Uric acid: is it time to give up routine testing in management of pre-eclampsia?

Vikram Sinai Talaulikar MD MRCOG* and **Hassan Shehata** MD FRCOG FRCPI†‡

*Department of Obstetrics & Gynaecology, St George's Hospital and Medical School, Cranmer Terrace, Tooting, London SW17 0RE;

†Maternal Medicine Unit, Department of Obstetrics and Gynaecology, Epsom & St Helier University Hospitals NHS Trust, Surrey SM5 1AA;

‡St George's Medical School, Blackshaw Road, London SW17 0QT, UK

Summary: Ever since it was first linked with the pathophysiology of pre-eclampsia, uric acid has been a routine test requested by many care-givers managing pregnant women with hypertensive disease of pregnancy for almost 100 years. Existing evidence however suggests that it has no definitive role in prediction, diagnosis or management of pre-eclampsia. We argue against routine uric acid testing in pregnancies complicated by hypertension not only because it has become a fruitless academic exercise but also because ceasing its routine use will ensure cost-savings for the health services.

Keywords: uric acid, pre-eclampsia, gestational hypertension, investigations

INTRODUCTION

Uric acid is a product of purine degradation catalysed by the enzyme xanthine oxidase/xanthine dehydrogenase.¹ Unlike in most other mammals, in humans, uric acid is the final oxidation product of purine metabolism and is chiefly excreted in the urine.² Renal pathway accounts for up to 70% of daily uric acid excretion. It is freely filtered by the glomeruli with re-absorption and secretion in the proximal convoluted tubule of the kidney. Although some new guidelines^{3,4} for diagnosis and management of pre-eclampsia do not include uric acid as a mandatory test, serum uric acid testing still continues to form a part of routine investigations performed for hypertensive disorders of pregnancy by other guidelines⁵ or hospital protocols. A review of recent evidence raises questions over such a policy of routine testing.

URIC ACID AND NORMOTENSIVE PREGNANCY

Due to the physiological adaptations of a normal pregnancy, glomerular filtration rate (GFR) and renal plasma flow increase by at least 50%, starting soon after conception and lasting until term. There is a gradual fall (25–35%) in serum uric acid level in normal pregnancy until 16 weeks of gestation. The uric acid levels then tend to stabilize between 17 and 28 weeks of pregnancy and start rising during the third trimester.^{6–8} The normal ranges of serum uric acid values for each trimester of pregnancy are shown in Table 1. The initial drop in levels is

explained by an increase in GFR and filtered load with reduced tubular re-absorption as well as the uricosuric action of oestrogen.¹ The rise in late pregnancy may be secondary to increased fetal production, decreased binding to albumin and increased tubular re-absorption with falling renal clearance.

A study that attempted to evaluate serial changes in serum uric acid concentrations in healthy women before conception, at regular intervals throughout pregnancy and finally 12 weeks after delivery, found that after 24 weeks, uric acid concentrations increased and by term, they were greater than the prepregnancy values in the majority of patients and remained elevated until 12 weeks postpartum.⁹ The authors cautioned that clinical management based on rising serum uric acid concentration in the second half of pregnancy needed careful scrutiny against the background of physiological increase in serum uric acid in later pregnancy.

FACTORS AFFECTING SERUM URIC ACID LEVELS IN PREGNANCY

The following factors can significantly affect the levels of uric acid in pregnancy:

- Racial variation – A prospective study undertaken in New Zealand to measure serum uric acid levels in normal pregnant women of different races reported significantly higher levels in Polynesian, Maori and Cook Island women than European women in the third trimester;¹⁰
- Diet – Uric acid concentrations are influenced by diet containing high protein or fructose content;¹
- Alcohol consumption increases levels of uric acid;
- Conditions with increased cell turnover can increase serum urate levels, e.g. haemolytic anaemias, sickle cell disease, malignancies, organ transplant or cancer treatment;
- Enzymatic defects in purine metabolism;

Correspondence to: Vikram Sinai Talaulikar, Department of Obstetrics & Gynaecology, St George's Hospital and Medical School, Cranmer Terrace, Tooting, London SW17 0RE, UK
Email: vtalauli@sgul.ac.uk

Table 1 Normal ranges of serum uric acid values for each trimester of pregnancy⁹

	Non-pregnant	First trimester	Second trimester	Third trimester
Uric acid (mmol/L)	0.18–0.35	0.14–0.23	0.14–0.28	0.21–0.38

SI units for uric acid measurements are either mmol/L or more commonly $\mu\text{mol/L}$. Multiply the mmol/L value by 1000 to get $\mu\text{mol/L}$ value and then divide the $\mu\text{mol/L}$ value by 59.48 (conversion factor) to get the mg/dL value

- Altered renal function;
- Smoking – it has been reported that the higher uric acid concentrations in women who smoke may be secondary to increased production through the xanthine oxidase pathway;¹¹
- Number of fetuses – serum uric acid concentrations are higher in multiple gestations. A study found significantly higher mean uric acid concentrations at term in twin and triplet pregnancies compared with singletons (0.27, 0.30 and 0.22 mmol/L respectively).¹² The authors suggested that for clinical purposes, the upper limit of the uric acid cut-off concentrations at term should be adjusted using mean + 2 standard deviations as follows: 0.309, 0.428 and 0.452 mmol/L for singleton, twin and triplets, respectively. The changes in renal circulation and increased cell turnover have been suggested as the possible mechanisms leading to hyperuricaemia in these women;¹³
- Diurnal variation – a study reported that the mean serum uric acid value between 08:00 and 09:00 hours was higher than that observed between 17:00 and 18:00 hours.¹⁴ It was concluded that when attempting to interpret the serum uric acid concentration, it is important to consider its diurnal rhythms. Daily monitoring of serum uric acid in pre-eclamptic pregnancies therefore ought to be at a time of day when serum value is least likely to be affected by the diurnal rhythm. The authors recommended sampling after 11:00 hours and establishing appropriate sets of reference intervals for making pertinent comments on laboratory results for uric acid;
- Test assay – variations in the methods for estimating uric acid levels may affect results;
- Antihypertensive therapy – levels of uric acid could be raised due to the use of antihypertensives.¹⁵

With so many variables affecting the levels of serum uric acid, it is easy to realize why measurements of uric acid have produced conflicting results in various different clinical studies.

URIC ACID AND PRE-ECLAMPSIA

What may be the first report of increased uric acid in pre-eclampsia was published back in 1917.¹⁶ Reduced uric acid clearance secondary to reduced GFR, increased tubular re-absorption and decreased secretion have been cited as the main reasons for elevated serum uric acid levels in women with pre-eclampsia.^{17–19} Besides these mechanisms, the pathophysiology of pre-eclampsia is associated with increased trophoblastic tissue shedding, endothelial dysfunction and reduced blood flow in the fetomaternal unit and these may also contribute to the hyperuricaemia.

There is evidence for increased generation of uric acid from the ischaemic placenta. With tissue ischaemia there is metabolism of adenosine triphosphate to adenosine and xanthine, in addition to an increase of the enzyme xanthine oxidase within the ischaemic tissue.²⁰ In pre-eclampsia, serum adenosine²¹ and placental xanthine oxidase are increased.²² Xanthine is then converted by xanthine oxidase to uric acid with the generation of oxidants (superoxide anion). Some authors have hypothesized that hyperuricaemia may actually contribute to the development of hypertension and renal disease in pre-eclampsia.²³ It has been suggested that uric acid may contribute to the pathogenesis through attenuation of normal trophoblast invasion and integration into endothelial cell mono layers, leading to defective spiral artery vascular remodelling.²⁴ The hypothesis has been further supported by *in vitro* culture studies and hyperuricaemic animal models demonstrating several pathogenic effects of uric acid including proinflammatory effects, stimulation of smooth muscle cell proliferation, inhibition of endothelial cell proliferation/migration and promotion of endothelial dysfunction or damage.¹ However, because uric acid is a marker of oxidative stress, tissue injury and renal dysfunction, it is possible that uric acid is merely associated with a more severe form of pre-eclampsia and that the underlying metabolic syndrome, tissue damage, oxidative stress and inflammation may contribute to the increase in uric acid observed in hypertensive pregnancies.²⁵

From the time its association with pre-eclampsia was first described, it was hoped that uric acid would become the marker of choice allowing accurate prediction of onset or severity of pre-eclampsia or its complications, and thus leading to timely intervention such as termination of pregnancy so as to prevent any adverse outcomes. Unfortunately, the initial enthusiasm faded as more and more conflicting data about its usefulness appeared in the literature.

ROLE OF URIC ACID IN CURRENT CLINICAL PRACTICE

In current clinical practice, pre-eclampsia is diagnosed when there is onset or first detection of hypertension after 20 weeks of pregnancy with blood pressure readings of 140/90 mmHg or more on two occasions at least four hours apart and associated with proteinuria of at least 300 mg of protein over 24 hours. A urine dipstick testing for protein 1+ or a protein/creatinine ratio of 0.03 g/mmol appears to be equivalent to 0.3 g/24 hours of proteinuria. Many hospital protocols still consider estimation of serum uric acid level to be a standard part of the investigative work-up in women with suspected or confirmed pre-eclampsia to monitor disease severity and aid in the management of these women. This is despite the fact that hyperuricaemia is neither used as a primary diagnostic criterion for pre-eclampsia nor typically considered a basis for management decisions.

EXISTING EVIDENCE FOR SERUM URIC ACID TESTING IN GESTATIONAL HYPERTENSION/PRE-ECLAMPSIA

Many studies have shown a positive correlation between serum uric acid levels and the clinical severity of gestational hypertension/pre-eclampsia.^{26–35} A number of studies have also reported that serum uric acid can predict fetal outcome in

women with pre-eclampsia.³⁶⁻³⁹ One study reported an increase in small for gestational age fetuses among gestation induced hypertensive women with proteinuric and non-proteinuric hyperuricaemia.⁴⁰ Roberts *et al.*²⁸ suggested that hyperuricaemia is as effective as proteinuria in identifying gestational hypertensive pregnancies at increased risk of fetal complications, while other investigators have cited uric acid as a predictor of fetal risk comparable to blood pressure.⁴¹ Gowri *et al.* reported increased admissions to neonatal unit and caesarean sections in pre-eclamptic women with elevated uric acid.⁴² Yet another study suggested that the uric acid levels in the highest quartile of the normal range during the first 20 weeks of pregnancy were associated with higher risk for the development of gestational diabetes mellitus and mild pre-eclampsia.⁴³

However other studies have reported contrasting results. Calvert *et al.*⁴⁴ were unable to demonstrate any relationship between serum uric acid levels and the outcome of the pregnancies studied. Fay *et al.*⁴⁵ found that the rise in uric acid levels in patients who developed pre-eclampsia was only significantly higher than in non-hypertensive patients the week prior to delivery. Masse *et al.*⁴⁶ in their prospective study of 1366 nulliparous women, in whom uric acid was measured between 15 and 24 weeks gestation and again between 25 and 34 weeks gestation, also found that measurement of serum uric acid levels was not helpful in predicting pre-eclampsia. There are several other reports suggesting that uric acid is not a good predictor of pre-eclampsia or its complications and studies have disputed the association between perinatal morbidity/mortality and higher uric acid levels in patients with pre-eclampsia.^{15,47-49}

Although some reports demonstrated increased uric acid levels in women with pre-eclampsia prior to the onset of clinical disease,²⁵ Myers *et al.* did not find a significant difference in uric acid levels at 22 and 26 weeks in their cohort of women. Across all gestations investigated, they found no correlation between plasma uric acid levels and the effect of plasma on *in vitro* endothelial function.⁵⁰ Lim *et al.*⁵¹ reported a significant overlap in uric acid values among the hypertensive women leading to the conclusion that it was not clinically useful in distinguishing pre-eclampsia from gestational hypertension. Paula *et al.*⁵² reported that a serum uric acid level equal to or above 0.357 mmol/L in the pregnant hypertensive women was associated with proteinuria and diastolic blood pressure, but not with fetal outcome.

In 2006 a systematic review of five studies with a total of 572 women, including 44 who developed pre-eclampsia, concluded that there was insufficient evidence to draw firm conclusions about the accuracy of serum uric acid testing in the disorder.⁵³ Another systematic review¹⁷ published in 2006 evaluated the accuracy of serum uric acid in predicting complications of pre-eclampsia. The authors concluded that serum uric acid does not seem to be a clinically useful test to predict maternal or fetal complications in women with pre-eclampsia. There was no strong evidence to justify the use of therapeutic measures like magnesium sulphate or early delivery aimed at reducing maternal and fetal complications based on the levels of uric acid.¹⁷ Koopmans *et al.*⁵⁴ subsequently repeated the meta-analysis in 2009 with a bivariate meta-analytic model and a decision analysis to assess the value of serum uric acid in the management of women with pre-eclampsia and suggested that serum uric acid seemed to be a useful test in predicting eclampsia. Based on their decision analysis, in which they combined test accuracy both with the prevalence of disease and with the impact of clinical outcomes, the authors

found measurement of serum uric acid to be a useful test to predict maternal complications in the management of women with pre-eclampsia.⁵⁴

Since uric acid as a single marker on its own failed to accurately predict onset of pre-eclampsia, a combination of serum uric acid level, roll-over test result and body mass index was suggested to improve the predictive value of these markers of pre-eclampsia.⁵⁵ Others suggested that the clinical utility of blood pressure measurements, uric acid and creatinine assessments may be improved by the use of gestation specific cut-off values and z scores. However, the positive likelihood ratios associated with the use of z scores were still low, indicating limited clinical utility.⁵⁶

The conflicting results from the above studies and the conclusions of the systematic reviews point to the fact that serum uric acid measurements cannot be used to predict onset of pre-eclampsia or its complications with reliability. Also, hyperuricaemia cannot form the basis for decision to induce labour or start magnesium sulphate therapy if other maternal parameters like clinical symptoms or blood pressure measurements are reassuring.

WHY URIC ACID SHOULD NOT FORM A PART OF ROUTINE INVESTIGATIONS FOR PREGNANCY-INDUCED HYPERTENSION/ PRE-ECLAMPSIA

Uric acid levels do not form a part of essential diagnostic criteria for pregnancy-induced hypertension or pre-eclampsia. There is sufficient evidence that uric acid levels do not accurately predict the onset or complications of pre-eclampsia and there are several variables or patient characteristics which can affect these measurements significantly. Most obstetricians do not base management decisions on level of uric acid. It is the severity of clinical signs/symptoms, hypertension, proteinuria and other maternal/fetal parameters that form the basis of management of pre-eclampsia. In addition, if uric acid did influence delivery decisions, this would account for an increased frequency of indicated preterm birth.²⁸ Apart from re-establishing the well known association of hyperuricaemia with pre-eclampsia, what other benefit does repeated routine uric acid testing confer in hypertensive pregnancies?

The cost-benefit analysis of uric acid testing in cases of pre-eclampsia also does not favour the routine testing approach. A study was carried out to investigate the accuracy of predictive tests as well as the effectiveness of preventive interventions for pre-eclampsia and to assess the cost-effectiveness of strategies (test-intervention combinations) to predict and prevent pre-eclampsia. It estimated a cost of £5 for serum uric acid test and approximately £20 for Doppler ultrasonography tests. The authors reported that the best estimate of additional average cost associated with an average case of pre-eclampsia was high at approximately £9000. They reported that none of the tests including uric acid appeared sufficiently accurate to be clinically useful.⁵⁷ Another study found that the costs for the management of a pregnancy with pre-eclampsia after 20 weeks of gestation amounted to an estimated £2726 with standard practice of diagnostic testing for pre-eclampsia.⁵⁸ The results of these studies are particularly important in the present economic scenario. In the UK, pre-eclampsia complicates over 4%⁵⁹ or about 31,000 pregnancies each year.⁶⁰ Even if a conservative estimate of 30,000 pregnancies complicated by pre-eclampsia was considered every year, based on an

estimate of £5 cost for the measurement of uric acid approximately 5–6 times in a pregnancy, it would amount to a saving of nearly a million pounds for the National Health Service.

CONCLUSION

It is beyond any doubt that hyperuricaemia is a finding associated with pre-eclampsia. However increased uric acid level is not useful for prediction, diagnosis and/or management of pre-eclampsia. While we welcome uric acid testing for specific indications such as complex cases of superimposed pre-eclampsia on chronic hypertension with underlying renal damage and encourage further research into whether uric acid contributes to the pathogenesis of the pre-eclampsia syndrome, we strongly believe that the current practice of repeated routine uric acid testing for every suspected or diagnosed case of pregnancy induced hypertension or pre-eclampsia must stop.

DECLARATIONS

Guarantor: VST.

Funding: No funding was received for preparation of this manuscript.

Conflicts of interest: None of the authors has any potential conflicts of interests to declare.

Contributorship: VST and HS researched literature. VST wrote the first draft of the manuscript. Both authors reviewed and edited the manuscript and approved the final version of the manuscript.

REFERENCES

- Bainbridge SA, Roberts JM. Uric acid as a pathogenic factor in pre-eclampsia. *Placenta* 2008;**29**(Suppl A):S67–72. Epub 21 February 2008
- Vitart V, Rudan I, Hayward C, et al. SLC2A9 is a newly identified urate transporter influencing serum urate concentration, urate excretion and gout. *Nat Genet* 2008;**40**:437–42. Epub 9 March 2008
- Hypertension in Pregnancy. NICE Clinical Guideline 107. National Institute for Health and Clinical Excellence, August 2010
- Diagnosis and management of pre-eclampsia and eclampsia. ACOG practice bulletin. Number 33, January 2002. *Obstet Gynecol* 2002;**99**:159–67
- Magee L, Helewa M, Moutquin JM, Dadelszen PV. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. Society of Obstetricians and Gynaecologists of Canada (SOGC) Clinical Practice Guideline No. 206, March 2008. *J Obstet Gynaecol Canada (JOGC)* 2008;**30** (Suppl 1):S1–S48
- Merviel P, Baa R, Beaufilesc M, Breartb G, Salat-Barouxa J, Uzan S. Lone hyperuricemia in pregnancy maternal and fetal outcomes. *Eur J Obstet Gynecol Reprod Biol* 1998;**77**:145–50
- Beaufils M, Uzan S, Don Simoni R, Brault D, Colau JC. Metabolism of uric acid in normal and pathologic pregnancy. *Contrib Nephrol* 1981;**25**:132–6
- Carter J, Child A. Serum uric acid levels in normal pregnancy. *Aust NZ J Obstet Gynaecol* 1989;**29**:313–4
- Lind T, Godfrey KA, Otun H, Philips PR. Changes in serum uric acid concentrations during normal pregnancy. *Br J Obstet Gynaecol* 1984;**91**:128–32
- Barry CL, Royle GA, Lake Y. Racial variation in serum uric acid concentration in pregnancy: a comparison between European, New Zealand Maori and Polynesian women. *Aust N Z J Obstet Gynaecol* 1992;**32**:17–9
- Lain KY, Markovic N, Ness RB, Roberts JM. Effect of smoking on uric acid and other metabolic markers throughout normal pregnancy. *J Clin Endocrinol Metab* 2005;**90**:5743–6. Epub 26 July 2005
- Cohen SB, Kreiser D, Erez I, Kogan I, Seidman DS, Schiff E. Effect of fetal number on maternal serum uric acid concentration. *Am J Perinatol* 2002;**19**:291–6
- Igarashi M, Miyake H, Suzuki S. Effect of changes in renal circulation on serum uric acid levels in women with twin pregnancy. *Clin Exp Nephrol* 2010;**14**:436–9
- Devgun MS, Dhillon HS. Importance of diurnal variations on clinical value and interpretation of serum urate measurements. *J Clin Pathol* 1992;**45**:110–3
- Odendaal HJ, Pienaar ME. Are high uric acid levels in patients with early pre-eclampsia an indication for delivery? *S Afr Med J* 1997;**87**:213–8
- Slemons JM, Bogert LJ. The uric acid content of maternal and fetal blood. *J Biol Chem* 1917;**32**:63–9
- Thangaratinam S, Ismail KM, Sharp S, Coomarasamy A, Khan KS. Accuracy of serum uric acid in predicting complications of pre-eclampsia: a systematic review. *Br J Obstet Gynaecol* 2006;**113**:369–78
- Fadel HE, Northrop G, Misenhimer HR. Hyperuricemia in pre-eclampsia. A reappraisal. *Am J Obstet Gynecol* 1976;**125**:640–7
- Chesley LC, Williams LO. Renal glomerular and tubular function in relation to the hyperuricemia of pre-eclampsia and eclampsia. *Am J Obstet Gynecol* 1945;**50**:367–75
- Many A, Hubel CA, Roberts JM. Hyperuricemia and xanthine oxidase in pre-eclampsia, revisited. *Am J Obstet Gynecol* 1996;**174**:288–91
- Suzuki S, Yoneyama Y, Sawa R, Otsubo Y, Tekeuchi T, Araki T. Relation between serum uric acid and plasma adenosine in women with pre-eclampsia. *Gynecol Obstet Invest* 2001;**51**:169–72
- Many A, Hubel CA, Fisher SJ, Roberts JM, Zhou Y. Invasive cytotrophoblasts manifest evidence of oxidative stress in pre-eclampsia. *Am J Pathol* 2000;**156**:321–31
- Kang DH, Finch J, Nakagawa T, et al. Uric acid, endothelial dysfunction and pre-eclampsia: searching for a pathogenetic link. *J Hypertension* 2004;**22**:229–35
- Bainbridge SA, Roberts JM, Versen-Höyneck FV, Koch J, Edmunds L, Hubel CA. Uric acid attenuates trophoblast invasion and integration into endothelial cell monolayers. *Am J Physiol Cell Physiol* 2009;**297**:C440–50
- Powers RW, Bodnar LM, Ness RB, et al. Uric acid concentrations in early pregnancy among pre-eclamptic women with gestational hyperuricemia at delivery. *Am J Obstet Gynecol* 2006;**194**:160
- Lancet M, Fisher IL. The value of blood uric acid levels in toxemia of pregnancy. *J Obstet Gynaecol Br Empire* 1956;**63**:116–9
- Voto LS, Illia R, Darbon-Grosso HA, Imaz FU, Margulies M. Uric acid levels: a useful index of the severity of pre-eclampsia and perinatal prognosis. *J Perinat Med* 1988;**16**:123e6
- Roberts JM, Bodnar LM, Lain KY, et al. Uric acid is as important as proteinuria in identifying fetal risk in women with gestational hypertension. *Hypertension* 2005;**46**:1263–9
- Koopmans CM, Zwart JJ, Groen H, et al. Risk indicators for eclampsia in gestational hypertension or mild pre-eclampsia at term. *Hypertens Pregnancy* 2011;**30**:433–46
- Leidholm H, Montan S, Aberg A. Risk grouping of 113 patients during pregnancy with respect to serum urate, proteinuria and the time of onset of hypertension. *Acta Obstet Gynaecol Scand Suppl* 1984;**118**:43–8
- Redman CWG, Williams GF, Jones DD, Wilkinson RH. Plasma urate and serum deoxycytidylate deaminase measurements for the early detection of pre-eclampsia. *Br J Obstet Gynaecol* 1977;**84**:904–8
- Delic R, Stefanovic M. Optimal laboratory panel for predicting pre-eclampsia. *J Maternal-Fetal Neonatal Med* 2010;**23**:96–102
- Redman CW, Beilin LJ, Bonnar J, Wilkinson RH. Plasma-urate measurements in predicting fetal death in hypertensive pregnancy. *Lancet* 1976;**1**:1370–3
- Martin JN Jr, May WL, Magann EF, Terrone DA, Rinehart BK, Blake PG. Early risk assessment of severe pre-eclampsia: admission battery of symptoms and laboratory tests to predict likelihood of subsequent significant maternal morbidity. *Am J Obstet Gynecol* 1999;**180**:1407–14
- Witlin AG, Saade GR, Mattar F, Sibai BM. Risk factors for abruptio placentae and eclampsia: analysis of 445 consecutively managed women with severe pre-eclampsia and eclampsia. *Am J Obstet Gynecol* 1999;**180**:1322–9
- Sagen N, Haram K, Nilsen ST. Serum urate as a predictor of fetal outcome in severe pre-eclampsia. *Acta Obstet Gynecol Scand* 1984;**63**:71–5
- Gupta KB, Randhawa I, Pal A, Premi HK, Ganeshan J. Perinatal outcome in pregnancy induced hypertension. *J Indian Med Assoc* 1996;**94**:6–7
- Schuster E, Weppelmann B. Plasma urate measurements and fetal outcome in severe pre-eclampsia. *Gynecol Obstet Invest* 1981;**12**:162–7
- Plouin PF, Chatellier G, Bréart G, et al. Factors predictive of perinatal outcome in pregnancies complicated by hypertension. *Eur J Obstet Gynecol Reprod Biol* 1986;**23**:341–8
- D'Anna R, Baviera G, Scilipoti A, Leonardi I, Leo R. The clinical utility of serum uric acid measurements in pre-eclampsia and transient hypertension in pregnancy. *Panminerva Med* 2000;**42**:101–3
- Shah DM, Reed G. Parameters associated with adverse perinatal outcome in hypertensive pregnancies. *J Hum Hypertens* 1996;**10**:511–5
- Gowri V, Al-Zakwani I. Prevalence of cesarean delivery in pre-eclamptic patients with elevated uric acid. *Hypertens Pregnancy* 2010;**29**:231–5

- 43 Wolak T, Sergienko R, Wiznitzer A, Paran E, Sheiner E. High uric acid level during the first 20 weeks of pregnancy is associated with higher risk for gestational diabetes mellitus and mild pre-eclampsia. *Hypertens Pregnancy* 2010 7 Sep. [Epub ahead of print]
- 44 Calvert SM, Tuffnell DJ, Haley J. Poor predictive value of platelet count, mean platelet volume and serum urate in hypertension in pregnancy. *Eur J Obstet Gynecol Reprod Biol* 1996;**64**:179–84
- 45 Fay RA, Bromham DR, Brooks JA, GebSKI VJ. Platelets and uric acid in the prediction of pre-eclampsia. *Am J Obstet Gynecol* 1985;**152**:1038–9
- 46 Masse J, Forest JC, Moutquin JM, Marcoux S, Brideau NA, Belanger M. A prospective study of several potential biologic markers for early prediction of the development of pre-eclampsia. *Am J Obstet Gynecol* 1993;**169**:501–7
- 47 Dekker GA, Sibai BM. Early detection of pre-eclampsia. *Am J Obstet Gynecol* 1991;**165**:160–72
- 48 Conde-Agudelo A, Lede R, Belizán J. Evaluation of methods used in the prediction of hypertensive disorders of pregnancy. *Obstet Gynecol Surv* 1994;**49**:210–22
- 49 Williams KP, Galerneau F. The role of serum uric acid as a prognostic indicator of the severity of maternal and fetal complications in hypertensive pregnancies. *J Obstet Gynaecol Can* 2002;**24**:628–32
- 50 Myers JE, Jewsbury S, Sheikh N, Crocker I, Baker PN. Plasma uric acid levels do not correlate to plasma-evoked changes in endothelial function in women with pre-eclampsia. *Eur J Obstet Gynecol Reprod Biol* 2008;**137**:118–9
- 51 Lim K-H, Friedman SA, Ecker JL, Kao L, Kilpatrick SJ. The clinical utility of serum uric acid measurements in hypertensive diseases of pregnancy. *Am J Obstet Gynecol* 1998;**178**:1067–71
- 52 Paula LG, da Costa BE, Poli-de-Figueiredo CE, Antonello IC. Does uric acid provide information about maternal condition and fetal outcome in pregnant women with hypertension? *Hypertens Pregnancy* 2008;**27**:413–20
- 53 Cnossen JS, de Ruyter-Hanhiarvi H, van der Post JA, Mol BW, Khan KS, ter Riet G. Accuracy of serum uric acid determination in predicting pre-eclampsia: a systemic review. *Acta Obstet Gynecol Scand* 2006;**85**: 519–25
- 54 Koopmans CM, van Pampus MG, Groen H, Aarnoudse JG, van den Berg PP, Mol BWJ. Accuracy of serum uric acid as a predictive test for maternal complications in pre-eclampsia: bivariate meta-analysis and decision analysis. *Eur J Obstet Gynecol Reprod Biol* 2009;**146**:8–14
- 55 Kaypour F, Masomi Rad H, Ranjbar Novin N. The predictive value of serum uric acid, roll-over test, and body mass index in pre-eclampsia. *Int J Gynecol Obstet* 2006;**92**:133–4
- 56 Anumba DO, Lincoln K, Robson SC. Predictive value of clinical and laboratory indices at first assessment in women referred with suspected gestational hypertension. *Hypertens Pregnancy* 2010;**29**:163–79
- 57 Meads CA, Cnossen JS, Meher S, et al. Methods of prediction and prevention of pre-eclampsia: systematic reviews of accuracy and effectiveness literature with economic modelling. *Health Technol Assess* 2008;**12**:(iii–iv)1–270
- 58 Hadker N, Garg S, Costanzo C, et al. Financial impact of a novel pre-eclampsia diagnostic test versus standard practice: a decision-analytic modeling analysis from a UK healthcare payer perspective. *J Med Econ* 2010;**13**:728–37
- 59 Bhattacharya S, Campbell DM. The incidence of severe complications of pre-eclampsia. *Hypertens Pregnancy* 2005;**24**:181–90
- 60 UK Office for National Statistics. Key Population and Vital Statistics, Series VS No. 34, PPI No. 30, 2007 data, corrected version issued on 27 April 2009. See http://www.statistics.gov.uk/downloads/theme_population/KPVS34-2007/KPVS2007.pdf (last checked August 2009)

(Accepted 13 December 2011)