Proteinuria during pregnancy: definition, pathophysiology, methodology, and clinical significance

Michal Fishel Bartal, MD; Marshall D. Lindheimer, MD; Baha M. Sibai, MD

Introduction

Urinalysis for protein is one of the most commonly performed antenatal screening tests. During pregnancy, proteinuria has traditionally been a hallmark of preeclampsia, but it is also a nonspecific indicator of renal disease and may result from an elevated plasma protein concentration, increased glomerular permeability, decreased tubular protein reabsorption, and renal hemodynamic alterations. It has been reported that the rate of isolated proteinuria in pregnancy may reach 8%, whereas preeclampsia occurs among 3% to 8% of pregnancies. Starting in 2013, proteinuria is considered sufficient but not necessary for the diagnosis of preeclampsia; however, there is an ongoing debate regarding the importance of protein excretion in risk assessment, particularly in women with hypertensive disorders. The purpose of this review is to describe the current knowledge regarding the pathophysiology, definition, methods of assessment, and clinical significance of proteinuria in pregnancy.

From the Division of Maternal-Fetal Medicine, Department of Obstetrics, Gynecology and Reproductive Sciences, McGovern Medical School, The University of Texas Health Science Center at Houston, Houston, TX (Drs Fishel Bartal and Sibai); and Departments of Medicine and Obstetrics and Gynecology, Pritzker School of Medicine, The University of Chicago, Chicago, IL (Dr Lindheimer).

Received July 5, 2020; revised Aug. 24, 2020; accepted Aug. 27, 2020.

The authors report no conflict of interest.

This paper is part of a supplement.

Corresponding author: Michal Fishel Bartal, MD, Michal.f.bartal@uth.tmc.edu

0002-9378/$36.00
Published by Elsevier Inc.
https://doi.org/10.1016/j.ajog.2020.08.108

Qualitative and quantitative measurement of urine protein excretion is one of the most common tests performed during pregnancy. For more than 100 years, proteinuria was necessary for the diagnosis of preeclampsia, but recent guidelines recommend that proteinuria is sufficient but not necessary for the diagnosis. Still, in clinical practice, most patients with gestational hypertension will be diagnosed as having preeclampsia based on the presence of proteinuria. Although the reference standard for measuring urinary protein excretion is a 24-hour urine collection, spot urine protein-to-creatinine ratio is a reasonable “rule-out” test for proteinuria. Urine dipstick screening for proteinuria does not provide any clinical benefit and should not be used to diagnose proteinuria. The classic cutoff cited to define proteinuria during pregnancy is a value of >300 mg/24 hours or a urine protein-to-creatinine ratio of at least 0.3. Using this cutoff, the rate of isolated proteinuria in pregnancy may reach 8%, whereas preeclampsia occurs among 3% to 8% of pregnancies. Although this threshold is widely accepted, its origin is not based on evidence on adverse pregnancy outcomes but rather on expert opinion and results of small studies. After reviewing the available data, the most important factor that influences maternal and neonatal outcome is the severity of blood pressures and presence of end organ damage, rather than the excess protein excretion. Because the management of gestational hypertension and preeclampsia without severe features is almost identical in frequency of surveillance and timing of delivery, the separation into 2 disorders is unnecessary. If the management of women with gestational hypertension with a positive assessment of proteinuria will not change, we believe that urine assessment for proteinuria is unnecessary in women who develop new-onset blood pressure at or after 20 weeks’ gestation. Furthermore, we do not recommend repeated measurement of proteinuria for women with preeclampsia, the amount of proteinuria does not seem to be related to poor maternal and neonatal outcomes, and monitoring proteinuria may lead to unindicated preterm deliveries and related neonatal complications. Our current diagnosis of preeclampsia in women with chronic kidney disease may be based on a change in protein excretion, a baseline protein excretion evaluation is critical in certain conditions such as chronic hypertension, diabetes, and autoimmune or other renal disorders. The current definition of superimposed preeclampsia possesses a diagnostic dilemma, and it is unclear whether a change in the baseline proteinuria reflects another systemic disease such as preeclampsia or whether women with chronic disease such as chronic hypertension or diabetes will experience a different “normal” pattern of protein excretion during pregnancy. Finally, limited data are available regarding angiogenic and other biomarkers in women with chronic kidney disease as a potential aid in distinguishing the worsening of baseline chronic kidney disease and chronic hypertension from superimposed preeclampsia.

Key words: 24-hour urine collection, biomarker, chronic hypertension, diagnosis, gestational hypertension, hypertensive disorder of pregnancy, preeclampsia, pregnancy, pregnancy outcome, podocytes, prognosis, proteinuria, renal disease, superimposed preeclampsia, urine protein-to-creatinine ratio
TABLE 1
Glossary of terms

<table>
<thead>
<tr>
<th>Term</th>
<th>Explanation</th>
</tr>
</thead>
</table>
| Bowman’s capsule          | 1. Part of the nephron that forms a cup-like sack surrounding the glomerulus. It consists of inner (visceral) layer surrounding the glomerulus and outer (parietal) layer.  
2. The Bowman’s capsule encloses a space between those 2 layers, known as the Bowman’s space, which represents the beginning of the urinary space and is contiguous with the proximal convoluted tubule of the nephron. |
| Podocytes                 | Terminally differentiated epithelial cells that have a number of radiating processes (pediciles) that cover the glomerular basement membrane and face the renal pelvis. |
| Slit diaphragm            | Adjacent podocyte foot processes are connected by a specialized intercellular junction known as the slit diaphragm. |
| GFR                       | 1. The volume of fluid filtered from the renal glomerular capillaries into the Bowman’s capsule per unit time.  
2. Can be assessed using the following equation: GFR = (ΔP - πGC) × Kf |
| Transcapillary hydraulic pressure difference (ΔP) | Transcapillary hydraulic pressure difference or the pressure generated across the glomerulus. |
| Mean glomerular intracapillary oncotic pressure (πGC) | Mean of the colloid osmotic pressure within the glomerular capillaries and within the Bowman’s capsule. |
| Glomerular ultrafiltration coefficient (Kf) | The product of the surface area available for filtration and the hydraulic permeability (k), which is the permeability to ultrafiltrate across the glomerulus. |
| Filtration fraction       | 1. The portion of plasma filtered through the cellular layers of the glomerulus.  
2. Calculated by dividing the GFR by the renal plasma flow. |

**GFR:** glomerular filtration rate.


Pathophysiology of Proteinuria
Glomerular and tubular handling of protein

In nonpregnant populations, the urine is almost free of protein and healthy adults excrete <150 mg of protein per day in urine every day. Within the nephron, the glomerular filtration barrier is responsible for the selective filtration of blood from the afferent arteriole to the Bowman’s space (Table 1). The filtration barrier includes 3 layers: the glomerular epithelium, the basement membrane, and the slit diaphragms, which are formed by the foot processes of the podocytes. Podocytes are terminally differentiated epithelial cells, which cover the glomerular basement membrane and face the renal pelvis. They have octopus-like extensions from the cell body, known as primary processes, which further branch to form secondary and tertiary processes. The junction between the tertiary foot processes is a specialized region, known as the slit diaphragm, and is thought to be a modified adherent junction. The slit diaphragm contains transmembrane proteins such as nephrin and Nephrin1, which are unique to the podocytes; adherens junction proteins such as FAT1, P-cadherins, and catenins; and tight junction proteins such as junctional adhesion molecule A, occludin, and cingulin. The foot processes have an important role in maintaining the integrity of the membrane and will affect the protein filtration rate. The filtrate that passes through the Bowman’s space continues into the proximal tubule and the loop of Henle for further processing.

The intact glomerular filter is almost impermeable to large proteins, and proteinuria may result from excessive permeability of the glomerular barrier for protein or impaired reabsorption of protein in the proximal tubule. With normal renal function, the amount of plasma protein entering the proximal tubule through the glomerulus depends on the glomerular plasma flow and the concentration and the filtration rate of each protein. Molecular weight, shape, and electrical charge of each protein will affect its filtration rate. The relationship between glomerular filtration rate (GFR) and its determinants can be assessed using the following equation: GFR = (ΔP - πGC) × Kf. In this equation, ΔP is the transcapillary hydraulic pressure difference or the pressure generated across the glomerulus and πGC is the mean glomerular intracapillary oncotic pressure. The determinants of GFR that can be measures or approximated in humans include Kf and πGC. Kf is the glomerular ultrafiltration coefficient, calculated as the product of the surface area available for filtration and the hydraulic permeability (k), which is the permeability to ultrafiltrate across the glomerulus. To compute πGC, one first calculates the oncotic pressure of plasma entering the efferent arteriole from the glomerular tuft. The oncotic pressure can be calculated by using the following equation: πG = πA/(1 - FF). In this equation, πA is the afferent oncotic pressure that can be measured directly from human plasma and filtration fraction (FF) is the portion of plasma filtered through the cellular layers of the glomerulus.
calculated by dividing the GFR by the renal plasma flow.13

Once proteins enter the proximal tubule, there may be tubular reabsorption, even with large proteins such as albumin.8,14,15 Proteinuria of glomerular origin occurs only when the tubular ability to reabsorb the filtered protein becomes saturated. It seems that the reabsorption capacity rapidly approaches to a maximum because pregnant women with underlying glomerular disorders have indicated that a small increase in albumin filtration will result in considerable increment in measured proteinuria.16–18

Renal adaptation in pregnancy
In a healthy pregnancy, an approximate doubling of urine protein level can be expected. Early maternal renal adaptation to pregnancy includes a 75% increase in renal plasma flow by 16 weeks’ gestation and a 50% increase in GFR by 5 to 7 weeks’ gestation compared with nonpregnant levels. GFR remains 50% above the nonpregnant level throughout pregnancy.19–22 Creatinine clearance is the most commonly used method for estimating glomerular filtration, although it is the least precise. This is because creatinine is secreted by the tubules in addition to being cleared by the glomeruli. Creatinine clearance is moderately increased in pregnancy (to 110–150 mL/minute).

Increased protein excretion during pregnancy is thought to be caused by the increase in GFR. The increase in GFR could result from a combination of the following: (1) hypervolemia and hemoconcentration lowering protein concentration and oncotic pressure and (2) the increase in renal blood flow. This theory is challenged by the timing of proteinuria in serial studies; the increase in proteinuria occurs in the second half of pregnancy, which does not correspond to the timing of the peak increase in glomerular filtration.23 There is also evidence from studies using dextran sieving that the physiological increase in total protein excretion in normal pregnancy is related to increased ultrafiltration coefficients and glomerular basement membrane permeability in late pregnancy.24–26

These 2 bodies of evidence suggest that the increase in GFR hypothesis does not completely explain the timing and pathophysiology of proteinuria in normal pregnancy. Alterations in tubular reabsorption capacity may also play a role in increased protein excretion during pregnancy.27,28

Pathophysiology of proteinuria in preeclampsia
Proteinuria was first described in a woman with eclampsia by Rayer in 1840, and in 1884, Schedoff and Porockjakoff described a link between hypertension and eclampsia.29–31 The first theory of the pathogenesis of proteinuria in preeclampsia was related to glomerular changes and increased permeability to proteins. As with other types of proteinuria of glomerular origin, the proteinuria of preeclampsia involves high-molecular-weight proteins such as albumin. With the introduction of electron microscopy techniques, better visualization and localization of glomerular components became available. Preeclampsia was found to be associated with a distinctive glomerular appearance of endothelial vacuolization and hypertrophy of the cytoplasmic organelles.32 The glomeruli are enlarged and solidified (bloodless), and the swelling of the endothelial cells and to a lesser extent the mesangial cells will cause narrowing or occlusion of capillary lumens. Spargo et al33 referred to these lesions by the now widely accepted term glomerular capillary endotheliosis. The pathologic finding of endotheliosis was later found to be present not only in women with preeclampsia but also in women with gestational hypertension without proteinuria and similarly in normal healthy pregnancies.34 Therefore, in recent years, the pathobiology of renal damage in preeclampsia has shifted from the glomerular endothelial cells to the podocytes.35,36 Current data suggest that the number of urinary podocytes in women with preeclampsia is higher than in women with gestational hypertension or normal pregnancies (Figure 1).36,37 Furthermore, the function of the podocyte and the slit diaphragm depends on the physiological concentrations of circulating factors, such as vascular endothelial growth factor (VEGF) and its antagonist, the soluble receptor fms-like tyrosine kinase 1 (sFlt-1).38–40 In the kidney, podocytes produce VEGF, and VEGF receptors have been found in endothelial cells and podocytes themselves. Thus, paracrine and autocrine pathways could affect the integrity of the glomerular filtration barrier with tight regulation of VEGF signaling to maintain a healthy glomerulus.41,42,43 Women with preeclampsia have increased serum concentrations of sFlt-1 and soluble endoglin (sEng) and reduced concentrations of free VEGF and free placental growth factor (PIGF), which are proangiogenic proteins that are bound and neutralized by sFlt-1. The angiogenic imbalance in preeclampsia may play an important key role in the development of both podocyte and endothelial damage in the glomerular filtration barrier.42,43 The recent link between VEGF and the glomerular filtration barrier in women with preeclampsia was studied in animal models of podocyte-specific VEGF knockout mice that showed glomerular endothelial cell swelling and podocyte foot process effacement.40,44 Furthermore, animal studies found that replacement with VEGF-121 had beneficial effects with partially reversing the glomerular lesion and decreasing proteinuria.45

Definition of Pathologic Proteinuria During Pregnancy
During normal pregnancy, urinary protein excretion increases from normal nonpregnant levels and in healthy women can reach 200 to 260 mg per day by the third trimester.35,46,47 The classic cutoff cited to define proteinuria during pregnancy is a value >300 mg/24 hours. Alternatively, a timed excretion that is extrapolated to this 24-hour urine value or a urine protein-to-creatinine ratio (UPCR) of at least 0.3 is used.4 Although this threshold is widely accepted for defining abnormal protein excretion, its origin does not seem to be based on clinical outcomes but rather on expert opinion and small studies that have attempted to establish statistically normative values for pregnancy.35,46–48
In the largest prospective study evaluating 270 women, the mean protein excretion was 116.9 mg/day with the upper limit of confidence interval (CI) being 259.4 mg/24 hours. This cutoff was recently challenged in a small prospective longitudinal study of 65 nulliparous healthy women who completed a 24-hour urine collection at 2 time points: before conception and during 30 to 32 weeks' gestation. In this study, 45% of healthy women with uncomplicated pregnancies exceed the diagnostic threshold for abnormal proteinuria with a mean protein excretion of 254 mg/24 hours (interquartile range, 166–396 mg/24 hours). Another study of 142 pregnant women who completed a 24-hour urine collection. More convenient methods used in practice involve urinary dipstick or measurement of the UPCR in a spot urine sample. In many locations, the spot UPCR is utilized rather than 24-hour collections.

**How Should We Evaluate Proteinuria During Pregnancy?**
The reference standard for measuring urinary protein excretion is a 24-hour urine collection. More convenient methods used in practice involve urinary dipstick or measurement of the UPCR in a spot urine sample. In many locations, the spot UPCR is utilized rather than 24-hour collections.

**Urine dipsticks**
The use of a dipstick to screen the urine for protein is an integral part of the current antenatal care plan and usually the first screening for proteinuria. This method is based on a change in pH in the presence of anionic proteins, that is, albumin and transferrin. Outside of pregnancy, urine dipsticks have good sensitivity as a screening tool for albumin loss of >30 mg per day, but specificity is limited. Urine dipstick measures urine protein concentration and hydration or diuresis will influence the sensitivity and specificity of the test.

Based on the current available data, the accuracy of dipstick urinalysis in pregnancy with 1+ threshold for predicting proteinuria of 300 mg/day is poor with a positive likelihood ratio of 3.48 (95% CI, 1.66–7.27), a negative likelihood ratio of 0.6 (95% CI, 0.45–0.8), sensitivity of 59% (95% CI, 37%–79%), and specificity of 28% (95% CI, 18%–41%). Accuracy may be improved with a higher threshold but the available data are limited. A recent prospective observational study evaluating the accuracy of urine dipstick in pregnancy included 2212 urine samples from 1033 pregnant women who underwent simultaneous dipstick and UPCR tests in the same spot urine samples at least once. For the prediction of proteinuria (defined as UPCR of >0.27), the dipstick was associated with false-negative test results in 8.8% of samples and false-positive test results in 59% of samples compared with UPCR. Furthermore, the false-positive rate was 78% for 1+ on dipstick test, 21% for 2+ on dipstick test, and 1.3% for 3+ on dipstick test. It was notable that creatinine was consistently higher in urine specimens without an abnormal UPCR than in those with abnormal UPCR at any dipstick test result. In comparison between normotensive and hypertensive women with similar dipstick test results, the risk of having proteinuria detected by a dipstick was consistently higher in hypertensive than normotensive women. For example, among women with a result of 1+ on dipstick test, proteinuria was present in 47% of hypertensive women vs 8.7% of normotensive women.

Routine urine dipstick screening for low-risk women does not provide any clinical benefit and proteinuria, with dipstick analysis, cannot be accurately detected or excluded at the +1 threshold and is not recommended for diagnosing preeclampsia.
Urine protein-to-creatinine ratio

In the spot urine tests, albumin concentration is normalized for the urinary creatinine concentration to approximate a 24-hour albumin or protein loss. It is important to emphasize that creatinine production and excretion are dependent on both kidney function and muscle mass. Urinary protein loss can vary substantially with the time of day, so morning samples are preferable. As discussed previously, a UPCR value of \( \geq 0.3 \) would represent abnormal proteinuria during pregnancy based on the current cutoff. A UPCR of \(<0.3\) may give a false-negative result for abnormal 24-hour urine collections but, in such cases, the total protein excretion is usually \(<400\) mg/day. A systematic review and meta-analysis evaluating the accuracy of spot urinary protein and albumin to creatinine ratios for the detection of proteinuria in women with suspected preeclampsia included 20 studies (2978 women). Threshold values for UPCR ranged between 0.13 and 0.5, with sensitivity ranging from 65% to 89% and specificity from 63% to 87%; the area under the receiver operating curve was 0.69. On average, across all studies, the optimum threshold (relating to sensitivity and specificity values of \( >75\% \)) seems to be between 0.30 and 0.35. However, no threshold gave a summary estimate of \( >80\% \) for both sensitivity and specificity. Another meta-analysis included 13 studies (1214 women) of the spot UPCR in hypertensive pregnant women (not only suspected preeclampsia). A cutoff of UPCR of \( >0.3 \) had a sensitivity of 91% (range, 73%–97%), specificity of 90% (range, 41%–100%), median positive likelihood ratio of 9.1 (range, 1.54 to infinity), and median negative likelihood ratio of 0.14 (range, 0.04–0.37). The current data suggest that the spot UPCR is a reasonable “rule-out” test for proteinuria of \( \geq 300 \) mg/day among otherwise healthy women with gestational hypertension with or without proteinuria on dipstick.

The UPCR is not a reliable measure of pathologic proteinuria during labor, because an elevated UPCR (\( >0.3\)) can be found in one-third of uncomplicated pregnancies at term with an increase in UPCR during labor with the highest levels seen in the postpartum period.

24-hour urine collection

The gold standard test remains a 24-hour urine protein measurement, but this method is not practical especially for women requiring a rapid diagnosis. Moreover, the 24-hour urine collection may have other limitations as a result of inadequate collection, inconvenience, spillage, and other factors. If performed, it should be accompanied by measurement of creatinine excretion to assess completeness of collection. The rate of inaccurate 24-hour urine collection is much higher during pregnancy than nonpregnant state and may approach 50%. This is not surprising, given the pregnancy-related reasons for measurement error, including physiological dilatation of the ureters and incomplete bladder emptying.

A systematic review and meta-analysis of 7 studies (265 patients) comparing 24-hour urine with 12-hour urine collection suggested that a 12-hour urine protein collection performed well compared with a 24-hour urine collection for the diagnosis of proteinuria. A cutoff of 150 mg for 12-hour urine collection had a high sensitivity of 92% (95% CI, 86%–96%) and specificity of 99% (95% CI, 75%–100%) compared with the 24-hour urine collection. Furthermore, a recent prospective observational study of 12-hour urine collection in 99 women with suspected preeclampsia reported a sensitivity of 85.9% (95% CI, 81%–90%) and a specificity of 91.7% (95% CI, 88%–95%) compared with the 24-hour urine collection.

Proteinuria and preeclampsia

An important question to be answered in order to assess the importance of proteinuria during pregnancy is whether pregnant women with new-onset hypertension with proteinuria have different maternal or perinatal outcomes compared with hypertensive women without proteinuria. Proteinuria in combination with hypertension has long been considered to be predictive of increased maternal and neonatal adverse outcomes compared with women with gestational hypertension alone, and before the Task Force on Hypertension in Pregnancy 2013, proteinuria was an essential part of the diagnosis of preeclampsia. Furthermore, the amount of protein was previously related to the severity of the disease. Patients were considered to have mild preeclampsia if they had mild gestational hypertension and proteinuria. Patients were considered to have severe preeclampsia if they developed any of the following: blood pressure of \( \geq 160/110 \) mm Hg on 2 measurements 4 hours apart or 1 diastolic blood pressure of \( \geq 110 \) mm Hg treated with antihypertensive medication; \( >5 \) g of protein excreted in a 24-hour urine sampling; thrombocytopenia; hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome; pulmonary edema; or a convulsion.

The first prospective study evaluating the impact of elevated blood pressures and proteinuria on pregnancy outcomes included 12,954 women. In this study, proteinuria was defined as a urine dipstick of \( >2+\). This study found an increase in stillbirth, perinatal mortality, and neonatal morbidity in pregnancies complicated with hypertension and proteinuria compared with hypertension alone. The presence of proteinuria was considered an essential marker for poor pregnancy outcome, and there was a tendency to consider the absence of proteinuria as reassuring when managing pregnancies complicated by hypertension. This assumption was readdressed with a secondary analysis from the Calcium for Preeclampsia Prevention trial, which evaluated the relationship between the severity of hypertension (with and without proteinuria) and pregnancy outcomes. This analysis found that women with severe hypertension were at the highest risk of adverse maternal or perinatal outcomes. Severe gestational hypertension was associated with a higher rate of low birthweight infants and lower gestational age at delivery than mild gestational hypertension or mild preeclampsia. Another secondary analysis from the low-dose aspirin to prevent preeclampsia in...
women with previous preeclampsia aimed to compare the rates of adverse perinatal outcomes in those who developed hypertensive disorders with those that remain normotensive in a subsequent pregnancy. The analysis compared the outcomes of women who developed various degrees of hypertension with or without proteinuria. Women who developed severe gestational hypertension had higher rates of preterm deliveries (spontaneous and indicated) and small for gestational age neonates than patients who remained normotensive or those who developed mild gestational hypertension. In contrast, there were no differences in perinatal outcomes between the normotensive or mild gestational hypertension and the mild preeclampsia groups. Overall, women who had severe gestational hypertension had more adverse perinatal outcomes than women who had mild gestational hypertension or mild preeclampsia (Table 2).

### New definitions and clinical significance of proteinuria assessment for women with hypertensive disorders

Based on the studies described earlier and a review of maternal mortality data revealing that interventions in acutely ill women with multiple organ dysfunction were sometimes delayed because of the absence of proteinuria, the American College of Obstetricians and Gynecologists Task Force on Hypertension in Pregnancy and the International Society for the Study of Hypertension in Pregnancy removed the requirement of proteinuria for the diagnosis of preeclampsia if there are other findings suggestive of end organ involvement (thrombocytopenia, elevated liver transaminases, renal insufficiency, pulmonary edema, or new-onset neurologic symptoms) (Table 3).

Is gestational hypertension different from preeclampsia?

There is an ongoing debate about whether the quantification of urinary protein remains an important diagnostic step for the evaluation of hypertension in pregnancy and whether gestational hypertension and preeclampsia are really 2 different entities. With the updated definitions, most women with the diagnosis of preeclampsia will differ from women with gestational hypertension only by the presence of proteinuria, and only 10% of women will present with hypertension and systemic sign of preeclampsia (thrombocytopenia, impaired liver function, renal dysfunction, and respiratory or cerebral disturbances) in the absence of proteinuria. Furthermore, up to 50% of women with gestational hypertension will eventually develop proteinuria or end organ dysfunction consistent with the diagnosis of preeclampsia. After the publication of the new guidelines, limited data are available on whether preeclampsia with or without proteinuria will have different outcomes. Although some studies revealed similar outcomes for women with preeclampsia with and without proteinuria, others found worse outcomes for women with preeclampsia with proteinuria. A secondary analysis of a randomized controlled trial (RCT) of vitamin C and E supplementation evaluated whether hypertensive women with proteinuria (defined as proteinuria of 300–499 mg/day) have comparable outcomes with women with gestational hypertension or preexisting chronic hypertension without additional proteinuria. Women with proteinuria had a higher risk of severe hypertension, induction of labor, preterm delivery, and small for gestational age neonates than women with gestational hypertension or chronic hypertension. Furthermore, a subgroup of women with proteinuria of >500 mg/day had worse pregnancy outcomes than those with 300 to 400 mg/day, including earlier delivery, higher risk of cesarean delivery, and magnesium sulfate use.

In studies with reported differences in outcome with or without proteinuria, it is possible that proteinuria influences the

<table>
<thead>
<tr>
<th>TABLE 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcomes in gestational hypertension vs preeclampsia</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Gestational hypertension</td>
</tr>
<tr>
<td>Maternal outcomes</td>
</tr>
<tr>
<td>Elevated liver enzymes</td>
</tr>
<tr>
<td>Placental abruption</td>
</tr>
<tr>
<td>Disseminated intravascular coagulation</td>
</tr>
<tr>
<td>Induction of labor</td>
</tr>
<tr>
<td>Cesarean delivery</td>
</tr>
<tr>
<td>Neonatal outcomes</td>
</tr>
<tr>
<td>Preterm delivery at &lt;37 wk gestation</td>
</tr>
<tr>
<td>Preterm delivery at &lt;34 wk gestation</td>
</tr>
<tr>
<td>Small for gestational age</td>
</tr>
<tr>
<td>Birthweight of &lt;2500 g</td>
</tr>
<tr>
<td>Intensive care unit admission</td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
</tr>
<tr>
<td>Perinatal death</td>
</tr>
</tbody>
</table>

Values are expressed as percentage unless indicated otherwise.

Data adapted from Hauth et al and Buchbinder et al.

management of those patients and affects clinical decisions such as surveillance and timing of delivery. If patients with preeclampsia are followed up more closely, have more inpatient management, and have more blood pressure measurements than gestational hypertension, a bias could arise regarding the assessment of outcome related to the timing of delivery such as preterm delivery and neonatal complications, simply because there are more opportunities to make these decisions. Based on current available data, we believe that the most important factor that influences maternal and neonatal outcome is the severity of blood pressure and the presence of end organ damage, rather than the excess protein excretion. As a corollary, the separation of gestational hypertension and preeclampsia into 2 separate disorders is unnecessary, because the management of gestational hypertension and preeclampsia without severe features is almost identical in frequency of surveillance and timing of delivery (Table 4). The only difference in the recommended management between gestational hypertension and preeclampsia is weekly assessment of proteinuria in women with gestational hypertension. If the management of women with gestational hypertension with a positive assessment of proteinuria will not change, we believe that this assessment is unnecessary.

We recommend that any patient with new-onset hypertension (blood pressure of ≥140 mm Hg systolic or ≥90 mm Hg diastolic) at or after 20 weeks' gestation will undergo maternal and fetal evaluation. If there are signs or symptoms for preeclampsia with severe features (ie, blood pressure of ≥160 mm Hg systolic or ≥110 mm Hg diastolic, thrombocytopenia, impaired liver function, renal insufficiency, pulmonary edema, new-onset headache, or visual disturbances), the patient should be admitted to the hospital and managed according to the guidelines for preeclampsia with severe features. If there are no signs of severe disease, weekly follow-up is

---

**TABLE 3**

**Diagnostic criteria for preeclampsia**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New-onset hypertension (blood pressure of ≥140 mm Hg systolic or ≥90 mm Hg diastolic) at or after 20 wk gestation</td>
<td>New-onset hypertension (blood pressure of ≥140 mm Hg systolic or ≥90 mm Hg diastolic) at or after 20 wk gestation</td>
<td></td>
</tr>
<tr>
<td>On 2 occasions at least 4 h apart</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Proteinuria</strong></td>
<td>Not mandatory</td>
<td>Not mandatory</td>
</tr>
<tr>
<td>≥300 mg in 24-h urine collection (or this amount extrapolated from a timed collection)</td>
<td>Proteinuria should be assessed initially by automated dipstick urinalysis when possible</td>
<td></td>
</tr>
<tr>
<td>UPCR of ≥0.3 or</td>
<td>If positive (≥1+), then UPCR should be performed</td>
<td></td>
</tr>
<tr>
<td>Dipstick reading of 2+ (used only if other quantitative methods are not available)</td>
<td>A UPCR of ≥0.3 is abnormal</td>
<td></td>
</tr>
<tr>
<td>A negative dipstick test result can usually be accepted and further UPCR testing is not required at that time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Massive proteinuria (&gt;5 g/24 h) is associated with more severe neonatal outcomes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In the absence of proteinuria

<table>
<thead>
<tr>
<th>Hematologic</th>
<th>Thrombocytopenia of &lt;100 × 10⁹/L</th>
<th>Thrombocytopenia of &lt;150 × 10⁹/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemolysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>Creatinine of ≥1.1 mg/dL or a doubling of the serum creatinine in the absence of other renal disease</td>
<td>Creatinine of &gt;1.0 mg/dL</td>
</tr>
<tr>
<td>Impaired liver function</td>
<td>Elevated liver transaminases to twice the normal concentration</td>
<td>Elevated liver transaminases (&gt;40 IU/L) with or without right upper quadrant or epigastric abdominal pain</td>
</tr>
<tr>
<td>Neurologic symptoms</td>
<td>New-onset headache unresponsive to medication and not accounted for by alternative diagnoses or visual symptoms</td>
<td>Examples include eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, and persistent visual scotomata</td>
</tr>
<tr>
<td>Other</td>
<td>Pulmonary edema</td>
<td>Uteroplacental dysfunction (such as fetal growth restriction, abnormal umbilical artery Doppler wave form analysis, or stillbirth)</td>
</tr>
</tbody>
</table>


*Adapted from American College of Obstetricians and Gynecologists’ Committee on Practice Bulletins—Obstetrics; †Adapted from Brown et al; ‡Indicate differences between the ACOG and ISSHP criteria.

recommended with close monitoring of blood pressure, weekly laboratory (ie, complete blood count, serum creatinine, aspartate aminotransferase, alanine aminotransferase), serial ultrasound to determine fetal growth every 3 to 4 weeks, and weekly antepartum testing. If there is no progression to preeclampsia with severe features, induction of labor at 37 weeks’ gestation is recommended (Figure 2).

Of note, patients with preeclampsia with severe features should receive magnesium sulfate for seizure prophylaxis. Although the design of most available trials for seizure prophylaxis with magnesium sulfate had an inclusion criteria including proteinuria, the largest RCT evaluating magnesium sulfate for seizure prophylaxis in women with preeclampsia provided data about the rate of eclampsia according to the presence or absence of symptoms (severe headaches, blurred vision, or epigastric pain). The number needed to be treated to prevent 1 case of eclampsia was 36 in women with symptoms compared with 1 in 129 in women without symptoms. Based on the current recommendations, patient with symptoms or severe range blood pressure will receive magnesium sulfate whether she has proteinuria or not. Given the low risk of eclampsia in patients without symptoms, we do not think further clinical trials are needed to address the need for magnesium sulfate in women with severe range blood pressures with or without proteinuria and proteinuria since that should not affect the clinical decision making regarding seizure prophylaxis.

Based on the current management recommendations and the data available regarding the progression of the disease, there is no strong evidence for the utility of urine protein assessment except for the following scenarios:

1. Evaluate baseline existence of proteinuria in women with preexisting conditions such as chronic hypertension, diabetes, and autoimmune disorders (Table 5).
2. If a woman presents with pre-eclamptic symptoms such as headache, blurry vision, and epigastric pain and is found to have normal or high normal blood pressures, we suggest that assessment of proteinuria would help to evaluate a possible diagnosis of preeclampsia.
3. Evaluation of women presenting with signs or symptoms of nephrotic range proteinuria such as severe generalized edema (Figure 3).

### Does the amount of proteinuria matter in women with preeclampsia?

The natural course of urine protein excretion during the conservative management of preeclampsia with severe features was previously studied, and there are conflicting results whether the amount of proteinuria will affect maternal or neonatal outcomes. Some studies have reported that the level of proteinuria is not associated with adverse maternal or perinatal outcomes, whereas others have reported that heavy proteinuria increases both maternal and perinatal morbidities including severe hypertension, preterm delivery, cesarean delivery, small for gestational age infants, maternal symptoms, and perinatal mortality rate.

In a retrospective cohort study, 90% of women with preeclampsia managed conservatively had an increase in protein excretion during pregnancy. Furthermore, 30% of women progressed to a nephrotic range proteinuria (>5 g/day). In this study, outcomes noted similar rates in major maternal or fetal outcomes (ie, gestational age at delivery, HELLP syndrome, eclampsia, placental abruption, and stillbirth) between pregnancies associated with marked increase in proteinuria (≥2 g) and those with modest or no increase (<2 g). A study evaluating whether severe (≥5 g/day) or

---

**TABLE 4**

Current American College of Obstetricians and Gynecologists recommendations for the surveillance and timing of delivery for women with gestational hypertension and preeclampsia

<table>
<thead>
<tr>
<th>Initial evaluation</th>
<th>Gestational hypertension</th>
<th>Maternal and fetal evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Complete blood count, serum creatinine, LDH, AST, ALT, and testing for proteinuria</td>
<td>Complete blood count, serum creatinine, LDH, AST, ALT, and testing for proteinuria</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outpatient management</th>
<th>Optional</th>
<th>Optional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up</td>
<td>1. At least 1 visit per wk in clinic</td>
<td>1. At least 1 visit per wk in clinic</td>
</tr>
<tr>
<td></td>
<td>2. Serial ultrasound to determine fetal growth every 3–4 wk</td>
<td>2. Serial ultrasound to determine fetal growth every 3–4 wk</td>
</tr>
<tr>
<td></td>
<td>3. Amniotic fluid volume assessment at least once weekly</td>
<td>3. Amniotic fluid volume assessment at least once weekly</td>
</tr>
<tr>
<td></td>
<td>4. Weekly antepartum testing</td>
<td>4. Weekly antepartum testing</td>
</tr>
<tr>
<td></td>
<td>5. Close monitoring of blood pressure</td>
<td>5. Close monitoring of blood pressure</td>
</tr>
<tr>
<td></td>
<td>7. Once weekly assessment of proteinuria is recommended</td>
<td>7. Additional quantification of proteinuria no longer necessary</td>
</tr>
</tbody>
</table>

| Delivery | Expectant management up to 37 0/7 wk gestation | Expectant management up to 37 0/7 wk gestation |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase.

---

massive (≥10 g/day) proteinuria affects maternal and perinatal outcomes also found similar rates of maternal complications (ie, eclampsia, placental abruption, HELLP syndrome) among all groups. However, women with massive proteinuria delivered at an earlier gestation with an associated higher rate of neonatal morbidities. A multicenter prospective international study of women with preeclampsia explored whether there is correlation between maternal adverse outcomes and the degree of proteinuria (assessed either by dipstick testing, spot UPCR, or 24-hour urine collection). This study also failed to find any correlation between the incidence of adverse maternal or neonatal outcomes and degree of proteinuria. In contrast, a retrospective cohort study of 321 women with preeclampsia assessed whether a discriminant value of proteinuria (spot UPCR) at the time of diagnosis predicts adverse maternal and neonatal outcomes. Increased maternal and neonatal risk occurred in women at the age of ≥35 years and with a protein excretion of ≥5 g/day. However, it is important to emphasize that in this cohort adverse maternal outcomes were defined as severe hypertension, elevated liver enzymes, elevated creatinine, thrombocytopenia, and neurologic symptoms.

Moreover, a recent secondary analysis from a multicenter prospective study of women with the diagnosis of preeclampsia evaluated whether proteinuria is associated with worse maternal or neonatal outcomes. Preeclamptic pregnancies were classified into the following 3 groups according to the degree of proteinuria measured by a 12- or 24-hour urine protein collection: (1) non-proteinuria preeclampsia (proteinuria of <165 mg in 12 hours or <300 mg in 24 hours); (2) mild proteinuria preeclampsia (proteinuria between 165 mg and 2.7 g in 12 hours or from 300 mg to 4.9 g in 24 hours); and (3) massive proteinuria preeclampsia (proteinuria of >2.7 g in 12 hours or >5.0 g in 24 hours). Composite adverse maternal outcome was defined as the presence of any of the following: acute renal failure, liver hematoma or rupture, acute myocardial infarction, cortical blindness, retinal detachment, cerebrovascular accident, pulmonary edema or adult respiratory distress syndrome (RDS), placental abruption, eclampsia, need for a third intravenous agent to control blood pressure, disseminated intravascular coagulation, or maternal death. Composite adverse neonatal outcome was defined as any of the following: RDS, any grade of intraventricular hemorrhage, necrotizing enterocolitis, bronchopulmonary dysplasia, periventricular leukomalacia, retinopathy of prematurity, seizure, or neonatal intensive care unit admission for >48 hours for full-term infant. This analysis included 406 women, of whom 66% had mild proteinuria preeclampsia, 25.1% had non-proteinuria preeclampsia, and 8.8% had massive proteinuria preeclampsia.
Composite adverse maternal outcomes were not increased in women with pre-eclampsia with massive proteinuria compared with those with mild or non-proteinuria preeclampsia. However, massive proteinuria preeclampsia was associated with preterm delivery at <34 0/7 weeks’ gestation in >80% of cases, which was almost twice as high as the mild proteinuria preeclampsia group and almost 4 times higher than in the nonproteinuria group. In addition, enrollment occurred much earlier in women with massive proteinuria indicating that the diagnosis was made at a more preterm gestational age. The higher neonatal morbidity rate observed in infants born to massive proteinuria women was most likely related to the earlier gestational age at delivery, with RDS being the most common neonatal complication affecting almost half of these infants. This analysis emphasized a very important confounding factor to consider in studies assessing severity of proteinuria and outcomes. Because proteinuria of \( \geq 5 \) g/day was previously one of the diagnostic criteria for severe preeclampsia, the test result may have influenced decisions regarding the timing of delivery management. For example, earlier delivery precipitated by heavy proteinuria may reduce maternal complications (leading to an underestimation of the predictive value of the test) or increase perinatal morbidity owing to prematurity (leading to an overestimation of its content). The amount of proteinuria could have an association with the outcome, rather than a predictive outcome.

In conclusion, we do not think that the progression of proteinuria in women with preeclampsia should change the management or outcomes, and we do not recommend repeated measuring of protein extraction for women with the diagnosis of preeclampsia.

**Isolated gestational proteinuria**

Isolated gestational proteinuria is defined as new-onset proteinuria after 20 weeks’ gestation with normal blood pressure and no other symptoms or signs of preeclampsia. Based on the current diagnostic criteria, women with proteinuria alone are not diagnosed as having preeclampsia until they also exhibit hypertension. Thus, isolated gestational proteinuria is a retrospective diagnosis. The exact incidence of isolated proteinuria is unknown, but a prospective study evaluating 11,651 low-risk women (excluding women with preexisting hypertension, diabetes or preeclampsia) who had at least 1 proteinuria measurement during pregnancy found single episodes of isolated gestational proteinuria of \( \geq 1+ \) on dipstick evaluation in 7.7% of the women. Of note, only 2% of women experienced proteinuria on more than 1 occasion. Furthermore, established risk factors for preeclampsia such as maternal age, higher prepregnancy body mass index, nulliparity, and twin pregnancy were associated with increased risk of developing proteinuria. Another observational study of 938 women with singleton pregnancies, who had at least 1 UPCR evaluation during pregnancy, noted isolated gestational proteinuria in 1.9% of women. The outcome of women with isolated proteinuria alone seems favorable, but up to 30% of women with isolated gestational proteinuria may progress to preeclampsia.

A retrospective study aimed to evaluate whether maternal outcome will differ between women with preeclampsia who first presented with hypertension without proteinuria compared with women who first presented with proteinuria alone without hypertension. Women presented with hypertension and proteinuria at the same time were

---

**TABLE 5**

List of conditions recommended for an evaluation of proteinuria either by 24-hour urine collection or by UPCR before pregnancy or in the first prenatal assessment

<table>
<thead>
<tr>
<th>Medical condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any woman with abnormal creatinine value on prenatal laboratory tests</td>
</tr>
<tr>
<td>Chronic hypertension</td>
</tr>
<tr>
<td>Diabetes mellitus (type 1 or type 2)</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Acute or chronic glomerulonephritis (ie, thin basement membrane nephropathy, IgA nephropathy, membranous glomerulonephritis, membranoproliferative glomerulonephritis, Pauci-immune glomerulonephritis, focal and segmental glomerulosclerosis, crescentic glomerulonephritis)</td>
</tr>
<tr>
<td>Chronic heart failure</td>
</tr>
<tr>
<td>Polycystic renal disease</td>
</tr>
<tr>
<td>Isolated proteinuria alone</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
</tr>
<tr>
<td>Autosomal dominant polycystic kidney disease</td>
</tr>
<tr>
<td>Solitary kidney or after renal transplant</td>
</tr>
</tbody>
</table>

\( \text{IgA, immunoglobulin A; UPCR, urine protein-to-creatinine ratio.} \)

excluded. Of 190 women with preeclampsia, 49 (25%) presented with proteinuria first with subsequent development of hypertension. Women with proteinuria onset preeclampsia were diagnosed earlier with preeclampsia, with an increased risk of fetal growth restriction, HELLP syndrome, and neonatal complications.109

As discussed previously, women with preeclampsia have increased serum concentrations of sFlt-1 and sEng and reduced concentrations of VEGF and PlGF.110,111 A study of 108 women with isolated gestational hypertension have also noted altered levels of angiogenic factors compared with health controls. Serum concentrations of PlGF were noted to be lower in women with gestational proteinuria than those of control subjects as early as 10 to 12 weeks’ gestation. However, levels of sFlt-1 and sEng are elevated only at term, when peak concentrations were attained. At term, levels of sFlt-1, sEng, and PlGF before the onset of gestational proteinuria were not altered as much as in women who later developed preeclampsia. Nevertheless, the authors concluded that gestational proteinuria might be a mild variant of preeclampsia.103 Because women with gestational proteinuria are at a high risk of progression to subsequent preeclampsia, we recommend close monitoring of blood pressures and other symptoms of preeclampsia in those women if a protein excretion test was done and proteinuria was diagnosed. Otherwise, because we do not recommend regular assessment of protein excretion during pregnancy, it is important to establish regular follow-up of blood pressures during pregnancy, especially in women with risk factors for preeclampsia such as advanced maternal age, nulliparity, obesity, and twin pregnancy.

**Proteinuria in women with preexisting conditions**

The best indicator of kidney function is the GFR. The current international guidelines define chronic kidney disease (CKD) as decreased kidney function of <60 mL/minute per 1.73 m² or markers of kidney damage or both of at least 3-month duration, regardless of the underlying cause.112,113 Proteinuria is one of the measures of kidney damage. The list of the conditions of which an evaluation of proteinuria either by 24-hour urine collection or by UPCR is recommended before pregnancy or in the first prenatal assessment is presented in Table 5. Because our current diagnosis of preeclampsia in women with CKD may be based on a change in protein excretion, a baseline evaluation is critical.

The presence of proteinuria before 20 weeks’ gestation is consistent with the presence of known or undetected renal disease. In many of these women, renal dysfunction may be minimal, and the presence of underlying renal diseases may not be suspected until proteinuria is detected during pregnancy. With advanced gestation, an exacerbation of maternal hypertension or an increase in urinary protein excretion could be related to the development of preeclampsia or may be caused by the exacerbation of the underlying renal disease.

Preeclampsia occurs in up to 40% of pregnancies of women with CKD. When pregnant women with CKD have increasing proteinuria or blood pressure during pregnancy, the main challenge is to decide whether they have renal worsening owing to preeclampsia or whether it is a worsening of their basic renal dysfunction.114 Regular diagnostic criteria for preeclampsia are not useful in women with CKD because most patients will have baseline blood pressures, proteinuria, and creatinine above the diagnostic threshold of preeclampsia. Furthermore, for example, previous studies examining changes in 24-hour urine protein in pregnant women with diabetic nephropathy revealed a 2.1- to 5.3-fold increase during the third trimester compared with preconception or first-trimester values; preeclampsia is being diagnosed in 42% to 73% of these pregnancies, with a higher risk of preeclampsia in patients with diabetes mellitus with early pregnancy proteinuria.115–119

**Chronic hypertension**

The cutoff for a normal baseline protein excretion or creatinine for women with chronic hypertension is also not well defined. In a subgroup analysis of women with chronic hypertension that were enrolled in a multicenter, randomized trial comparing low-dose aspirin with placebo for the prevention of preeclampsia, women with baseline proteinuria had an increased risk of preterm deliveries, small for gestational age infants, neonatal intensive care unit admission, and adverse neonatal outcomes compared with women without proteinuria early in pregnancy. Those adverse neonatal outcomes occurred despite the facts that the rates of superimposed preeclampsia were similar in the 2 groups and none of the women with proteinuria at baseline had placental abruption.120 Similar findings were noted in a retrospective study evaluating 447 women with chronic hypertension who received antihypertensive therapy in the first half of pregnancy and completed urine protein quantification before 20 weeks’ gestation. Women with baseline proteinuria had increased risks of preeclampsia, preterm birth, and growth restriction. In pregnant women with treated chronic hypertension, baseline proteinuria was
associated with increased rates of preeclampsia, preterm birth, and growth restriction compared with women who did not have proteinuria. A retrospective study of 755 women with chronic hypertension and a baseline assessment of renal function (UPCR and serum creatinine) before 20 weeks’ gestation found that baseline serum creatinine of ≥0.75 mg/dL and UPCR of ≥0.12 were associated with increased risks of severe preeclampsia before 34 weeks’ gestation and preeclampsia at any gestational age. These thresholds are much lower than typically considered abnormal. Furthermore, 33.3% of women with chronic hypertension and baseline renal function tests above the objectively determined cutoffs developed severe preeclampsia at <34 weeks’ gestation, and 66.7% developed any type of preeclampsia during the pregnancy. Preeclampsia is considered superimposed when it complicates preexisting chronic hypertension. Up to 25% of women with chronic hypertension will be diagnosed as having superimposed preeclampsia. Superimposed preeclampsia is not always easy to diagnose and is often a diagnosis of exclusion. Based on the current available guidelines, a sudden increase in baseline hypertension or a sudden increase of proteinuria (above the threshold for normal or a clear change from baseline) would prompt an assessment for a possible diagnosis of superimposed preeclampsia. The definition of superimposed preeclampsia possess a diagnostic dilemma, and it is unclear whether changes in the baseline proteinuria reflect another systemic disease such as preeclampsia or whether women with chronic hypertension will experience a different “normal” pattern of protein excretion during pregnancy. The consequences of diagnosing a patient with superimposed preeclampsia may not be significant if it occurs close to term, but if the blood pressure rises to a severe range earlier in pregnancy it may lead to more maternal-fetal testing, hospitalization, and interventions leading to preterm delivery instead of just adjusting the blood pressure medications. Limited data are available regarding the angiogenic profile in women with chronic hypertension or CKD as a potential marker in distinguishing the worsening of baseline disease and superimposed preeclampsia. Most of the predictive studies on the use of angiogenic factors for prediction of preeclampsia in high-risk population have also included women with chronic hypertension, but the interpretation of those studies only for women with chronic hypertension is limited. A secondary analysis on the low-dose aspirin to prevent preeclampsia in women with previous preeclampsia evaluated the differences in circulating concentrations of sFlt1, sEng, and the proangiogenic PlGF in high-risk pregnancy. This cohort included 313 women with chronic hypertension and 194 women with preexisting diabetes. Significant differences in angiogenic factors during the third trimester were found in women who develop preeclampsia compared with appropriate controls in all high-risk groups. However, the sFlt1 concentrations were not elevated before the onset of preeclampsia in the chronic hypertension or diabetes group compared with the control group. Another prospective study evaluating 78 women with chronic hypertension found that women with uncontrolled blood pressure had higher levels of sFlt1 and a higher sFlt1-to-PlGF ratio before delivery, whereas an observational study including 60 women with chronic hypertension found only higher sFlt1-to-PlGF ratio in women who developed superimposed preeclampsia with similar levels of sFlt1 or PlGF compared with women who did not develop preeclampsia. A longitudinal prospective cohort of women with CKD (n=121) and chronic hypertension (n=44) quantified PlGF in the diagnosis of superimposed preeclampsia requiring delivery within 14 days of diagnosis. Lower maternal PlGF concentrations had a high diagnostic accuracy for superimposed preeclampsia requiring delivery within 14 days (receiver operator characteristic, 0.85). The sensitivity, specificity, and positive and negative predictive values of PlGF concentrations below the fifth percentile (100 pg/mL) for predicting delivery within 2 weeks for women with chronic hypertension or CKD were 75%, 77.5%, 26%, and 96%, respectively, although these data included only 40 women with superimposed preeclampsia. The diagnostic utility of low PlGF concentrations was also confirmed in women with CKD or chronic hypertension (n=123) for superimposed preeclampsia requiring delivery within 14 days with a receiver operator characteristic of 0.82 in a validation cohort. More research is needed on normal and abnormal protein secretion for women with chronic hypertension or other preexisting renal disorders during pregnancy to define a pathologic cutoff in this population and to better define the existence of preeclampsia in this population. Summary and Future Directions Preeclampsia is a common disorder and evaluating protein excretion has become one of the most common screening tests performed during pregnancy. This review and clinical opinion focused on proteinuria in pregnancy and its correlation to clinical outcomes. There are no convincing data that support 300 mg/day as a cutoff for abnormal protein excretion. The lack of appropriate validation of normal protein excretion during pregnancy in low-risk and high-risk population challenges the clinicians’ ability to trust the current cutoff as a guideline for management. Furthermore, during the past 10 years, there have been a significant change in the demographics of obstetrical population in the United States and most of the western countries. Pregnant women who are older, obese, undergoing in vitro fertilization, or carrying multifetal gestation may have protein excretion that exceeds the established thresholds in the absence of clinically apparent disease. Although proteinuria is essential for diagnosis and follow-up in women with chronic hypertension, diabetes mellitus, and other chronic renal disorders, it has limited value in patients who develop hypertension during pregnancy. Based on current data and our
experience, we suggest that the current management of women with gestational hypertension or preeclampsia should be based on more reliable signs and symptoms such as blood pressure control or end organ damage. There are needs to (1) determine the necessity for protein assessment during pregnancy for women without chronic renal disorders or predisposing conditions; (2) assess normal and abnormal protein excretion in pregnancy for women with risk factors for preeclampsia such as advanced maternal age, obesity, and fertility treatment; (3) readdress the subclassification of hypertensive disorder in pregnancy and assess whether there is a value to define preeclampsia differently from gestational hypertension; (4) better understand normal protein excretion during pregnancy in women with chronic hypertension and explore whether worsening of proteinuria affects outcomes and justifies the diagnosis of superimposed preeclampsia; and (5) design and evaluate studies addressing other biomarkers that could be used for the diagnosis of preeclampsia in women with chronic renal disorders.

REFERENCES


