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Salivary uric acid as a predictive test of pre-eclampsia, pregnancy-induced hypertension and preterm delivery: a pilot study

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Conflict of interest

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ABSTRACT

Introduction: There remains a need for a non-invasive, low cost and easily accessible way of identifying women at risk of developing hypertensive disorders in pregnancy. This study evaluated the predictive value of longitudinal salivary uric acid measurement. **Material and methods:** Pregnant women (N = 137) from 20 weeks of gestation were recruited at St. Richards Hospital, Chichester, UK, for this prospective cohort study. Weekly samples of salivary uric acid were analyzed until delivery. Information regarding pregnancy and labor were obtained from the patient's record after delivery. Independent t-tests were used to compare mean levels of salivary uric acid in women with hypertensive complications and adverse fetal outcomes to women with normal pregnancies. Main outcome measures were pre-eclampsia, pregnancy-induced hypertension, spontaneous preterm delivery and babies small-for-gestational-age. **Results:** From 21 weeks of gestation until delivery, levels of salivary uric acid increased significantly in women who subsequently developed pre-eclampsia and pregnancy-induced hypertension compared to women with normal pregnancies (pre-eclampsia (mean at gestational age 21-24(CI 95%) (mean $_{GA21-24}$): 108(63;185) µmol/L vs 47(39;55) µmol/L; *P*=0.005)), pregnancy-induced hypertension(mean $_{GA21-24}$: 118(54;258) µmol/L vs 47(39;55) µmol/L; *P*=0.004). In women who had spontaneous preterm delivery, salivary uric acid levels increased significantly from 29-32 weeks of gestation compared to women with normal pregnancies(mean $_{GA29-32}$: 112(57;221) µmol/L vs 59(50;71) µmol/L; *P*=0.04). In women who had

babies small-for-gestational-age < 10th percentile and small-for-gestational-age < 3rd percentile, differences in salivary uric acid levels were insignificant. **Conclusions:** Elevated levels of salivary uric acid precede the onset of pre-eclampsia, pregnancy-induced hypertension and preterm delivery. Salivary uric acid may prove to be an early biomarker of hypertensive complications of pregnancy and spontaneous preterm delivery.

Keywords

uric acid, pre-eclampsia, pregnancy-induced hypertension, preterm delivery, hypertensive disorders in pregnancy

Abbreviations

PE	pre-eclampsia
PIH	pregnancy-induced hypertension
GA	gestational age
SGA	Small for gestational age
$SGA_{<10}$	Small for gestational age < lower 10th percentile
$SGA_{<3}$	Small for gestational age < lower 3rd percentile
CI	confidence interval

Key message

There remains a need for early identification of women at risk of hypertensive pregnancy disorders. In this pilot study, raised levels of salivary uric acid preceded the onset of pre-eclampsia, gestational hypertension and spontaneous preterm delivery by several weeks.

INTRODUCTION

Pre-eclampsia (PE) is one of the main complications of pregnancy and childbirth and affects 2-5% of all pregnancies. PE is a global problem accounting for at least 60 000 maternal deaths worldwide(1,2), and remains a major cause of maternal morbidity and mortality in developed countries (3). PE is diagnosed when onset of hypertension after 20 weeks of gestation is noted in combination with either proteinuria, maternal organ dysfunction or intrauterine growth restriction (4,5). Despite years of research, the pathophysiology of PE remains unclear. However, a two-stage model describing how inadequate placental perfusion leads to a maternal syndrome is widely accepted (6). In this model, pathophysiological changes are thought to occur as early as first trimester, even though the clinical onset of PE occurs later in pregnancy (6). Serum biomarkers, uterine artery Doppler ultrasound and maternal risk have been evaluated as potential predictive tests for PE both individually and in combination but all lack sufficient sensitivity and specificity (7,8) (9–11). Though accuracy of the placental growth factor/ soluble fms-like tyrosine kinase-1 (PlGF/sFlt-1) test is promising in triage of women at risk of early-onset PE in the third trimester, its use as a first and second trimester marker appears limited (12,13). A combination, however, of maternal factors, mean arterial blood pressure, PlGF and uterine artery pulsatility index has shown promising results for detecting preterm PE but lacked sufficient detection rates with respect to overall PE(14).

In 1976, Redman et al. showed, that plasma-urate measurements were a better predictor of fetal death in hypertensive pregnancies than the blood-pressure measurements itself. Since then, measurements of plasma-urate have been investigated as a predictor of PE and pregnancy-induced hypertension (PIH). Conclusions, however, have been inconsistent, leading it to be largely discredited as a serum marker (15). However, there is little doubt that, as a part of a two-stage model for its pathophysiology, PE is strongly associated with poor placental vascularization leading to placental hypoxia, endoplasmatic reticulum stress and production of excess free radicals leading to and associated with oxidative stress (16,17). Hypoxia increases the production of uric acid, shown by Tereda et al. in 1997 (18). In addition, it has been shown that oxidative stress changes the enzymatic pathway of production of uric acid, favoring formation of oxidative radicals, possibly contributing to the pathophysiology (19). In 1998, Owen-Smith showed that during metabolic stress, salivary uric

acid is a far more sensitive biomarker than serum uric acid detecting physiological changes of activity levels and diurnal variation; changes not detectable in serum uric acid (20).

Furthermore, studies of radioactive labelled uric acid isotopes have shown that there appears to be a redirection of uric acid metabolism towards the enteral route during metabolic stress. This indicates that salivary uric acid does reflect levels of serum uric acid, but may be a better biomarker of metabolic stress itself as it is less susceptible to volume shifts in circulating volume than the serum level (21). Salivary uric acid might therefore have an improved predictive value for PE, even though levels of serum uric acid do not.

This study examines the hypothesis that levels of salivary uric acid differ from women with normal pregnancies to women with PE, PIH, spontaneous preterm delivery and babies small-for-gestational-age (SGA).

MATERIAL AND METHODS

Design

Prospective cohort study for which IRB approval was obtained (REC Number 06/Q1911/6).

Subjects and setting

Pregnant women (N=137) attending antenatal care at hospital and community-based pregnancy care programs at St. Richards Hospital, Chichester, UK, between 1st of March 2007 and 1st of March 2008.

Recruitment

Prior to inclusion, the women received oral and written information during their midwife antenatal booking appointment. Informed consent was obtained. Participants were registered in order of arrival. Women were included at 20 weeks of gestation. Lack of communicative English skills was the only exclusion criteria.

Sample collection and analysis

The women donated a weekly salivary sample from recruitment and until delivery. The sample was made using a buccal swab. The test was made first thing in the morning before exercising, eating, brushing teeth or smoking. The women delivered it in a sealed tube to the hospital on the same day. Without centrifugation, clear samples were collected from the buccal swabs using a piston syringe. A saliva drop from each sample was expressed onto a test strip in a hand-held reader (Apex Biotechnology, Taiwan (22)). This system of test-strips was commercially available for tests of uric acid in whole blood and pre-trial checks on salivary uric acid tests showed a correlation coefficient of R = 0.8110 (N=20) compared to the laboratory's automated system for salivary uric acid. Tests of reproducibility on saliva samples showed a coefficient of variation of 5-6 %. The analytical range was from 45 µmol/l – 440 µmol/l. The same reader was used for all samples. All samples were analyzed between Jan. 2009 – Sept. 2009. After giving birth, information on gestational age (GA) at delivery, birthweight, parity, maternal age at delivery, gender of the newborn and diagnoses of PE or PIH was obtained from the patient record. Levels of salivary uric acid were not disclosed to the clinical staff.

Statistical analyses

Main outcomes were PE and PIH as classified by the International Society for the Study of Hypertension in Pregnancy (ISSHP)(23). PE with delivery before 34 weeks of gestation was defined as a severe adverse outcome. Main outcomes were in addition spontaneous preterm delivery (GA at delivery < 37+0 weeks) in women without PE and PIH and SGA defined by birthweight <10th percentile ($SGA_{<10}$) and a subgroup of these with severe SGA defined by birthweight <3rd percentile ($SGA_{<3}$), respectively, based on the Marsal weight reference (24) from the Royal College of Obstetricians and Gyneacologists guidelines (25). Inclusion in the SGA group was solely based on birthweight and GA at delivery, regardless of any additional maternal diagnosis of hypertensive disorder.

Continuous variables are presented as mean values with standard error of the mean (SEM) and categorical variables as frequencies. For comparisons of baseline characteristics, unpaired t-tests were used for continuous variables and Pearson's X^2 tests for dichotomous variables. Values of salivary uric acid were log transformed due to the normal distribution and independent samples t-tests were used for comparisons of concentrations of salivary uric acid in women with normal pregnancies

compared to women with PE, PIH, spontaneous preterm delivery and SGA. Since elevated salivary uric acid values appeared in peaks independently of a woman's values in previous or subsequent weeks of gestation, and not as a continuous or exponential rise during pregnancy, anti-logged results of salivary uric acid are presented collectively in four-week intervals with 95 % confidence intervals (CI). The significance level was set to 0.05. Data analysis were performed using SAS 9.4 (SAS Institute, Cary, NC, USA).

Ethical approval

Approval was granted by the Regional Ethics Committee (Brighton West), REC Number 06/Q1911/6 amended version 2 of the 13th of February 2007.

RESULTS

A total of 137 women were recruited before 20 weeks of gestation. A woman was reported as a *partial drop-out*, if not contributing any samples during a four-week interval. During GA 21-24, 136 women provided at least one sample, equal to a compliance rate on 99% for this four-week period of time. Compliance rate for GA 25-28 was 100% (137/137), GA 29-32 was 97% (133/137), GA 33-36 was 96% (131/137) and GA 37-40 98% (122/125), respectively. Mean maternal age for the total population was 31.7 years, mean GA at delivery was 39+3 and 97 (71%) women were nulliparous (Table 1).

Of all, nine (6.6%) women were diagnosed with PE of which one (0.7%) delivered < 34 weeks of gestation Eight (5.8%) women were diagnosed with PIH, nine (6.6%), women had spontaneous preterm delivery, 20 (14.6%) women delivered babies who were $SGA_{<10}$ of which 12(8.8%) were severe SGA defined by $SGA_{<3}$. Five of the women with PE had SGA babies, of whom three were severe SGA. None of the women with PIH delivered preterm or had SGA babies. (Table 2). Women with PE had a significantly lower GA at delivery and lower birthweights compared to women with normal pregnancies (Table 1). From 21 weeks of gestation until delivery, women developing PE had significantly higher levels of salivary uric acid compared to normal pregnancies (mean salivary uric acid level for GA 21-24w was 108 µmol/L (CI; 63 to185) vs 47 µmol/L (CI; 39 to

55); *P*=0.005) (Figure 1) (Table 3). From 21-24 and 29-37 weeks of gestation, women who went on to develop PIH had significantly higher levels of salivary uric acid compared to normal pregnancies (PIH(mean $_{GA21-24}$): 118 µmol/L (CI; 54 to 258) vs 47 µmol/L (CI; 39 to 55); *P*=0.004) (Figure 1) (Table 3). From 29 to 32 weeks of gestation , women with spontaneous preterm delivery had significantly increased levels of salivary uric acid compared to normal pregnancies (mean $_{GA29-32}$: 112 µmol/L (CI; 57 to 221) vs 59 µmol/L (CI; 50 to 71); *P*=0.04) (Figure 1) (Table 3). Regarding women with $SGA_{<10}$ and $SGA_{<3}$, differences in salivary uric acid concentrations were insignificant, $SGA_{<10}$(mean $_{GA33-36}$: 89 µmol/L (CI; 52 to155) and 62 µmol/L (CI; 51 to 76); *P*=0.15) (Table 3) and $SGA_{<3}$ (mean $_{GA33-36}$: 105 µmol/L (CI; 52 to 212) and 62 µmol/L (CI; 51 to 71); *P*=0.08) (Table 3).

DISCUSSION

In this prospective cohort study of 137 pregnant women, we report the first prospective cohort data on longitudinal measurement of salivary uric acid levels from 20 weeks of gestation until delivery. We found that, compared with normal pregnancies, salivary uric acid concentrations were significantly increased in women who subsequently developed PE and PIH, as well as in women with spontaneous preterm delivery. The increased values of salivary uric acid preceded preterm delivery and the clinical onset of PE and PIH by several weeks.

Since mechanistic studies of the association of salivary uric acid and PE, PIH and preterm delivery are not yet available, the exact mechanism behind the findings has yet to be elucidated.

However, with respect to PE and PIH, placental ischemia and inflammation could be the cause of increased uric acid production as argued in the introduction. Furthermore, in non-pregnant individuals uric acid is known to be related to severity of cardiovascular disease and might be involved in the transition from pre-hypertension to hypertension even though the pathophysiology is not yet elucidated(26,27). Therefore, salivary uric acid might not only reflect placental pathology but also maternal cardiovascular dysfunction.

With respect to preterm birth, maternal age is known to be a risk factor. However, in our cohort there is no significant difference of maternal age compared to normal pregnancies. A review on

preterm birth describe that many cases of preterm birth might be caused by placental insufficiency. This might be the cause for our findings as well (28).

The findings we observed for SGA were not significant. A possible explanation of this is that we used SGA instead of fetal growth restriction. In our study population, fetal growth restriction is most likely caused by placental insufficiency. Therefore, a significantly increased level of salivary uric acid in women with fetal growth restriction would be expected. However, SGA babies include the genetically small children as well. Therefore, this group might vary with respect to placental functioning. Unfortunately, information on fetal growth restriction was not available for this study, why SGA was analyzed instead.

The findings of this pilot study are promising. There remains a need for a simple, predictive test regarding hypertensive complications in pregnancy,. The fact that increased levels of salivary uric acid were detected several weeks prior to clinical onset of PE and PIH is of great clinical value. This would help increase clinicians' awareness of women-at-risk.

Since performance of a saliva sample does not need assistance from a health care worker, it has potential as a self-sampling test. A self-sampling test can be an attractive alternative to point-of-care testing. It can help monitor pregnancies in places with long distance to health professionals, and in developed health care systems it might reduce costs. Also, self-sampling can increase empowerment in pregnancy. Self-sampling can be combined with technological communication techniques, and it has been reported, that pregnant women in general are positive towards the use of information and communication technologies for perinatal health including mobile phones. (29)

Further studies should focus on the predictive value of salivary uric acid in relation to hypertensive disorders and spontaneous preterm birth. Further studies with larger sample sizes should examine the association between salivary uric acid levels and severe complications to hypertensive disorders of pregnancy. Further research into the pathophysiology of raised salivary uric acid levels in women with hypertensive complications in pregnancies is also warranted, including how levels of uric acid are affected by maternal and fetal distress.

The major strength of the study is the prospective cohort design. Uptake of the salivary test was high and the non-invasive character of this screening method was confirmed, making this

strategy a promising addition to the current practice of serial blood pressure measurements and urinary dipstick analysis to detect PE.

There are some limitations that need to be addressed. Being a pilot study, the sample size was not very large. Prevalence's of the outcomes in our population are low, as were the number of positive outcomes. This is reflected by the 95 % CI and standard errors, which are broader with respect to positive outcomes than to normal pregnancies (Table 3) (Figure 1). Also, we did not have information on possible influential factors on salivary uric acid levels such as obesity, smoking and chronic diseases. Obesity is a known risk factor of PE and studies have shown that salivary uric acid levels can be affected by obesity (30,31). This factor would need to be taken into account in a future clinical trial to tease out causal pathways and potential confounders. . The data of the study have only become available for analysis in the last two years, why a significant period of time has passed since the data were collected. The results, however, remain novel and important given the continuing lack of a low cost, easily accessible screening test for identifying women at risk of hypertensive complications of pregnancy and spontaneous preterm delivery.

Our findings support the hypothesis that salivary uric acid might be developed into a longitudinal predictive test strategy to improve early detection of adverse pregnancy outcomes.

CONCLUSION

This study showed that elevated levels of mean salivary uric acid in pregnant women preceded the clinical onset of PE, PIH and spontaneous preterm delivery from as early as 21 weeks of gestation. These findings indicate proof-of-concept for potential use of salivary uric acid as a simple, low-cost predictive test for early detection of women at risk of PE, PIH and spontaneous preterm delivery. Based on these findings, we recommend further validation studies using updated technologies to measure and interpret salivary uric acid levels.

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Legends

Table 1. Baseline characteristics (N=137).

Table 2. Main outcomes (N=137).

Table 3. Levels of salivary uric acid.

Figure 1. Salivary uric acid levels with standard error in women with pre-eclampsia, pregnancy-induced hypertension and preterm birth compared to normal pregnancies

Table 1. Baseline characteristics (N=137)								
Characteristics								
		Total (N=137)	**Normal pregnancies (n=94)**	**Pre-eclampsia (n=9)**	**Pregnancy-induced hypertension (n=8)**	**Spontaneous preterm delivery (n=9)**	**Small for gestational age < 10th percentile (n=20)**	**Small for gestational age < 3rd percentile (n=12)**
Maternal age [years]		31.7 (0.4)	31.9 (0.5)	29.6 (1.3)	32.5 (1.8)	31.2 (2.4)	31.0 (1.1)	31.9 (1.2)
Gestational age at delivery [days]		275.9 (1.2)	279.4 (0.9)	257.8 (8.5)*	277.4 (1.8)	245.3 (5.2)*	267.6 (5.3)*	267.6 (6.2)
Birthweight [grams]		3340 (49.5)	3532.8 (39.0)	2679.4 (343.1)*	3520.1 (110.1)	2525.4 (241.8)*	2497.3 (133.1)*	2390.1 (157.4)*
Parity								
	Primipara	97 (70.8)	30 (31.9)	2 (22.2)	2 (25.0)	1 (11.1)	5 (25.0)	3 (25.0)
	Multipara	40 (29.2)	64 (68.1)	7 (77.8)	6 (75.0)	8 (88.9)	15 (75.0)	9 (75.0)
Mean (SEM); N (%)								
*=Significantly different from normal pregnancies, P-value < 0.05								

Table 2. Main outcomes (N=137)		
		N (%)
Total number of women		137 (100)
Normal pregnancies		94 (68.6)
Pre-eclampsia		9 (6.6)
	Outcome specific missing*	2 (1.5)
	Adverse severe outcome (GA of delivery < 34 weeks)	1 (0.7)
Pregnancy-induced hypertension		8 (5.8)
	Outcome specific missing	12 (8.8)
Spontaneous preterm birth		9 (6.6)
	Outcome specific missing	0 (0)
Small for gestational age		
	<10th percentile (incl. <3rd percent	20 (14.6)
	Outcome specific missing	3 (2.2)
	<3rd percentile	12 (8.8)
	Outcome specific missing	4 (2.9)
Frequencies are n (%) based on the total population		
*No information on the specific outcome obtained from the patient record		

Table 3. Levels of salivary uric acid	**Means [µmol/L] , 95 % confidence intervals and P-values**						
Pre-eclampsia	PE (n=9)			NP (n=94)			
GA (weeks)	Mean	CI 95%	Partial drop-outs (n)	Mean	CI 95%	Partial drop-outs (n)	**P-value**
21-24	108.09	(63.05 , 185.35)	0	46.48	(39.26 , 55.49)	1	**0.005 ***
25-28	138.07	(70.60 , 269.96)	1	59.39	(49.05 , 71.93)	0	**0.015 ***
29-32	136.08	(60.88 , 304.23)	1	59.47	(49.87 , 70.93)	4	**<0.001 ***
33-36	219.03	(134.74 , 356.04)	3	62.04	(50.97 , 75.53)	6	**0.001 ***
37-40	266.87	(92.38 , 770.90)	5	80.89	(66.10 , 98.10)	15	**0.01 ***
Pregnancy-induced hypertension	PIH (n=8)			NP (n=94)			
GA (weeks)	Mean	CI 95%	Partial drop-outs (n)	Mean	CI 95%	Partial drop-outs (n)	**P-value**
21-24	118.20	(54.16 , 257.87)	0	46.68	(39.26 , 55.45)	1	**0.004 ***
25-28	109.04	(41.19 , 288.67)	0	59.39	(49.05 , 71.93)	0	**0.09**
29-32	122.10	(50.44 , 295.53)	1	59.47	(49.87 , 70.93)	4	**0.03 ***
33-36	138.80	(70.86 , 271.89)	1	62.04	(50.97 , 75.53)	6	**0.03 ***
37-40	158.85	(89.64 , 281.51)	1	80.89	(66.10 , 100.00)	15	**0.06**
Spontaneous preterm delivery	Spontaneous preterm delivery (n=9)			NP (n=94)			
GA (weeks)	Mean	CI 95%	Partial drop-outs (n)	Mean	CI 95%	Partial drop-outs (n)	**P-value**
21-24	53.90	(29.48 , 98.56)	0	46.68	(39.26 , 55.49)	1	**0.62**
25-28	82.00	(38.63 , 174.06)	0	59.39	(49.05 , 71.93)	0	**0.33**
29-32	111.89	(56.60, 221.26)	1	59.47	(49.87 , 70.93)	4	**0.04 ***
33-36	108.94	(44.08 , 269.21)	5	62.04	(50.97 , 75.53)	6	**0.15**
Small for gestational age < 10th percentile (incl. <3rd percentile)	SGA < 10th percentile (n=20)			NP (n=94)			
GA (weeks)	Mean	CI 95%	Partial drop-outs (n)	Mean	CI 95%	Partial drop-outs (n)	**P-value**
21-24	59.88	(40.54 , 88.47)	1	46.68	(39.26 , 55.49)	1	**0.23**
25-28	62.85	(42.05 , 93.95)	1	59.39	(49.05 , 71.93)	0	**0.80**
29-32	67.80	(41.31 , 111.28)	2	59.47	(49.87 , 70.93)	4	**0.55**
33-36	89.43	(51.59 , 155.02)	4	62.04	(50.97 , 75.53)	6	**0.15**
37-40	102.61	(55.13 , 190.99)	6	80.89	(66.10 , 100.00)	15	**0.37**
Small for gestational age < 3rd percent	SGA < 3rd percentile (n=12)			NP (n=94)			
GA (weeks)	Mean	CI 95%	Partial drop-outs (n)	Mean	CI 95%	Partial drop-outs (n)	**P-value**
21-24	53.36	(30.76 , 92.53)	0	46.68	(39.26 , 55.49))	1	**0.61**
25-28	60.56	(37.18 , 98.63)	0	59.39	(49.05 , 71.93)	0	**0.95**
29-32	66.27	(35.38 , 124.14)	0	59.47	(49.87 , 70.93)	4	**0.68**
33-36	104.98	(52.01 , 211.88)	1	62.04	(50.97 , 75.53)	6	**0.08**
37-40	115.56	(50.70 , 263.45)	2	80.89	(66.10 , 100.00)	15	**0.26**
[b]The number of women who did not provide any samples during this four-weeks interval							
*Significant P-value <0.05							

Figure 1. Salivary uric acid levels in women with pre-eclampsia, pregnancy-induced hypertension and preterm birth compared to normal pregnancies