1. A primigravida presents at 28 weeks of gestation for a routine obstetric visit. For the first time in her pregnancy, she is found to have a 2+ to 3+ proteinuria reading on an office urine dipstick measurement. She has no risk factors, symptoms, or other signs of preeclampsia. How would you manage this particular problem?

Response from Drs. Marshall D. Lindheimer and David Kanter:

*If blood pressure and renal function are “normal” as implied in the description above, the first thing to do is to have the dipstick reading verified. Recall that medicine is a discipline where most tests are performed as a single analysis on the sample, while our brethren scientists, when designing studies, perform all their tests in duplicate or triplicate. (Presumably, costs dictate our own sins!!) In addition, far too often our clinics, offices, etc omit training and some form of certification on the ability of the technician or nurses to accurately read dipsticks (and to measure blood pressure correctly, for that matter). Assuming the repeat test is positive, the next*
step is a quantitative measurement. Our article gives you the choice of, as well as the pros and cons of, the 24-hour collection measuring both protein and creatinine excretion, or a protein/creatinine ratio on a spot urine. Once excessive proteinuria is established, a microscopic analysis of the urine is in order, and, if not included in the description above of “no risk factors, symptoms, or signs of preeclampsia,” a serum creatinine level should be measured.

Based on the urinanalysis, a urine culture and sensitivity might be in order in this otherwise symptomless patient. Some might request other “preeclampsia tests” (eg, platelet number, serum albumin, urate, and certain liver function tests), noting that proteinuria occasionally precedes other manifestations of preeclampsia, and that some blood pressure readings exceeding 120/70 mm Hg but still below 140/90 mm Hg may occur in so-called normotensive preeclamptic and eclamptic patients. (Remember those days when a rise of 15 mm Hg diastolic pressure and/or 30 mm Hg systolic pressure to values still below 140/90 mm Hg were in many preeclampsia guidelines?) Our view, though, is in a patient like that described above, normotensive and symptomless but with excessive proteinuria, the likelihood of true abnormal results is quite low, raising the percentage of false positives (and the conundrums they lead to). Thus, we would not do all this testing immediately.

Of greatest importance here is that establishing the presence of excessive proteinuria in a pregnant normotensive woman is best followed by seeking a nephrology consultation. The consultant may suggest tests to determine whether the proteinuria is functional (if so, it should have been noted earlier in the gestation) and whether further diagnostic testing is in order, and will advise the frequency with which certain parameters such as repeat serum creatinine levels, quantitative proteinuria, and blood elements such as serum albumin and lipids—the latter two often affected when proteinuria is in the nephrotic range—should be checked. (Hopefully, he does a urinanalysis himself!) As the probability of a successful pregnancy in a normotensive woman with proteinuria, normal renal function, and no hypertension approaches that for an uncomplicated gestation, most of the evaluation may be deferred to the postpartum period. Most important, however, contact with a nephrologist at 28 weeks will ensure the patient’s course is followed up correctly after delivery.
2. If urine dipstick measurements have been proven to be inaccurate, do you recommend that the prevailing practice of monitoring proteinuria in pregnant patients with dipstick measurements at the time of routine visits be discontinued? Do you have suggestions for better methods for screening for proteinuria in the pregnant patient? How do you screen for proteinuria in your practice?

Response from Drs. Marshall D. Lindheimer and David Kanter:
A debated question indeed: The urine dipstick is still considered to have value for screening by many, for at least positive results can be investigated further. Obviously, this area could utilize more outcome research. There is hope on the horizon as technology to determine semi-quantitative determination of urine albumin/creatinine ratios within a clinical setting are under investigation. This and other more preferable methods of screening are mentioned in the article, with further information in the references cited.

3. Twenty-four–hour urine collection remains the diagnostic gold standard in assessing proteinuria, especially in the evaluation of preeclampsia. What measures should be taken to standardize the process of collecting a 24-hour urine sample? Do you provide outpatients with written instructions summarizing the process of collecting urine? If so, what are they? How do these instructions differ for inpatients with indwelling catheters?

Response from Drs. Marshall D. Lindheimer and David Kanter:
Actually, our article suggested that the approach to proteinuria in pregnant women had been hampered by a failure to consider the changes in the renal tract during gestation, as well as a failure to apply our knowledge of how the kidney handles protein. Among the first questions asked were, should the obstetricians, as the nephrologists have, abandon 24-hour collections, and adopt the protein/creatinine ratio? Our goal was to emphasize the many flaws in the use of the timed collections, underscored by one report that noted about 50% inaccuracy, and likewise
that the criteria that would allow validation of the ratio also had yet to be assessed correctly. We further hoped to convince the reader that literature that assessed sensitivity and specificity of the ratio, using the 24-hour collection as a “fool’s gold” standard, was in this “expert’s (!)” opinion almost useless, suggesting other ways of validating. Actually, given the data as reviewed, we stopped 24-hour collections, replacing them with the protein/creatinine ratios over a year ago, but await more definitive data. (It must be that nephrologist blood in the first author!)

Concerning the question regarding the best ways to collect timed urines during pregnancy: This was described toward the end of page 2 of the article in the section discussing the relevance of knowing the normal changes in the urinary tract accompanying pregnancy. “The best way to avoid both retention and timing errors is to have the patient hydrated and positioned in lateral recumbency (the definitive nonobstructive posture) for 45 minutes or 1 hour before starting (ie, the discard), and again before completing the collection. This minimizes dead-space errors by producing a modest diuresis and at the same time ensures that any residual urine in the urinary tract or bladder is dilute and of recent origin. One might pause here and state that while such maneuvers are possibly enforceable for inpatient studies, they are impractical for outpatient collections, and this may well be true. However, the general principle, assuring that an almost identical procedure is used to perform the ‘discard’ that starts the collection, and the ‘finish’ that ends collection, will still eliminate substantial error.” The indwelling catheter, of course, makes collections easier, but as also noted in the text, the catheter does not entirely eliminate the retention and timing errors due to the physiological dilation of the urinary tract of gravidas. We further cautioned that studies in which catheterized patients were sampled periodically throughout the day to validate or invalidate the constancy of the protein/creatinine ratio were problematic as such patients often do not have steady-state glomerular filtration rates.
4. Is significant proteinuria, either on urine dipstick measurement or 24-hour urine collection, always a sign of an organic process or condition? If not, how can the practitioner differentiate between functional and pathophysiological causes of proteinuria?

Response from Drs. Marshall D. Lindheimer and David Kanter:

Significant proteinuria can be totally functional, and this is especially true of young patients, pregnant or not, who have postural proteinuria. It is claimed that postural proteinuria may be greater in gravida when they assume an exaggerated lordotic position. There is a standard test to determine if proteinuria is postural in origin whereby urine is collected with the patient supine (in pregnancy it might be preferable to try maintaining lateral recumbence for the given period of time, usually 8 hours, and then the quantity of protein excreted during this timed collection is extrapolated to 24 hours). If the individual has postural proteinuria, the amount should now be within the normal range, while the amount collected during upright activity extrapolates to an abnormal quantity. Other causes of functional proteinuria such as fever and congestive failure (fortunatel rare in pregnancy) abate when the inciting event is reversed, and are usually easily diagnosed.

5. In cases of proteinuria in which preeclampsia has been excluded, what additional laboratory or radiographic studies might the general obstetrician consider in the workup? When should the patient be referred to a specialist? Should the patient be referred to a maternal–fetal medicine specialist or a nephrologist?

Response from Drs. Marshall D. Lindheimer and David Kanter:

This question was partially answered in the responses to query 1. There we suggested only serum creatinine levels and a urinanalysis, then ruling out infection if the initial results indicated doing so. We noted that we do not recommend the various tests to determine specific glomerular diseases as the specialist consulted will repeat most of them anyway. Ironically,
most of the consultations one of us (MDL), a nephrologist, has received during his 40-year career have been requested by Maternal–Fetal Medicine subspecialists. Fortunately, no one has ever consulted him on the management of a footling breech (our indirect answer to the question of who should be consulted). However, if a renal subspecialist is not available where one practices, most board-eligible or certified Internists are able to handle the initial phases of the investigation.

6. You recommend that individual hospital laboratories establish their own population norms and upper limits of 95% confidence intervals for 24-hour urine protein. How feasible is this for the typical institution, and what would be the process to develop these norms? Have you established such criteria in your institution?

Response from Drs. Marshall D. Lindheimer and David Kanter:

The implied criticism in this question that what we wrote may have contained a little egghead elitism is justified. Our statements noting that it may be time to have regional or hospital laboratories determine means and confidence levels in their populations was included to underscore the best way to approach the subject in (as the old philosopher said) the best of all worlds. It was further meant to remind us not to allow those important lessons we learned in medical schools to slip from our minds, and we were tweaking the readers, a little, reminding them of the fallacies we daily accept in the literature. one example being, for instance, an article, text, or guideline proclaiming the “value” above which an increased lactate dehydrogenase (LDH) level enters into the diagnosis of hemolysis, elevated liver enzymes, and low platelets (HELLP), etc, etc. When we read a laboratory report, or read a position paper, we should remember all laboratories do not regularly produce the exact same results, and the more appropriate way to approach these issues is by exceeding some value above their own upper limit of a 95% confidence level. Though it sounds impractical today, we agree this approach would not be that hard to introduce or learn, and would be a better way to think of normal and abnormal in relation to our patients. (N’est ce pas?)