Uric Acid
A Clinically Useful Marker to Distinguish Preeclampsia From Gestational Hypertension

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See related article, pp 704–708

During early pregnancy, serum uric acid levels fall, often to ≤3 mg/dL, related to the uricosuric effects from estrogen and from the increase in renal blood flow. Uric acid levels then increase during the third trimester, reaching levels of 4 to 5 mg/dL by term (reviewed in Reference 1). However, it is known that subjects destined to develop preeclampsia show slightly higher serum uric acid levels during the first trimester in association with a relative reduction in urinary urate excretion.2,3 At the time of presentation, subjects with preeclampsia frequently have significantly elevated serum uric acid levels, and some studies suggest that the degree of elevation correlates with the severity of the maternal syndrome and fetal morbidity, including small-for-gestational-age infants and fetal death.4,5

As a consequence of these observations, obstetricians frequently measure serum uric acid to both help diagnose preeclampsia and to predict maternal and fetal complications. However, the clinical use of such an approach has been challenged, because numerous studies have suggested that the predictive value of serum uric acid is relatively poor both for diagnosis and prognosis, especially for distinguishing preeclampsia from gestational hypertension.6–8 However, a classic problem with diagnostic tests relates to the population studied. According to Bayes’ theorem, the ability of a test to be useful in diagnosis relates to the frequency of the condition relative to the false-positive rate. Thus, if a disease is common for the particular population and the false positive rate is relatively low, the test has high predictive value, whereas in a setting where the disease is infrequent, a higher false positivity rate will lead to a low predictive value. Thus, a major problem with most of the negative studies is that they include all pregnant patients, in which only a small percentage will eventually develop preeclampsia, or, conversely, study subjects at or near term when serum uric acid levels are already rising in normal pregnancy yielding a higher false-positive rate.6–8

In the article by Bellomo et al9 in this issue of the journal, the authors have readdressed this issue in light of Bayes’ theorem by evaluating the role of uric acid in high-risk patients (primigravida, after 20 weeks) presenting with hypertension in the absence of proteinuria. This is clinically relevant, because this is exactly the type of patient in which the obstetrician typically measures serum uric acid to aid in diagnosis and prognosis. In this population of 163 subjects, the mean time of presentation was ~34 weeks, and a large percentage went on to develop preeclampsia (45%) or deliver small-for-gestational-age infants (26%). The data collection was particularly strong and included carefully defined methods for blood pressure measurement, including 24-hour ambulatory blood pressure monitoring. The results were remarkable. Uric acid conferred an 8- to 9-fold risk for preeclampsia and a 1.6- to 1.7-fold risk for small-for-gestational-age infants. A receiver operating characteristic analysis showed that a uric acid of 5.2 mg/dL (309 μmol/L) conferred excellent sensitivity, specificity, and likelihood ratios for diagnosis and prognosis. These studies suggest that measurement of serum uric acid is clinically useful and should be part of the evaluation of the pregnant patient presenting with hypertension but specifically in the primiparous patient presenting after 20 weeks of pregnancy.

Increasing evidence suggests that an elevated serum uric acid in pregnancy may not only be a valuable biomarker for preeclampsia but may also have a contributory role in the pathogenesis of the maternal and fetal manifestations (Fig-
Uric acid is a potent inhibitor of endothelial function, induces systemic and glomerular hypertension in animals, and passes freely into the fetal circulation. Uric acid has been found to block vascular endothelial growth factor–induced endothelial proliferation and, thus, may have a direct role in blocking fetal angiogenesis, resulting in small-for-gestational-age infants. Uric acid can also block trophoblast invasion in vitro. Uric acid has also been found to mediate insulin resistance in animals, and levels correlate with the development of insulin resistance in the pregnant patient. Thus, it is time to carefully revisit the role of uric acid as a possibly modifying factor in the pathogenesis of this important disease.

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