INTRODUCTION — In non-pregnant individuals, abnormal total protein excretion is typically defined as greater than 150 mg daily. In normal pregnancy, urinary protein excretion increases substantially; hence, total protein excretion is considered abnormal in pregnant women when it exceeds 300 mg/24 hours [1].

Proteinuria is one of the cardinal features of preeclampsia (table 1), a common and potentially severe complication of pregnancy. However, two important points should be noted. First, the severity of proteinuria is only weakly associated with adverse maternal and neonatal outcomes, and should not be used to guide management [2-5]. Second, proteinuria may be absent: Up to 10 percent of women with clinical and/or histological manifestations of preeclampsia and 20 percent of women with eclampsia have no proteinuria at the time of initial presentation [6,7]. These observations are reflected in the 2013 American Society of Obstetrics and Gynecology Task Force on Hypertension in Pregnancy recommendations, which no longer require proteinuria for the diagnosis of preeclampsia if other severe preeclampsia features are present (table 1). (See "Preeclampsia: Clinical features and diagnosis").

Although less prevalent, primary renal disease and renal disease secondary to systemic disorders, such as diabetes or primary hypertension (formerly called "essential" hypertension), are usually characterized by proteinuria and may first present in pregnancy. To further complicate this picture, 20 to 25 percent of women with chronic hypertension and diabetes develop superimposed preeclampsia [8,9].

It is important for clinicians caring for pregnant women to understand how to identify proteinuria, and how to determine whether preeclampsia or renal disease (or both) is the cause. This topic will discuss the approach to the evaluation of pregnant women with proteinuria and management of nephrotic syndrome in pregnancy. The evaluation of proteinuria in nonpregnant individuals and measurement of protein excretion are discussed in detail separately. (See "Assessment of urinary protein excretion and evaluation of isolated non-nephrotic proteinuria in adults").

RENA L CHANGES IN NORMAL PREGNANCY — Glomerular filtration rate (GFR) and renal blood flow rise markedly during pregnancy, resulting in a physiologic fall in the serum creatinine concentration. Urinary protein excretion increases substantially due to a combination of increased GFR and increased permeability of the glomerular basement membrane [10]. Additionally, tubular reabsorption of filtered protein is reduced in pregnancy, along with other nonelectrolytes, such as amino acids, glucose, and beta-microglobulin. (See "Assessment of urinary protein excretion and evaluation of isolated non-nephrotic proteinuria in adults").

Women with uncomplicated twin pregnancies have greater increases in urinary protein excretion than do women with singleton pregnancies [11,12].

Additional information on pregnancy-related changes in renal function and the urinary tract can be found separately. (See "Renal and ur inary tract physiology in normal pregnancy").

SCREENING FOR PROTEINURIA — Routine antepartum care includes dipstick protein testing of a random voided urine sample at each prenatal visit. In the second half of pregnancy, one purpose of the urinalysis is detection of preeclampsia. (See "Preeclampsia: Clinical features and diagnosis").

Standard urine dipstick testing is commonly performed on a fresh, clean voided, midstream urine specimen obtained before pelvic examination to minimize the chance of contamination from vaginal secretions. The urinary dipstick for protein is a semi-quantitative colorimetric test that primarily detects albumin. Results range from negative to 4+, corresponding to the following estimates of protein excretion:

- Negative
- Trace - between 15 and 30 mg/dL
- 1+ - between 30 and 100 mg/dL
- 2+ - between 100 and 300 mg/dL
- 3+ - between 300 and 1000 mg/dL
- 4+ - >1000 mg/dL
A positive reaction (+1) for protein develops at the threshold concentration of 30 mg/dL, which roughly corresponds to a 24-hour urinary protein excretion of 300 mg/day, depending on urine volume.

Although inexpensive and commonly used, the urinary dipstick has a high false-positive and false-negative rate when used to screen for abnormal proteinuria in pregnancy, especially at the 1+ level [13]. This is due primarily to variability in urine concentration (osmolality), which can substantially affect random urine protein concentration (ie, the dipstick result) even though there is no change in total daily urinary protein excretion.

False positive tests may occur in the presence of gross (macroscopic) blood in the urine, semen, very alkaline urine (pH >7), quaternary ammonium compounds, detergents and disinfectants, drugs, radio-contrast agents, and high specific gravity (>1.030). Positive tests for protein due to blood in the urine seldom exceed 1+ by dipstick. False negatives may occur with low specific gravity (<1.010), high salt concentration, highly acidic urine, or with nonalbumin proteinuria. Despite these limitations, routine urinary dipstick testing remains the mainstay of proteinuria screening in obstetric practice.

**QUANTIFYING PROTEIN EXCRETION** — Urinary protein can be measured as either albumin or total protein. Non-pregnant women normally excrete less than 30 mg of albumin [14] and less than 150 mg of total protein daily. In normal pregnancy, total protein excretion increases to 150 to 250 mg daily [1], and is even higher in twin pregnancies [11,12].

Accurate quantification of proteinuria in pregnancy is important in several clinical settings. If preeclampsia is suspected, proteinuria quantitation is helpful, though not required, for diagnosis (see "Preeclampsia: Clinical features and diagnosis"). In women with pre-existing proteinuria, a large gestational increase in proteinuria can herald superimposed preeclampsia. In women with chronic kidney disease, proteinuria >1 g/day is associated with increased risk of adverse pregnancy and neonatal outcomes (odds ratio 3.69; 95% CI 1.63-8.36), including preterm delivery, small for gestational age infants, and need for neonatal intensive care [15].

There are two approaches to a definitive quantitative measurement of protein excretion.

**24-hour collection** — The traditional method requires a 24-hour urine collection to directly determine the daily total protein or albumin excretion. An extra benefit of this approach, if creatinine is also measured, is that it provides the information necessary to estimate the glomerular filtration rate (GFR) from the creatinine clearance. The 24-hour collection is begun at the usual time the patient awakens. At that time, the first void is discarded and the exact time noted. Subsequently, all urine voids are collected with the last void timed to finish the collection at exactly the same time the next morning. The time of the final urine specimen should vary by no more than 5 or 10 minutes from the time of starting the collection the previous morning. An inexpensive basin urinal that fits into the toilet bowl facilitates collection. The bottle(s) may be kept at normal room temperature for a day or two, but should be kept cool or refrigerated for longer periods of time. No preservatives are needed. (See "Patient education: Collection of a 24-hour urine specimen (Beyond the Basics)".)

Although generally considered the "gold standard" for diagnosis of proteinuria in both preeclampsia and renal disease, the 24-hour urine protein excretion in pregnant women is frequently inaccurate due to undercollection or overcollection [16]. Thus, when interpreting the results of a 24-hour urine collection, it is critical to assess the adequacy of collection by quantifying the 24-hour urine creatinine excretion, which is based on muscle mass. The 24-hour urine creatinine excretion should be between 15 and 20 mg/kg body weight, calculated using pre-pregnancy weight. Values substantially above or below this estimate suggest over- and undercollection, respectively, and should call into question the accuracy of the 24-hour urine protein result.

In addition to the high rate of inaccurate/incomplete collection, the 24-hour urine sample is cumbersome for ambulatory patients, and the result is not available for at least 24 hours while the collection is being completed and analyzed [16]. Hence, there has been longstanding interest in alternative methods to quantify urine protein excretion in pregnancy.

**Urine protein to creatinine ratio** — The spot urine protein-to-creatinine ratio (PC ratio) has become the preferred method for the quantification of proteinuria in the non-pregnant population due to high accuracy, reproducibility, and convenience when compared to timed urine collection [17]. (See "Assessment of urinary protein excretion and evaluation of isolated non-nephrotic proteinuria in adults").

The majority of studies evaluating the urine PC ratio in pregnant women were performed in women with suspected preeclampsia. In these studies, the PC ratio was highly correlated with the 24-hour urine protein measurement [18,19], as it is in non-pregnant adults. Use of the PC ratio has also been validated for baseline proteinuria quantification in early pregnancy [20]. Routine bladder catheterization for measurement of urine PC ratio is not necessary; mid-stream clean-catch samples are accurate in pregnant women [21]. The time of day of urine specimen collection does not impact accuracy [22].

Over a dozen studies have validated the urine PC ratio for the detection of abnormal proteinuria in women with hypertensive pregnancy; most used the 24-hour urine collection as the "gold standard" [19,23-36]. Most studies have focused on accurate determination of greater than 300 mg/day of proteinuria, as this is the cut-off for preeclampsia diagnosis. Three systematic reviews have evaluated this literature, and came to similar conclusions [36].

- In a 2012 meta-analysis including 2978 women from 20 studies, spot urine ratio had a pooled sensitivity of 83.6 percent (95% CI 77.5-89.7) and specificity of 76.3 percent (95% CI 72.6-80.0) using a cut-off of 0.26 mg protein/mg creatinine to
predict proteinuria >300 mg/day by 24-hour urine collection [37]. The authors concluded that a low spot protein:creatinine ratio is a reasonable "rule-out" test for excluding proteinuria >300 mg/day in hypertensive pregnancy.

- In a 2008 meta-analysis including 1717 women from seven studies, a lower cut-off of 0.13 to 0.15 mg protein/mg creatinine provided higher (90 to 99 percent) sensitivity, albeit with more false-positive results (specificity 33 to 65 percent) [38]. A higher cutoff of 0.6 to 0.7 mg protein/mg creatinine had a high specificity (96 percent) for significant proteinuria (>300 mg in a 24-hour specimen), but at the cost of lower sensitivity (85 to 87 percent). Midrange protein/creatinine ratios (greater than 0.15 mg/mg but less than 0.7 mg/mg) did not reliably predict abnormal proteinuria.

- Another 2012 meta-analysis, including 2790 women from 15 studies, had similar findings. A single diagnostic threshold of approximately 0.30 mg protein/mg creatinine had sensitivity and specificity of 81 and 76 percent, respectively, for the detection of >300 mg/day proteinuria by 24-hour urine collection [39]. A lower cut-off (0.13 mg/mg) had better (89 percent) sensitivity for the exclusion of proteinuria.

Taken together, these data suggest that a urine PC ratio above 0.7 mg protein/mg creatinine strongly predicts significant proteinuria. A urine PC ratio less than 0.15 mg protein/mg creatinine can be considered normal (predictive of less than 300 mg protein in a 24-hour collection). Confirmatory testing with 24-hour urine collection probably is not necessary in these individuals. Women with urine PC ratio results between 0.15 and 0.7 mg protein/mg creatinine should have a 24-hour urine collection to accurately quantify proteinuria. Most international organizations endorse the use of the spot urine protein:creatinine ratio ≥0.26 to 0.3 mg protein/mg creatinine for the diagnosis of preeclampsia [40,41].

Some laboratories and international guidelines use urine protein:creatinine ratio in units of mg protein per mmol creatinine (mg/mmol). To convert mg/mmol to mg/mg, divide by 113.6.

A calculator is available for calculating the urine protein to creatinine using spot urine protein and spot urine creatinine values (calculator 1).

Urine albumin to creatinine ratio — The urine albumin:creatinine ratio (ACR), like the PC ratio, is measured using a random "spot" urine specimen. Originally developed for the detection of albuminuria in patients with diabetes mellitus, the ACR is now recommended as the best initial screening test for proteinuria in non-pregnant adults, due to its increased sensitivity as compared with the PC ratio. (See "Assessment of urinary protein excretion and evaluation of isolated non-nephrotic proteinuria in adults").

The ACR also has the advantage that it can be performed using an automated analyzer, allowing immediate point-of-care testing that could be utilized in an antenatal clinic. Like the PC ratio, the ACR (using a threshold between 20 and 60 mg albumin/g creatinine) is strongly predictive of significant proteinuria (>300 mg protein/day by 24-hour urine collection) in a high-risk obstetric antenatal clinic [33,42] and in women with hypertensive pregnancies [43,44]. In one study, women with a spot urine ACR >312 mg albumin/g creatinine measured at 17 to 20 weeks of gestation were at almost eightfold higher risk of subsequently developing preeclampsia (relative risk [RR] 7.8) compared with women with ACR <312 mg albumin/g creatinine [45]. Although more data are needed, the spot ACR has the potential to supplant urinary dipstick as a rapid and accurate screening method for proteinuria in routine obstetric care.

Some laboratories report urine albumin:creatinine ratio in units of mg albumin per mmol creatinine (mg/mmol). To convert mg/mmol to mg/g, divide by 0.1136.

8- or 12-hour collection — Measurement of protein in an 8-hour [46] or 12-hour [47] urine collection is a reasonable alternative to the 24-hour urine collection for quantification of proteinuria. In a systematic review including seven studies, >150 mg of protein in a 12-hour collection was highly predictive of >300 mg protein in a 24-hour collection (pooled sensitivity 92 percent [95% CI 86-96], specificity 99 percent [75-100]) [47].

DIFFERENTIAL DIAGNOSIS OF PROTEINURIA

Renal disease versus preeclampsia — In the evaluation of a pregnant patient with proteinuria, the first consideration is to determine whether the proteinuria is due to preeclampsia or some other renal disease, whether pre-existing or de novo (table 2). In patients with established renal disease before conception or in whom proteinuria is documented before the 20th week of gestation, the diagnosis of pre-existing renal disease can be readily made because preeclampsia rarely occurs before that time. (See "Pregnancy in women with underlying renal disease").

Conversely, new-onset proteinuria after 20 weeks of gestation suggests preeclampsia. Approximately one-third of women who present with new proteinuria after 20 weeks gestation eventually progress to preeclampsia [48]. In such cases, adverse pregnancy and neonatal outcomes are more common as compared with women in whom hypertension was the first presenting sign of preeclampsia [49].

Of course, de novo renal disease (for example, lupus nephritis) can also occur later in pregnancy. Especially when information on the presence of proteinuria (and hypertension) in early pregnancy is lacking, distinguishing between underlying renal disease and preeclampsia can be difficult. For this reason, it is useful to quantify protein excretion in early pregnancy in women at risk for underlying renal disease (ie, women with chronic hypertension, diabetes mellitus, and systemic lupus
erythematous). Diagnostic evaluation in women when the etiology of proteinuria is unclear should include renal ultrasound, as urinary tract dilatation has been associated with proteinuria in pregnancy [50].

A novel serum test for early diagnosis of preeclampsia has been developed, which relies on detection of abnormal levels of placenta-derived angiogenic factors, sFlt1 (soluble fms-like tyrosine kinase-1) and PI GF (placental growth factor) [51]. This diagnostic test is available in Europe (Roche Diagnostics, Rotkreuz, Switzerland and Thermo Fisher/Brahms, Hennigsdorf, Germany) and is being evaluated by the FDA for use in the United States. Although more studies are needed to validate its use, this serum test may prove useful and cost-effective in distinguishing preeclampsia from other causes of proteinuria in pregnancy [52,53], and appears to be predictive of adverse maternal and neonatal outcomes in women with clinical suspicion of preeclampsia [54,55]. The sFlt1:PI GF ratio may be particularly helpful in distinguishing chronic kidney disease and preeclampsia [56]. (See "Preeclampsia: Pathogenesis", section on "sFlt-1, VEGF, PI GF").

The distinction between renal disease and preeclampsia is important because it affects clinical management. In patients with renal disease, the usual aim is term delivery, while patients with preeclampsia often develop progressive disease culminating in the need for iatrogenic preterm delivery. (See "Pregnancy in women with underlying renal disease" and "Preeclampsia: Management and prognosis").

In instances where the distinction between renal disease and preeclampsia cannot be resolved, it is prudent to assume preeclampsia as the working diagnosis, as it has the potential for rapid development of serious maternal and fetal complications.

In some cases, the distinction between renal disease and preeclampsia can only be made retrospectively, as clinical signs of preeclampsia generally resolve within 12 weeks after delivery [57], while proteinuria due to underlying renal disease does not. However, resolution of proteinuria after preeclampsia, especially when severe, can sometimes take much longer. In one cohort study of 205 women with preeclampsia, 14 percent had persistent proteinuria at 12 weeks after delivery, which resolved by two years postpartum in all but 2 percent of subjects [58]. Nevertheless, proteinuria (or hypertension) which persists longer than three months after delivery should prompt close follow-up and consideration of further evaluation and appropriate referral, so that underlying renal disease or chronic hypertension is detected and treated expeditiously.

Superimposed preeclampsia — When preeclampsia develops in women with preexisting renal disease and/or hypertension, it often occurs earlier in gestation and may be particularly severe. In such cases, significant clues to the diagnosis of superimposed preeclampsia can be provided by the systemic manifestations of the disorder, if present, such as thrombocytopenia, an increase in levels of liver enzymes, hemolysis, and/or evidence of fetal compromise (including intrauterine growth restriction) (table 3) [59].

Alternatively, worsening hypertension and proteinuria in a woman with renal disease may represent an exacerbation of the underlying disease. Studies in women with documented primary renal disease predating pregnancy have demonstrated that the majority of women with glomerular disease exhibit increasing proteinuria during the course of their gestation and nephrotic syndrome in the third trimester [60,61].

The differential diagnosis for hypertension and proteinuria in pregnancy is discussed in detail separately. (See "Preeclampsia: Clinical features and diagnosis", section on 'Differential diagnosis'.)

Nephrotic syndrome — Nephrotic-range proteinuria (>3.0 g/24 hours) is a sign of glomerular injury. Pathology limited to the renal tubules and interstitium typically results in protein excretion rates less than 2.0 g/24 hours unless glomerular disease is also present. Patients with protein excretion less than 3.0 g/24 hours are usually asymptomatic. In contrast, rates greater than 3.0 g/24 hours may cause the nephrotic syndrome, which consists of nephrotic-range proteinuria together with edema, hypoalbuminemia, and hyperlipidemia. (See "Overview of heavy proteinuria and the nephrotic syndrome").

Kidney biopsy in pregnancy — Preeclampsia is the most common cause of de novo nephrotic syndrome in pregnancy and rarely requires kidney biopsy [62]. However, the nephrotic syndrome in pregnancy may also be caused by preexisting renal disease (which is often accompanied by a large increase in proteinuria during pregnancy), and de novo renal disease that develops during pregnancy (eg, associated with invasive trophoblastic tumors [63]). Once it has been determined that the patient has heavy proteinuria, the etiology may be suggested from the history and physical examination. This is particularly true for patients who have a systemic disease such as diabetes mellitus, systemic lupus erythematosus, HIV infection, or intake of a commonly offending drug although this is much less common in pregnant women (NSAIDs, gold, penicillamine). In many cases, however, renal biopsy is required to establish the diagnosis. The decision to perform renal biopsy during pregnancy, or to defer until after delivery, is based on several factors, including the stage of pregnancy, the severity of the renal disease, and the suspected underlying diagnosis.

Several analyses have concluded that the presence of nephrotic syndrome, in the absence of significant renal insufficiency and/or significant hypertension, does not seem to affect the natural course of renal disease or fetal survival [64]. Hence, conservative management until delivery in such patients, particularly through the later stages of pregnancy, is a reasonable management option. When nephrotic syndrome presents early in pregnancy, and/or there is progressive decline in renal function, timely treatment of the underlying kidney disease is often indicated. In such cases, the potential benefits of kidney biopsy may outweigh the risks.
Although data on the safety of renal biopsy during pregnancy are limited, clinical experience suggests that it is technically easier if undertaken prior to about 30 weeks of gestation. Later in gestation, the gravid uterus makes the standard prone position difficult. In such cases, renal biopsy is frequently deferred until the patient has stabilized postpartum. The major complication of biopsy is bleeding. In a systematic review of reports of renal biopsies performed during pregnancy or postpartum, the risk of bleeding appeared to be higher when the biopsy was performed during pregnancy as compared with postpartum (7 percent [16/197] versus 1 percent [3/268]) [65]. All observed cases of major bleeding (ie, requiring blood transfusion) occurred in biopsies performed between 23 to 26 weeks of gestation, suggesting women in this gestational age range may be particularly vulnerable to complications.

**MANAGEMENT OF NEPHROTIC SYNDROME IN PREGNANCY** — The management of the nephrotic syndrome in pregnancy is based on expert opinion, as very little data are available to support evidence-based practice.

**Edema** — A major goal in the management of nephrotic syndrome is to reduce edema to a level that allows comfort during ambulation. The dietary intake of sodium may be limited to 1.5 g (approximately 60 mEq) of sodium per day to reduce new edema formation, provided normal blood pressure is maintained. Bed rest and leg elevation are safe and often effective methods to facilitate resolution of edema.

In general, the use of diuretics is discouraged because of the theoretical risk that they will impair the normal pregnancy-associated expansion of plasma volume, possibly decreasing placental perfusion. However, there is no clear evidence of adverse fetal effects with thiazide or loop diuretics, and their use is occasionally indicated for severe, intractable edema [66]. In such cases, therapy should aim to reduce excessive edema at a slow rate of no more than 1 to 2 pounds per day with a loop diuretic, while a low sodium diet is maintained. If treatment on a chronic basis is needed, diuretic therapy should be administered on an alternate-day schedule to avoid a reduction of plasma volume and electrolyte disturbances. A written record of daily weights, taken by the patient, is highly recommended. Diuretics should not be used in preeclampsia because this condition is characterized by a reduction in circulating plasma volume.

**Anticoagulation** — Nephrotic syndrome is associated with an increased risk of deep venous thrombosis (DVT). Routine prophylactic anticoagulation in severe nephrotic syndrome (ie, serum albumin <2.0 mg/dL) is controversial, and generally recommended only if another risk factor for thrombosis is present (see "Renal vein thrombosis and hypercoagulable state in nephrotic syndrome"). Since pregnancy is a prothrombotic state, we believe prophylactic anticoagulation should be considered in pregnant women with nephrotic syndrome and severe hypoalbuminemia (serum albumin <2.0 mg/dL, or <2.8 mg/dL in membranous nephropathy), especially if another risk factor (eg, bedrest) is present. However, this decision needs to be made on a case-by-case basis with consideration of the patient’s specific risk factors for bleeding complications, including pregnancy-related bleeding.

Low-molecular weight heparin or unfractionated heparin is appropriate for prophylactic anticoagulation in pregnancy. Warfarin should be avoided during pregnancy because it crosses the placenta and can have adverse fetal effects, but can be used postpartum, even in breastfeeding women. Anticoagulation should be continued in the immediate postpartum period, particularly in women undergoing cesarean delivery, as this period carries a particularly high risk for DVT. (See "Use of anticoagulants during pregnancy and postpartum").

**Hyperlipidemia** — Statins are contraindicated in pregnancy because of limited and contradictory data suggesting an increased risk of birth defects with first trimester exposure. This discordance may reflect confounding by indication. We suggest discontinuing statins in women who are planning pregnancy and resuming these drugs after delivery/breast feeding. (See "Statins: Actions, side effects, and administration", section on 'Risks in pregnancy and breastfeeding'.)

Bile acid sequestrants and fibrates have no established teratogenic effects and can be safely used in pregnancy to treat severe hyperlipidemia due to nephrotic syndrome.

**SOCIETY GUIDELINE LINKS** — Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Glomerular disease in adults" and "Society guideline links: Hypertensive disorders of pregnancy").

**INFORMATION FOR PATIENTS** — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Beyond the Basics topic (see "Patient education: Protein in the urine (proteinuria) (Beyond the Basics)")
SUMMARY AND RECOMMENDATIONS

- Evaluation of a fresh midstream urine specimen obtained as a clean voided specimen before pelvic examination minimizes the chance of contamination from vaginal secretions. (See 'Screening for proteinuria' above.)

- Urine dipstick to screen for proteinuria is associated with frequent false-positive and false-negative results, especially when the urine is particularly concentrated or dilute, respectively. It is most predictive of abnormal 24-hour proteinuria if +2 or greater. Positive urine dipsticks should be followed-up with a quantitative test. (See 'Screening for proteinuria' above.)

- The urinary protein-to-creatinine (PC) ratio (mg protein/mg creatinine) is an accurate, convenient, and relatively rapid method to quantify proteinuria in pregnancy. A urine PC ratio less than 0.15 mg/mg may be considered normal (predictive of less than 300 mg protein in a 24-hour collection) and values above 0.7 mg/mg are very likely to indicate significant proteinuria (more than 300 mg protein in a 24-hour collection). Ratios between 0.15 and 0.7 mg/mg should be further evaluated by 24-hour urine collection. If a 24 hour urine collection is not obtained, a protein:creatinine ratio of 0.26 mg/mg (30 mg/mmol) in a random urine sample is suggested as the threshold for significant proteinuria. (See 'Quantifying protein excretion' above.)

- The gestational age at which proteinuria is first documented is important in establishing the likelihood of preeclampsia versus other renal disease. Proteinuria documented prior to pregnancy or in early pregnancy (before 20 weeks of gestation) suggests preexisting renal disease. In late pregnancy, the presence of hypertension or other signs/symptoms of severe preeclampsia (e.g., thrombocytopenia, elevated liver transaminases), if present, also helps to distinguish preeclampsia from underlying renal disease. (See 'Differential diagnosis of proteinuria' above.)

- Preeclampsia is the most common cause of proteinuria in pregnancy and must be excluded in all women with proteinuria first identified after 20 weeks of gestation. If preeclampsia is excluded, then the presence of primary or secondary renal disease should be considered. If renal biopsy is indicated for diagnosis, it is usually better to wait until the patient is postpartum unless unexplained rapidly progressive loss of renal function is occurring. (See 'Differential diagnosis of proteinuria' above.)

- For women with nephrotic syndrome, discomfort from severe leg edema can be managed with sodium restriction (1.5 g, approximately 60 mEq), bedrest, and leg elevation. Prophylactic anticoagulation is reasonable in pregnant women with nephrotic syndrome and severe hypoalbuminemia (serum albumin <2.0 g/dL, or <2.8 g/dL in membranous nephropathy), especially if another risk factor (e.g., bedrest) is present. Bile acid sequestrants and fibrates can be safely used in pregnancy to treat severe hyperlipidemia due to nephrotic syndrome; statins should be avoided. (See 'Management of nephrotic syndrome in pregnancy' above.)

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REFERENCES


Topic 4808 Version 24.0
**Criteria for the diagnosis of preeclampsia**

<table>
<thead>
<tr>
<th>Systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg on two occasions at least four hours apart after 20 weeks of gestation in a previously normotensive patient</th>
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<tbody>
<tr>
<td>If systolic blood pressure is ≥160 mmHg or diastolic blood pressure is ≥110 mmHg, confirmation within minutes is sufficient</td>
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<tr>
<td><strong>Proteinuria</strong> ≥0.3 g in a 24-hour urine specimen or protein/creatinine ratio ≥0.3 (mg/mg)(30 mg/mmol)</td>
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<tr>
<td>Dipstick ≥1+ if a quantitative measurement is unavailable</td>
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</table>

**OR**

**New-onset hypertension with the new onset of any of the following (with or without proteinuria):**

- Platelet count <100,000/microL
- Serum creatinine >1.1 mg/dL (97.2 micromol/L)
- Liver transaminases at least twice the upper limit of the normal concentrations for the local laboratory
- Pulmonary edema
- Cerebral or visual symptoms (eg, new-onset and persistent headaches not responding to usual doses of analgesics; blurred vision, flashing lights or sparks, scotomata)

* Each measured as mg/dL.


Graphic 79977 Version 22.0
## Causes of proteinuria in pregnancy

<table>
<thead>
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<th><strong>Primary renal diseases</strong></th>
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<tbody>
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<td>Minimal change disease</td>
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<td>Membranous nephropathy</td>
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<td>Focal segmental glomerulosclerosis</td>
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<td>Allergic interstitial nephritis</td>
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<td>Polycystic kidney disease</td>
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<th><strong>Systemic causes</strong></th>
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<td>Diabetic nephropathy</td>
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<td>Lupus nephritis (diffuse proliferative, focal proliferative, membranous)</td>
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<td>Hypertensive nephrosclerosis</td>
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<td>Thrombotic thrombocytopenic purpura (TTP)</td>
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<td>Infection-associated glomerular disease (eg, HIV, hepatitis B/C)</td>
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<td>Systemic vasculitis</td>
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<td>Multiple myeloma</td>
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<td>Chronic vesicoureteral reflux</td>
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<tr>
<td>Antiphospholipid syndrome</td>
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<td>Symptomatic urinary tract obstruction</td>
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Findings which increase the certainty of the diagnosis of preeclampsia

<table>
<thead>
<tr>
<th>Finding</th>
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<tr>
<td>Systolic blood pressure ≥160 mm Hg</td>
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<tr>
<td>Diastolic blood pressure ≥110 mm Hg</td>
</tr>
<tr>
<td>Proteinuria occurring for the first time during pregnancy, especially if ≥2 g in 24 hours. A qualitative result of 2+ or 3+ is also suggestive.</td>
</tr>
<tr>
<td>Serum creatinine &gt;1.2 mg/dL, (106 mmol/L)</td>
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<tr>
<td>Platelet count &lt;100,000 cells per cubic millimeter</td>
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<td>Evidence of microangiopathic hemolytic anemia (eg, elevated indirect bilirubin or lactic acid dehydrogenase)</td>
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<td>Elevated liver chemistries (eg, alanine aminotransferase or aspartate aminotransferase)</td>
</tr>
<tr>
<td>Persistent headache or other cerebral or visual disturbances</td>
</tr>
<tr>
<td>Persistent epigastric pain</td>
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Graphic 60502 Version 3.0

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