2):330–1.
21. Almeida ST, Katz L, Coutinho I, Amorim MMR. Validation of fullPIERS model for prediction of adverse outcomes among women with severe pre-eclampsia. Int J Gynaecol Obstet. 2017;138(2):142–7.
22. Cote AM, Brown MA, Lam E, von Dadelszen P, Firoz T, Liston RM, et al. Diagnostic accuracy of urinary spot protein:creatinine ratio for proteinuria in hypertensive pregnant women: systematic review. BMJ. 2008;336(7651):1003–6.
23. Zhao M, Yin Y, Wei J, Wu M, Yang C, Chen Q. Trophoblastic debris extruded from hydatidiform molar placentae activates endothelial cells: possible relevance to the pathogenesis of preeclampsia. Placenta. 2016;45:42–9.
24. Granger JP, Alexander BT, Llinas MT, Bennett WA, Khalil RA. Pathophysiology of hypertension during preeclampsia linking placental ischemia with endothelial dysfunction. Hypertension. 2001;38(3 Pt 2):718–22.
25. Robertson WB, Brosens I, Dixon HG. The pathological response of the vessels of the placental bed to hypertensive pregnancy. J Pathol Bacteriol. 1967;93(2):581–92.
26. Redman CW, Sargent IL. Latest advances in understanding pre-eclampsia. Science. 2005;308(5728):1592–4.
27. Matthys LA, Coppage KH, Lambers DS, Barton JR, Sibai BM. Delayed postpartum preeclampsia: an experience of 151 cases. Am J Obstet Gynecol. 2004;190(5):1464–6.
28. Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. BMJ. 2005;330(7491):565.
29. Karumanchi SA, Maynard SE, Stillman IE, Epstein FH, Sukhatme VP. Preeclampsia: a renal perspective. Kidney Int. 2005;67(6):2101–13.
30. Xiong X, Demianczuk NN, Saunders LD, Wang FL, Fraser WD. Impact of preeclampsia and gestational hypertension on birth weight by gestational age. Am J Epidemiol. 2002;155(3):203–9.
31. Craici IM, Wagner SJ, Weissgerber TL, Grande JP, Garovic VD. Advances in the pathophysiology of pre-eclampsia and related podocyte injury. Kidney Int. 2014;86:275–85.
32. Maynard SE, Min JY, Merchan J, Lim KH, Li J, Mondal S, et al. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. J Clin Invest. 2003;111(5):649–58.
33. Zeisler H, Llurba E, Chantraine F, Vatish M, Staff AC, Sennstrom M, et al. Predictive value of the sFlt-1:PlGF ratio in women with suspected preeclampsia. N Engl J Med. 2016;374(1):13–22.
34. Rana S, Powe CE, Salahuddin S, Verlohren S, Perschel FH, Levine RJ, et al. Angiogenic factors and the risk of adverse outcomes in women with suspected preeclampsia. Circulation. 2012;125(7):911–9.
35. LaMarca BD, Ryan MJ, Gilbert JS, Murphy SR, Granger JP. Inflammatory cytokines in the pathophysiology of hypertension during preeclampsia. Curr Hypertens Rep. 2007;9(6):480–5.

36. Cubro H, Kashyap S, Nath MC, Ackerman AW, Garovic VD. The role of interleukin-10 in the pathophysiology of preeclampsia. Curr Hypertens Rep. 2018;20(4):36.
37. Piccoli GB, Cabiddu G, Attini R, Vigotti FN, Maxia S, Lepori N, et al. Risk of adverse pregnancy outcomes in women with CKD. J Am Soc Nephrol. 2015;26(8):2011–22.
38. Bartsch E, Medcalf KE, Park AL, Ray JG, High Risk of Pre-eclampsia Identification G. Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. BMJ. 2016;353:i1753.
39. Ibrahim HN, Akkina SK, Leister E, Gillingham K, Cordner G, Guo H, et al. Pregnancy outcomes after kidney donation. Am J Transplant. 2009;9(4):825–34.
40. Reisaeter AV, Roislien J, Henriksen T, Irgens LM, Hartmann A. Pregnancy and birth after kidney donation: the Norwegian experience. Am J Transplant. 2009;9(4):820–4.
41. Kendrick J, Holmen J, You Z, Smits G, Chonchol M. Association of unilateral renal agenesis with adverse outcomes in pregnancy: a matched cohort study. Am J Kidney Dis. 2017;70(4):506–11.
42. Kattah A, Milic N, White W, Garovic V. Spot urine protein measurements in normotensive pregnancies, pregnancies with isolated proteinuria and preeclampsia. Am J Phys Regul Integr Comp Phys. 2017;313(4):R418–R24.
43. Higby K, Suiter CR, Phelps JY, Siler-Khodr T, Langer O. Normal values of urinary albumin and total protein excretion during pregnancy. Am J Obstet Gynecol. 1994;171(4):984–9.
44. Lindheimer MD, Kanter D. Interpreting abnormal proteinuria in pregnancy: the need for a more pathophysiological approach. Obstet Gynecol. 2010;115(2 Pt 1):365–75.
45. Jones DC, Hayslett JP. Outcome of pregnancy in women with moderate or severe renal insufficiency. N Engl J Med. 1996;335(4):226–32.
46. Zhang JJ, Ma XX, Hao L, Liu LJ, Lv JC, Zhang H. A systematic review and meta-analysis of outcomes of pregnancy in CKD and CKD outcomes in pregnancy. Clin J Am Soc Nephrol. 2015;10(11):1964–78.
47. Rolfo A, Attini R, Nuzzo AM, Piazzese A, Parisi S, Ferraresi M, et al. Chronic kidney disease may be differentially diagnosed from preeclampsia by serum biomarkers. Kidney Int. 2013;83(1):177–81.
48. Masuyama H, Nobumoto E, Okimoto N, Inoue S, Segawa T, Hiramatsu Y. Superimposed preeclampsia in women with chronic kidney disease. Gynecol Obstet Investig. 2012;74(4):274–81.
49.•• Bramham K, Seed PT, Lightstone L, Nelson-Piercy C, Gill C, Webster P, et al. Diagnostic and predictive biomarkers for pre-eclampsia in patients with established hypertension and chronic kidney disease. Kidney Int. 2016;89(4):874–85 **This study addresses the use of angiogenic markers in differentiating pre-eclampsia superimposed on CKD from other changes in blood pressure and proteinuria that may occur normally in pregnancy. They found that a low PlGF predicted delivery within the next 2 weeks**.
50.• Kurlak LO, Broughton Pipkin F, Mohaupt MG, Mistry HD. Responses of the renin-angiotensin aldosterone system in pregnant chronic kidney disease patients with and without superimposed pre eclampsia. Clin Kidney J. 2019;12(6):847–54 **This study looks at markers of the RAAS system and how they may differentiate superimposed preeclampsia from preeclampsia and CKD**.
51.• Wiles K, Bramham K, Seed PT, Kurlak LO, Mistry HD, Nelson-Piercy C, et al. Diagnostic indicators of superimposed preeclampsia in women with CKD. Kidney Int Rep. 2019;4(6):842–53 **This study looks at the use of other biomarkers to diagnose superimposed preeclampsia and found that hyaluronan and V-CAM-1 did differentiate superimposed preeclampsia from preeclampsia and CKD alone**.
52. Leanos-Miranda A, Campos-Galicia I, Ramirez-Valenzuela KL, Berumen-Lechuga MG, Isordia Salas I, Molina-Perez CJ. Urinary IgM excretion: a reliable marker for adverse pregnancy outcomes in women with chronic kidney disease. J Nephrol. 2019;32(2):241–51.
53. Malyszko J. Mechanism of endothelial dysfunction in chronic kidney disease. Clin Chim Acta. 2010;411(19–20):1412–20.
54. Padberg JS, Wiesinger A, di Marco GS, Reuter S, Grabner A, Kentrup D, et al. Damage of the endothelial glycocalyx in chronic kidney disease. Atherosclerosis. 2014;234(2):335–43.
55.• Dane MJ, Khairoun M, Lee DH, van den Berg BM, Eskens BJ, Boels MG, et al. Association of kidney function with changes in the endothelial surface layer. Clin J Am Soc Nephrol. 2014;9(4):698–704 **This study demonstrates that chronic kidney disease is associated with poor integrity of the glycocalyx**.
56.• Weissgerber TL, Garcia-Valencia O, Milic NM, Codsi E, Cubro H, Nath MC, et al. Early onset preeclampsia is associated with glycocalyx degradation and reduced microvascular perfusion. J Am Heart Assoc. 2019;8(4):e010647 **This study demonstrates that early onset preeclampsia is characterized by poor glycocalyx integrity**.
57. Thurman JM. Complement in kidney disease: core curriculum 2015. Am J Kidney Dis. 2015;65(1):156–68.
58.• Burwick RM, Velasquez JA, Valencia CM, Gutierrez-Marin J, Edna-Estrada F, Silva JL, et al. Terminal complement activation in preeclampsia. Obstet Gynecol. 2018;132(6):1477–85 **Women with severe preeclampsia had elevated levels of terminal complement pathway in urine samples**.
59. Ma Y, Kong LR, Ge Q, Lu YY, Hong MN, Zhang Y, et al. Complement 5a-mediated trophoblasts dysfunction is involved in the development of pre-eclampsia. J Cell Mol Med. 2018;22(2):1034–46.
60. Burwick RM, Feinberg BB. Eculizumab for the treatment of preeclampsia/HELLP syndrome. Placenta. 2013;34(2):201–3.
61. Vaught AJ, Braunstein EM, Jasem J, Yuan X, Makhlin I, Eloundou S, et al. Germline mutations in the alternative pathway of complement predispose to HELLP syndrome. Jci Insight. 2018;3(6).
62. Salmon JE, Heuser C, Triebwasser M, Liszewski MK, Kavanagh D, Roumenina L, et al. Mutations in complement regulatory proteins predispose to preeclampsia: a genetic analysis of the PROMISSE cohort. PLoS Med. 2011;8(3):e1001013.
63. Sibai BM. Imitators of severe preeclampsia. Obstet Gynecol. 2007;109(4):956–66.
64. Odutayo A, Hladunewich M. Obstetric nephrology: renal hemodynamic and metabolic physiology in normal pregnancy. Clin J Am Soc Nephrol. 2012.
65. Irani RA, Xia Y. The functional role of the renin-angiotensin system in pregnancy and preeclampsia. Placenta. 2008;29(9):763–71.
66. Wallukat G, Homuth V, Fischer T, Lindschau C, Horstkamp B, Jupner A, et al. Patients with preeclampsia develop agonistic autoantibodies against the angiotensin AT1 receptor. J Clin Invest. 1999;103(7):945–52.
67. Xia Y, Wen H, Bobst S, Day MC, Kellems RE. Maternal autoantibodies from preeclamptic patients activate angiotensin receptors on human trophoblast cells. J Soc Gynecol Investig. 2003;10(2):82–93.
68. Zhou CC, Ahmad S, Mi T, Abbasi S, Xia L, Day MC, et al. Autoantibody from women with preeclampsia induces soluble Fms-like tyrosine kinase-1 production via angiotensin type 1 receptor and calcineurin/nuclear factor of activated T-cells signaling. Hypertension. 2008;51(4):1010–9.
69. Bar J, Kaplan B, Wittenberg C, Erman A, Boner G, Ben-Rafael Z, et al. Microalbuminuria after pregnancy complicated by preeclampsia. Nephrol Dial Transplant. 1999;14(5):1129–32.
70. North RA, Simmons D, Barnfather D, Upjohn M. What happens to women with preeclampsia? Microalbuminuria and hypertension

following preeclampsia. Aust N Z J Obstet Gynaecol. 1996;36(3): 233–8.
71. Nisell H, Lintu H, Lunell NO, Mollerstrom G, Pettersson E. Blood pressure and renal function seven years after pregnancy complicated by hypertension. Br J Obstet Gynaecol. 1995;102(11):876–81.
72. Jacquemyn Y, Jochems L, Duiker E, Bosmans JL, Van Hoof V, Van Campenhout C. Long-term renal function after HELLP syndrome. Gynecol Obstet Investig. 2004;57(2):117–20.
73. Lampinen KH, Ronnback M, Groop PH, Kaaja RJ. Renal and vascular function in women with previous preeclampsia: a comparison of low- and high-degree proteinuria. Kidney Int. 2006;70(10): 181822.
74. Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. JAMA. 2001;286(4):421–6.
75. Ray JG, Vermeulen MJ, Schull MJ, Redelmeier DA. Cardiovascular health after maternal placental syndromes (CHAMPS): population-based retrospective cohort study. Lancet. 2005;366(9499):1797–803.
76. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. BMJ. 2007;335(7627):974.
77. Garovic VD, Bailey KR, Boerwinkle E, Hunt SC, Weder AB, Curb D, et al. Hypertension in pregnancy as a risk factor for cardiovascular disease later in life. J Hypertens. 2010;28(4):826–33.
78. Murakami S, Saitoh M, Kubo T, Koyama T, Kobayashi M. Renal disease in women with severe preeclampsia or gestational proteinuria. Obstet Gynecol. 2000;96(6):945–9.
79. Nwoko R, Plecas D, Garovic VD. Acute kidney injury in the pregnant patient. Clin Nephrol. 2012;78(6):478–86.
80. Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. Kidney Int. 2012;81(5):442–8.
81. Stuart JJ, Tanz LJ, Missmer SA, Rimm EB, Spiegelman D, James-Todd TM, et al. Hypertensive disorders of pregnancy and maternal cardiovascular disease risk factor development: an observational cohort study. Ann Intern Med. 2018.
82. Heida KY, Franx A, van Rijn BB, Eijkemans MJ, Boer JM, Verschuren MW, et al. Earlier age of onset of chronic hypertension and type 2 diabetes mellitus after a hypertensive disorder of pregnancy or gestational diabetes mellitus. Hypertension. 2015;66: 1116–22.
83. Garovic VD, Wagner SJ, Petrovic LM, Gray CE, Hall P, Sugimoto H, et al. Glomerular expression of nephrin and synaptopodin, but not podocin, is decreased in kidney sections from women with preeclampsia. Nephrol Dial Transplant. 2007;22(4):1136–43.
84. Garovic VD, Wagner SJ, Turner ST, Rosenthal DW, Watson WJ, Brost BC, et al. Urinary podocyte excretion as a marker for preeclampsia. Am J Obstet Gynecol. 2007;196(4):320 e1–7.
85.•• Craici IM, Wagner SJ, Bailey KR, Fitz-Gibbon PD, Wood-Wentz CM, Turner ST, et al. Podocyturia predates proteinuria and clinical features of preeclampsia: longitudinal prospective study. Hypertension. 2013;61(6):1289–96 **Study demonstrating the podocyturia is identified in women who go on to develop preeclampsia**.
86. Penning ME, Bloemenkamp KW, van der Zon T, Zandbergen M, Schutte JM, Bruijn JA, et al. Association of preeclampsia with podocyte turnover. Clin J Am Soc Nephrol. 2014;9(8):1377–85.
87. White WM, Garrett AT, Craici IM, Wagner SJ, Fitz-Gibbon PD, Butters KA, et al. Persistent urinary podocyte loss following preeclampsia may reflect subclinical renal injury. PLoS One. 2014;9(3):e92693.
88. Vogelmann SU, Nelson WJ, Myers BD, Lemley KV. Urinary excretion of viable podocytes in health and renal disease. Am J Physiol Ren Physiol. 2003;285(1):F40–8.
89. Heaton JM, Turner DR. Persistent renal damage following preeclampsia: a renal biopsy study of 13 patients. J Pathol. 1985;147(2):121–6.

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