Volume 62, Number 2
OBSTETRICAL AND GYNECOLOGICAL SURVEY

CME REVIEW ARTICLE 4

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Clinical Significance of Proteinuria in Pregnancy

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Urinary protein excretion is considered abnormal in pregnant women when it exceeds 300 mg/24 hours at anytime during gestation, a level that usually correlates with 1+ on urine dipstick. Proteinuria documented before pregnancy or before 20 weeks' gestation suggests preexisting renal disease. The National High Blood Pressure Education Program Working Group recommended that that the diagnosis of proteinuria be based on the 24-hour urine collection. Preeclampsia is the leading diagnosis that must be excluded in all women with proteinuria first identified after 20 weeks of gestation. Given the vasospastic nature of this condition, when it is present, the degree of proteinuria may fluctuate widely from hour-to-hour. Hypertension or proteinuria may be absent in 10–15% of patients with HELLP syndrome and in 38% of patients with eclampsia. The acute onset of proteinuria and worsening hypertension in women with chronic hypertension is suggestive of superimposed preeclampsia, which increases adverse outcomes. However, because proteinuria is not independently predictive of adverse outcome, an exclusive proteinuric criterion as an indication for preterm delivery in preeclampsia should be discouraged.

Target Audience: Obstetricians & Gynecologists, Family Physicians

Learning Objectives: After completion of this article, the reader should be able to state that measurement of urinary protein levels by simple techniques are not sensitive or specific, recall that both hypertension and proteinuria may be absent in patients with preeclampsia, and explain that proteinuria is not predictive of adverse outcomes and that delivery should not be based on protein excretion alone.

During pregnancy, proteinuria has traditionally been regarded as a hallmark of preeclampsia and an indicator of its severity. Dieckmann attributed the first reported demonstration of proteinuria in pregnancy to Rayer in 1840, followed in 1843 by Lever's reports of the frequent occurrence of proteinuria in eclampsia (1). In spite of the quantitation and identification of proteins excreted in the urine in normal (2–5) and hypertensive (6,7) pregnancies, the mechanism and significance of proteinuria have been debated. Furthermore, the amount of proteinuria considered to be abnormal in pregnancy has been variously defined. The purpose of this article is to review the literature with regard to proteinuria and to help guide the management of the pregnant preeclamptic patient. Relevant studies were identified by searching MEDLINE and PUBMED from the inception of each database through January 2006 using the terms proteinuria, albuminuria, and preeclampsia.

The authors have disclosed that they have no financial relationships with or interests in any commercial companies pertaining to this educational activity.

Lippincott Continuing Medical Education Institute, Inc. has identified and resolved all faculty conflicts of interest regarding this educational activity.

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NORMAL PREGNANCY RENAL PHYSIOLOGY

Hemodynamic changes in renal physiology occur very early in pregnancy. Dunlop demonstrated that the effective renal plasma flow (ERPF) rises 75% over nonpregnant levels by 16 weeks' gestation (8). This increase is maintained until 34 weeks' gestation, when a decline in ERPF of about 25% occurs. Like ERPF, glomerular filtration rate (GFR) as measured by inulin clearance increases by 5–7 weeks' gestation. By the end of the first trimester, GFR is 50% higher than in the nonpregnant state, and this is maintained until the end of pregnancy. Three months postpartum, GFR values decline to normal levels (8,9). Because the ERPF increases more than the GFR early in pregnancy, the filtration fraction (ERPF/GFR) falls from nonpregnant levels until the late third trimester. At this time, because of the decline in ERPF, the filtration fraction returns to nonpregnant values of 20–21%.

Clinically, GFR is determined by measuring endogenous creatinine clearance. The creatinine clearance in pregnancy is increased to values of 150–200 mL/min (compared to a normal nonpregnant value of 120 mL/min) (10). Creatinine clearance reliably reflects renal function provided that a complete urine collection is achieved during an accurately timed period. During pregnancy, serum creatinine and blood urea nitrogen levels decrease from means of 0.7 and 12 mg/dL to 0.5 and 9 mg/dL, respectively. Values of at least 0.9 and 14 mg/dL, respectively, suggest underlying renal involvement. Even in most preeclamptic patients with proteinuria that qualifies as severe (at least 5 grams/24 hours), renal function as reflected by serum creatinine concentration or creatinine clearance is not significantly altered. Thus, these tests play a limited role in clinical management (10).

Serum uric acid declines in early pregnancy because of the rise in GFR, reaching a nadir of 2.0–3.0 mg/dL by 24 weeks (11). After 24 weeks, the uric acid level begins to rise, and by the end of pregnancy, the levels in most women are essentially the same as before pregnancy. The rise in uric acid levels is caused by increased renal tubular absorption of urate. Patients with preeclampsia have elevated uric acid levels; however, because uric acid levels normally rise during the third trimester, this test is generally of little value in the diagnosis and management of preeclampsia (11).

During pregnancy, urinary protein excretion increases from normal nonpregnant levels of 60–90 mg/24 hours to 180–250 mg/24 hours in the third trimester (12). Kuo also showed that there are only slight differences between nonpregnant and normal pregnancy urinary protein levels (13). Even if slightly increased during pregnancy, urine protein excretion seldom reaches levels that are detected by usual screening methods, such as 1+ on urinary dipstick (i.e., 30 mg/dL, which is roughly equivalent to 300 mg in 24 hours). Although the mechanism for this possible increase has not been established, it seems likely that absorption of filtered protein in the proximal tubule is reduced. Higby showed that in normal pregnant women without preeclampsia, underlying renal disease, or urinary tract infections, the mean 24-hour urine protein did not increase significantly by trimester (14). Protein excretion is considered abnormal in pregnant women when it exceeds 300 mg/24 hours at anytime during gestation, the level at which the dipstick becomes positive at the 1+ level (with ideal correlation) (14). The gestational age at which proteinuria is first documented is important in assessing the etiology of proteinuria. Proteinuria documented before pregnancy or before 20 weeks of gestation suggests preexisting renal disease. In women with preexisting proteinuria, in the absence of preeclampsia, pregnancy causes increases in the amount of proteinuria in both the second and third trimesters and even potentially in the first trimester. In a study by Gordon of women with diabetic nephropathy, the amount of proteinuria increased from a mean of 1.74 $\pm$ 1.33 grams/24 hour in the first trimester to a mean of 4.82 $\pm$ 4.7 grams/24 hour in the third trimester, irrespective of whether preeclampsia was diagnosed (15). Preeclampsia is the leading diagnosis to exclude in all women with proteinuria first identified after 20 weeks of gestation. If preeclampsia is excluded, then undiagnosed preexisting renal disease should be considered.

PATHOGENESIS

The pathogenesis of proteinuria in preeclampsia involves primarily glomerular changes. The normal near absence of protein from urine is due both to a relative impermeability of glomeruli to large proteins, and to the tubular resorption of smaller proteins that cross the glomeruli. As glomerular damage occurs, permeability to proteins increases and, as damage worsens, so does the size of the protein molecule that can cross the glomerular membrane. This enhanced permeability results in a decrease in selectivity, so that, with severe damage, both small and large proteins are present in the urine (16). As with other

types of proteinuria of glomerular origin, the proteinuria of preeclampsia involves predominantly high-molecular-weight proteins such as albumin. It has been known for many years that there is great variability in the hour-to-hour protein/creatinine ratio in women with preeclampsia (17). Given that the glomerular damage is constant, the variation in proteinuria must depend on a varying functional cause, i.e. vasospasm. Most electron microscopy studies of renal biopsies are consistent with glomerular capillary endothelial swelling. These changes, accompanied by subendothelial deposits of protein material, are referred to as glomerular capillary endotheliosis (18). The endothelial cells are often so swollen that they block or partially block the capillary lumens. This finding is the most logical explanation for the decreased glomerular filtration rate (as reflected by decreased creatinine clearance) seen in preeclampsia. Even so, in most preeclamptic patients with severe proteinuria (at least 5 grams/24 hours), renal function as reflected in serum creatinine concentration or creatinine clearance is not significantly altered.

In their extensive study of renal biopsy specimens obtained from hypertensive pregnant women, McCartney found proteinuria only when the glomerular lesion considered characteristic of preeclampsia was evident (19). Importantly, both proteinuria and alterations of glomerular histology may develop late in the course of preeclampsia.

PROTEINURIA AND PREECLAMPSIA

Proteinuria remains a hallmark of preeclampsia and is a requirement for its diagnosis. Proteinuria is defined by the National High Blood Pressure Education Program Working Group as excretion of 300 mg or more of protein in a 24-hour specimen (20). This will usually correlate with a concentration of 30 mg/dL ($\geq$1+ on dipstick) in a random urine determination and presumes that there is no evidence of a urinary tract infection. However, given the vasospastic nature preeclampsia, the degree of proteinuria may fluctuate widely from hour-to-hour, even in severe cases. This results in an inconsistently predictable discrepancy between random protein determinations and the 24-hour urinary total protein collection (13,21,22). Thus, the Working Group recommended that the diagnosis be based on the 24-hour urine collection for total protein if at all possible or, as an alternative, that it be based on a timed urinary protein/creatinine ratio (and not a random spot sample). As another alternative to the 24-hour collection, proteinuria is defined as a concentration of at least 30 mg/dL (at least 1+ on dipstick) in at least 2 random urine samples collected at least 6 hours, but no more than 7 days apart (20). The International Society for the Study of Hypertension in Pregnancy defined significant proteinuria as excretion of 300 mg of protein or more in a 24-hour time period, or a random spot urine protein/creatinine ratio of $>$30 mg/mmol (23).

The Working Group also stated that proteinuria of greater or equal to 2 grams in 24 hours denotes a higher severity of disease and increases the certainty of the diagnosis (20). The American College of Obstetrics and Gynecology (ACOG) recognizes 5 grams or more of protein per 24-hour urine collection as an indicator for the diagnosis of severe preeclampsia (24).

It is worth pointing out that hypertension or proteinuria may be absent in 10–15% of patients with HELLP syndrome (25) and in 38% of patients with eclampsia (26). Because proteinuria may develop late in the course of preeclampsia, some women may be delivered before it appears.

Women with underlying chronic hypertension, especially if severe, have up to a 50% chance of developing superimposed preeclampsia (27). They may also have underlying renal disease. Their fetuses are at risk for prematurity, poor growth, and perinatal mortality. The development of superimposed preeclampsia in a pregnant woman with chronic hypertension is difficult to distinguish from worsening hypertension. The acute onset of proteinuria and worsening hypertension is suggestive of superimposed preeclampsia. Therefore, in women with chronic hypertension, it is important to obtain a 24-hour urine collection for total protein as early in pregnancy as possible (28–30).

PROTEINURIA AND PREGNANCY OUTCOMES

Preeclampsia is strongly associated with poor fetal, neonatal, and maternal outcome (31,32). It is known that women with preeclampsia have worse pregnancy outcomes than those with gestational or chronic hypertension alone (33). Chan showed that, among women with preeclampsia, the degree of proteinuria is positively correlated with the risk of adverse maternal and fetal outcomes (34). However, he could not identify a specific spot protein/creatinine ratio at the time of diagnosis that could be used as a definitive screening value for adverse outcomes. Freidman and Neff showed that worsening hypertension, especially if accompanied by proteinuria, increased the risk of fetal death (35). However, proteinuria without

hypertension had little overall effect on the fetal death rate. Newman reported that women with preeclampsia and proteinuria >10 grams/24 hours did not have increased maternal morbidity compared with women with less protein excretion (36). Proteinuria >10 grams/24 hours was associated with earlier onset of preeclampsia, earlier gestational age at delivery, and higher rates of prematurity complications. However, after correction for prematurity, this degree of proteinuria had no significant effect on neonatal outcome, thus suggesting that neonatal morbidity appeared to be a function of prematurity rather than the proteinuria itself.

Schiff showed that proteinuria increases in most women with severe preeclampsia who are managed conservatively (median increase 660 mg over each 24 period) (37). No differences in maternal or fetal outcomes were found between pregnancies with marked increases in proteinuria and those with modest or no increases. They concluded that neither the amount of proteinuria nor the rate of increase in proteinuria during conservative management of preeclampsia is important predictors of maternal or perinatal outcome. The change in urinary protein excretion did not correlate with the admission-to-delivery interval, demonstrating that proteinuria does not portend the appearance of other factors that would necessitate delivery. They recommended that pregnancies complicated by severe preeclampsia remote from term and managed conservatively not be terminated on the basis of proteinuria or an increment therein, as long as other maternal and fetal clinical assessments are reassuring. They did not recommend repeating the 24-hour urine collection for protein determination, a relatively inconvenient test, after the diagnosis of severe preeclampsia has been established. Moreover, Chua and Redman (38) have demonstrated that patients with marked proteinuria caused by preeclampsia showed no evidence of residual renal dysfunction several weeks after delivery, including those who had undergone conservative management for a median duration of 2 weeks. The findings in these 2 studies support elimination of an exclusive proteinuric criterion as an indication for preterm delivery.

LABORATORY MEASUREMENTS OF PROTEINURIA

Dipstick Protein

The initial presence of proteinuria is usually determined by the use of a protein reagent dipstick in a random urine sample. However, the concentration of urinary protein is known to vary markedly (39). It is influenced by several factors, including contamination (blood or infection), specific gravity, pH, exercise, and posture (40). Evaluation of a fresh midstream urine specimen obtained as a clean voided specimen before pelvic examination minimizes the chance of contamination from vaginal secretions. Clearly urine dipstick is a protein concentration, not an absolute value, and thus hydration status can greatly affect this result. False-positive tests may occur in the presence of blood, highly alkaline urine, quaternary ammonium compounds, detergents and disinfectants, drugs, radio-contrast agents, and high specific gravity (>1.030). False negatives can occur with low specific gravity (<1.010), high salt concentration, highly acidic urine, or with nonalbumin proteinuria. Since this test is a concentration test, one must remember that during the day, pregnant women tend to accumulate water in the form of dependent edema, and at night, while recumbent, they mobilize this fluid and excrete it via the kidneys. Thus, the time of day when a dipstick is performed can affect the results.

Urinary dipstick determinations correlate poorly with the amount of proteinuria found in 24-hour urine determinations (13,22,41,42). Kuo et al (13) demonstrated a large number of both false-positive and false-negative results with dipstick analysis, partly because of the limited quantitative accuracy of the dipstick and partly because of interobserver variation. Meyer concluded that urinary protein dipstick values ≥1+ have a positive predictive value of 92% for predicting ≥300 mg/24 hours (22). In contrast, a dipstick of negative to trace should not be used to rule out significant proteinuria because its negative predictive value is only 34% in hypertensive patients. Moreover, urine dipstick values of 3+ to 4+ should not be used to diagnose severe preeclampsia because their positive predictive value is only 36%. Waugh in a recent review demonstrated that the accuracy of dipstick urinalysis with a 1+ threshold in the prediction of significant proteinuria (>300 mg/24 hour) is poor (43). In summary, the definitive test for diagnosing proteinuria is not the urine dipstick test due to the many factors that can affect this concentration measurement, creating both false positives and false negatives.

Random Protein/Creatinine Ratio

Proteinuria can also be measured in both pregnant and nonpregnant states by calculating the protein/

creatinine ratio in a single random urine sample (44,45) This minimizes collection and laboratory errors, saves time in obtaining results, and is far more convenient for the patient. The use of a single random urinary protein/creatinine ratio to predict significant (>300 mg/24 hour) proteinuria is controversial. Most of the studies evaluating the protein/creatinine ratio studied hospitalized nonambulatory patients with suspected preeclampsia. Thus, the results may not be extrapolated to ambulatory patients in an outpatient setting, for whom protein/creatinine ratio testing has been advocated by some authors (23). Many studies have shown a strong linear association between the random urinary protein/creatinine ratio and the 24-hour total protein excretion in pregnant women (42,45–52). Neithardt et al also showed that the protein/creatinine ratio predicted trends in protein excretion over time in hospitalized women. Conversely, other studies have reported weaker correlations (53,54). Furthermore, Durnwald showed that the random protein/creatinine ratio did not reflect the protein/creatinine ratio from 24-hour urine collection accurately, which suggested that the random protein/creatinine ratio does not adjust adequately for variation in protein excretion from hour-to-hour (54).

Despite the multiple studies showing high degrees of correlation between the random protein/creatinine ratio and total protein in a 24-hour collection, the optimal best cutoff point to distinguish between significant and nonsignificant proteinuria has not been agreed upon. An adequate screening test must strike a balance between sensitivity and specificity. In evaluating a screening test and analyzing receiver–operator curves to evaluate the optimal cutoff point, it is important to evaluate the consequences of a lower sensitivity and thus a higher false-negative rate, versus a lower specificity and a higher false-positive rate. A false-positive test could potentially lead to unnecessarily hospitalization or even delivery, and result in greater anxiety and costs. However, a false negative could lead to a failure to diagnose preeclampsia. Thus, sensitivity should be as high as possible, balanced against a clinically acceptable false-positive rate.

Many studies have attempted to define the optimal cutoff point, using receiver–operator curves to find the best relationship between true positives and false positives. Most studies have evaluated hospitalized women admitted for evaluation of hypertension. Thus, these women were predominantly at bed rest. Rodriguez-Thompson showed that a ratio below 0.14 ruled out significant proteinuria, and a ratio of >0.19 was shown to be an optimal value for predicting significant proteinuria (47). Thus, the values between 0.14 and 0.19 would seem to be an indeterminate range, which may be troublesome for the clinician. Most of the false-positive and false-negative results in the Rodriguez-Thompson study were within 50 mg of the 300 mg cutoff point for a 24-hour collection. Only 1 woman had protein greater than 5 grams; however, the random protein/creatinine ratio has been previously shown to correlate well in pregnant women with severe (at least 5 grams in 24 hours) proteinuria (45,51). This same cutoff value (0.19) was also shown by Al to be optimal to predict significant proteinuria (53). Saudan calculated that a random protein/creatinine ratio of >30 mg/mmol creatinine was the optimum discriminant value for predicting significant proteinuria (42). The differing units for protein/creatinine ratio in this study reflect local standards. The optimal screening parameters from these 3 studies are shown in Table 1.

The protein/creatinine ratio has been evaluated in ambulatory women as well (55). Young showed that no value was ideal to distinguish between significant and insignificant proteinuria in ambulatory women; however, a ratio less than 0.15 efficiently ruled out significant proteinuria (>300 mg/24-hour collection) (55). It has been speculated that postural changes in the renin–angiotensin system might explain the difference in protein excretion (44). No other studies have evaluated this test in an ambulatory setting, which would be the ideal setting for a simple random spot test such as this. Thus, as a first line test, the protein/creatinine ratio of a single random voided urine specimen may play a role in the management of hospitalized women with suspected preeclampsia, al-

TABLE 1
Optimal cutoff values of the random urinary protein/creatinine ratio in predicting significant proteinuria (at least 300 mg) in a 24-hour collection

	Cutoff Value	Sensitivity	Specificity	PPV	NPV
Rodriguez-Thompson (47)	0.19	0.90	0.70	0.75	0.87
Al (53)	0.19	0.85	0.70	0.46	0.95
Saudan (42)	30 mg/mmol	0.93	0.92	0.95	0.90

though further study is needed in order to extrapolate these results to an ambulatory setting.

It is important to remember that a random urine protein/creatinine ratio provides a good estimation of total protein excretion per 24 hours, providing that glomerular filtration is stable, and urinary creatinine and protein excretion fairly constant (44). When this is true, the 24-hour protein excretion rate is accurately estimated by the concurrent rate of creatinine excretion. Protein excretion rates, however, can vary from hour-to- hour in preeclampsia, and for this reason, this test has not been universally endorsed for evaluating proteinuria when preeclampsia is suspected.

24-Hour Urine Collection for Total Protein

The 24-hour urine collection for total protein remains the gold standard in evaluation of proteinuria in preeclampsia. It is the most accurate means of quantification of proteinuria and will allow the determination of renal function as measured by the creatinine clearance. However, the 24-hour urine collection is subject to collection and laboratory errors. It is time consuming and inconvenient for the patient. In addition, the collection obviously takes 24 hours to complete, which leads to a delay in diagnosis. It should be noted that when one is performing serial 24-hour urine samples to evaluate a change in renal status, it is crucial that the collection be standardized. The best method of comparing 2 urine collections is to evaluate the total amount of creatinine excreted in a 24-hour period. The amount of creatinine cleared in a day should remain constant during the course of a pregnancy for a given patient. If there is a large discrepancy in total creatinine between 2 samples, the difference in protein measured should be suspect.

Shorter timed interval collections have been recently advocated. It has been demonstrated that a 12-hour collection can be substituted for the 24-hour collection without jeopardizing accuracy (56). While 8- and 12-hour urine collections correlate positively with values for 24-hour samples in pregnant women with proteinuria, only the 12-hour sample correlated with the 24-hour sample in women without proteinuria (57). Thus, a12-hour collection seems preferable to an 8-hour collection.

CLINICAL PEARLS

- Urinary protein excretion is considered abnormal in pregnant women when it exceeds 300 mg/24 hours at anytime during gestation, a level that usually correlates with 1+ on urine dipstick.
- The National High Blood Pressure Education Program Working Group recommended that that the diagnosis of proteinuria be based on the 24-hour urine collection. If a 24-hour collection is not feasible, the diagnosis should be based on a timed collection, not a random spot sample.
- The gestational age at which proteinuria is first documented is important in assessing the etiology of proteinuria. Proteinuria documented before pregnancy or before 20 weeks' gestation suggests preexisting renal disease.
- Preeclampsia is the leading diagnosis that must be excluded in all women with proteinuria first identified after 20 weeks of gestation. If preeclampsia is excluded, then undiagnosed, preexisting renal disease should be considered.
- The degree of proteinuria may fluctuate widely from hour-to-hour given the vasospastic nature of preeclampsia.
- In most preeclamptic patients with proteinuria (even those with 5 grams or more per 24 hours), renal function as reflected in serum creatinine concentration or creatinine clearance is not significantly altered. Thus, creatinine clearance and serum creatinine do not influence management greatly.
- Both proteinuria and alterations of glomerular histology may develop late in the course of preeclampsia.
- Hypertension or proteinuria may be absent in 10–15% of patients with HELLP syndrome and in 38% of patients with eclampsia.
- Pregnancies complicated by severe preeclampsia remote from term and managed conservatively should not be terminated on the basis of proteinuria or an increment therein, as long as other maternal and fetal clinical assessments are reassuring.
- The acute onset of proteinuria and worsening hypertension in women with chronic hypertension is suggestive of superimposed preeclampsia, which greatly increases adverse outcomes.
- There is no indication for repeating the 24-hour urine collection for protein determination after the diagnosis of severe preeclampsia has been established.
- An exclusive proteinuric criterion as an indication for preterm delivery should be discouraged.
- Urinary dipstick determinations correlate poorly with the amount of proteinuria found in 24-hour urine determinations.

- The use of a single random urinary protein/creatinine ratio to predict significant (>300 mg/24 hour) proteinuria is controversial. If used, a value of >0.19 (or 30 mg/mmol) has the best screening characteristics for significant proteinuria.
- The 24-hour urine collection for total protein remains the traditional gold standard in evaluation of proteinuria in preeclampsia. It is the most accurate means of quantification of proteinuria and will allow for the determination of renal function as measured by the creatinine clearance if so desired.
- A 12-hour urine collection has been found to be a reliable substitute for the 24-hour urine collection.

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