ปฏิสัมพันธ์ระหว่างผลบวกจากการตรวจโปรตีนในปัสสาวะด้วยแผ่นทดสอบสำเร็จรูป และภาวะความดันโลหิตสูงต่อการทำนายภาวะโปรตีนรั่วในปัสสาวะ ในหญิงตั้งครรภ์ที่มีความเสี่ยงสูง

Interaction of urine protein dipstick positive and hypertension on predicting a significant proteinuria in high-risk pregnancy

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บทคัดย่อ

การศึกษานี้มีวัตถุประสงค์เพื่อศึกษาความสัมพันธ์ของผลบวกการตรวจโปรตีนในปัสสาวะด้วยแผ่นทดสอบสำเร็จรูป และภาวะความดันโลหิตสูงกับการทำนายการเกิดภาวะโปรตีนรั่วในปัสสาวะ ทำการศึกษาในหญิงตั้งครรภ์ที่มีความเสี่ยงสูง จำนวน 39 ราย จากแผนกฝากครรภ์ผู้ป่วยนอก โรงพยาบาลสระบุรี ระหว่างเดือนมกราคม 2560 – ธันวาคม 2561 ตรวจโปรตีนเชิงปริมาณในปัสสาวะ 24 ชั่วโมงด้วยเครื่องวิเคราะห์อัตโนมัติ Unicel DxC 800 (Beckman Coulter, Inc., California, USA) และตรวจโปรตีนเชิงกึ่งปริมาณในปัสสาวะที่เก็บครั้งเดียวด้วยแผ่นทดสอบสำเร็จรูป Uriscan 2 GP strip (YD Diagnostics Co., Ltd., Thailand) วิเคราะห์ข้อมูลด้วย χ^2-test, Student T-test, binary logistic regression analysis และ Receiver Operating Characteristic (ROC) analysis พบว่ากลุ่มตัวอย่างมีอายุเฉลี่ย 28.4 ± 6.7 ปี พบภาวะโปรตีนรั่วในปัสสาวะ ความดันโลหิตสูง และเบาหวานขณะตั้งครรภ์ คิดเป็นร้อยละ 43.6, 58.9, และ 15.4 ตามลำดับ ไม่พบนัยสำคัญทางสถิติต่อความเสี่ยงในการเกิดภาวะโปรตีนรั่วในปัสสาวะจากผลบวกของการตรวจโปรตีนในปัสสาวะด้วยแผ่นทดสอบสำเร็จรูปหรือภาวะความดันโลหิตสูงเพียงอย่างเดียว [odd ratios (95%CI), *P*-value] = [4.0 (0.95, 16.93), 0.060] และ [1.5 (0.42, 5.61), 0.523) ตามลำดับ เมื่อทดสอบด้วย ROC analysis โดยใช้ผลบวกจากการตรวจโปรตีนในปัสสาวะด้วยแผ่นทดสอบสำเร็จรูปร่วมกับภาวะความดันโลหิตสูง พบความสัมพันธ์กับการเกิดภาวะโปรตีนรั่วในปัสสาวะอย่างมีนัยสำคัญทางสถิติ [area under curve (95% CI), *P*-value] = [0.710 (0.54, 0.87), 0.026] ดังนั้นการใช้ผลการตรวจโปรตีนในปัสสาวะด้วยแผ่นทดสอบสำเร็จรูปร่วมกับการมีภาวะความดันโลหิตสูงจึงเพิ่มความสามารถในการทำนายการเกิดภาวะโปรตีนรั่วในปัสสาวะในหญิงตั้งครรภ์ที่มีความเสี่ยงสูง มากกว่าการใช้ปัจจัยใดปัจจัยหนึ่งเพียงอย่างเดียว

คำสำคัญ: หญิงตั้งครรภ์ความเสี่ยงสูง, โปรตีนในปัสสาวะ 24 ชั่วโมง, แผ่นทดสอบสำเร็จรูป, ภาวะโปรตีนรั่วในปัสสาวะ

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Abstracts

The aim of this study was to explore the individual effects of the urine protein dipstick positive and hypertension including their interaction on predicting proteinuria. The cross-sectional study was conducted between January 2017 and December 2018 among 39 high-risk pregnancy in Antenatal Care Clinic, Saraburi Hospital, Thailand. The 24-h urine protein and urine protein dipstick was performed by using Unicel DxC 800 (Beckman Coulter, Inc., California, USA) and Uriscan 2 GP strip (YD Diagnostics Co., Ltd., Thailand), respectively. According to 24-h urine protein concentrations, in which proteinuria was defined as a urine protein of ≥ 300 mg/day. Statistical analysis was performed by using χ^2-test, Student's t-test, binary logistic regression, and receiver-operating characteristic (ROC) analysis. The results showed that the mean age and body weight of subjects were 28.4 years, and 86.5 kilograms; proteinuria, hypertension, and gestational diabetes mellitus were presented in 43.6%, 58.9%, and 15.4%, respectively. The individual effects of the urine protein dipstick positive and hypertension had no significant for predicting the proteinuria [odd ratios (95%CI), *P*-value] = [4.0 (0.95, 16.93), 0.060] and [1.5 (0.42, 5.61), 0.523)], respectively. The ROC analysis of an effect on proteinuria of the urine protein dipstick positive alone and combination with hypertension had area under the curve values of 0.644 and 0.710, respectively. In conclusion, the individual effect of the urine protein dipstick positive and hypertension on significant proteinuria was not observed. However, a combination of both factors enhances the proteinuria in high-risk pregnancy.

Keywords: High-risk pregnancy, 24-h urine protein, dipstick, proteinuria,

Statement and significance of problem

Pre-eclampsia**,** the most common medical complication and a major cause of maternal and fetal morbidity and mortality, was defined as the onset of hypertension and proteinuria after 20 weeks of gestation in previously normotensive women (Lowe et al., 2015). To the best of our knowledge, proteinuria is one of the fundamental criteria for the diagnosis of pre-eclampsia with quantitative assessment based on the 24-h urine protein measurement as the gold standard. However, it has some disadvantages such as inconvenience for patients, inaccuracy due to incomplete collection, and delay of diagnosis and management. For this reason, many investigators have explored simpler and more convenient diagnostic methods to quantify proteinuria. (Cote et al., 2008; Tormo, Lumbreras, Santos, Romero, & Conca, 2009). The urine protein dipstick test is one of the most commonly used screening tests because of its simplicity and low cost. Nevertheless, this method has high rates of false positive and false negative results associated with fluctuations throughout the day due to water intake, exercise, diet, posture, or improperly trained laboratory technicians.

A previous report has shown that random urine dipstick for protein results correlate poorly with 24-h urine samples for distinguishing patients with no disease or severe disease in hypertension woman with proteinuria (Somanathan N, Farrell T, & Galimberti A, 2003). In addition, Amin et al. suggests that random urinary protein/creatinine ratio is a reliable investigation compared to dipstick method to assess proteinuria in hypertensive pregnant women (Amin et al., 2014). Therefore this study is aimed to explore the effects of the urine protein dipstick positive and other risk factors including their interaction on predicting proteinuria.

Objectives

To study the effect of the interaction between urine protein dipstick positive and hypertension on proteinuria among high-risk pregnancies

Materials and methods

A cross-sectional study was performed among 39 subjects who were diagnosed with high-risk pregnancies at the Antenatal Care (ANC) Clinic, Out Patients Department, Saraburi Hospital during January 2017 to December 2018. The 24-h urine protein by using Unicel DxC 800 analyzer (Beckman Coulter, Inc., California, USA) and the spot urine protein by using Uriscan 2GP dipstick (YD Diagnostics Co., Ltd., Thailand) were measured in each subjects. All of diagnosed with high-risk pregnancies were divided in to non-proteinuria and proteinuria according to 24-hr protein concentrations, a total of subjects were divided into two groups include non-proteinuria (< 300 mg/day) and significant proteinuria (≥ 300 mg/day) as recommended by the International Society for the Study of Hypertension in Pregnancy and the American College of Obstetrics and Gynecology (ACOG Committee on Obstetric Practic, 2002). Subjects were reviewed to collect demographic data, including age, body weight, pulse rate, and maternal risk factors by using laboratory information system (LIS) (Rax Interdiagnostic Co. Ltd., Thailand).

24-h urine specimen collection

Urine sample were collected in one or more containers according to a standard protocol. Typically, the patient's first voided morning urine is discarded. Following urine excreted for next 24-h including the next morning's first voided urine, is collected in containers with toluene as a preservative that are provided by the laboratory staff.

Spot urine specimen collection

Patient was asked to submit random midstream urine sample in a 10 mL urine container for laboratory analysis of dipstick protein and glucose. The urine protein dipstick positive includes: a proteinuria reading of ≥30 mg (≥1+ on dipstick) (Park, J. H et al, 2013).

Statistical analysis

All data analyses were performed using the SPSS 17.0 statistic package (SPSS, Inc., Chicago, Illinois, USA). A significant difference was defined as a *P*-value of less than 0.05. The comparisons of the categorical variables were conducted by Chi-square tests. All clinical and biochemical data were expressed as either mean ± SD for normally distributed data or geometric mean ± SD for non-normal distribution. Data was tested for normal distribution with the Kolmogorov-Smirnov normality test. Means of non-normal distribution variables were logarithmically transformed. The difference in continuous variables between two groups was tested using independent Student's *t*-tests. Univariate logistic regression analysis was performed to determine the association of proteinuria and risk factors. Receiver operating characteristic (ROC) curve analysis was performed to demonstrate the interaction effect of the urine protein dipstick positive and hypertension on predicting the proteinuria in study subjects.

Results

The baseline characteristics of all subjects and proteinuria status are summarized in Table 1. Briefly, the mean age and body weight of subjects were 28.4 years, and 86.5 kilograms; maternal risk factors including proteinuria, hypertension, and gestational diabetes mellitus were presented in 43.6%, 58.9%, and 15.4%, respectively. Mean 24-h urine protein ± SD was 412.8 ± 2.1 mg/day, proteinuria was detected in 8 subjects (47.1%), and the urine protein dipstick positive was present in 12 subjects (30.8%). In accordance with 24-h urine protein concentration, subjects in subgroup with 24-h urine protein ≥ 300 mg/day demonstrated a higher proportion of the urine protein dipstick positive but had no significantly difference (47.1% vs. 18.2%, $P = 0.053$) (Table 1).

Univariate analysis was performed and is presented in Table 2. The individual effects of the urine protein dipstick positive and hypertension had no significant for predicting proteinuria [odd ratios (95%CI), *P*-value] = [4.0 (0.95, 16.93), 0.060] and [1.5 (0.42, 5.61), 0.523)], respectively. Statistical significances in other parameters were also not observed. The ROC curve analysis was performed using 24-h urine protein concentration in all subjects to distinguish between subjects with or without proteinuria.

Based on the ROC analysis, the combination of the urine protein dipstick positive and hypertension could predict proteinuria better than urine protein dipstick positive alone [AUC (95% CI) = 0.710 (0.54, 0.87), $P = 0.026$] (Figure 1).

Table 1 Characteristics of the study subjects according to proteinuria status

Variable	Overall (n = 39)	Non-proteinuria (n = 22)	Proteinuria (n = 17)	*P* -value
Age (years)	28.4 ± 6.7	28.3 ± 8.2	28.5 ± 4.5	0.901
Blood pressure				
Systolic blood pressure (mmHg)	140.8 ± 20.5	139.7 ± 25.1	142.2 ± 16.6	0.725
Diastolic blood pressure (mmHg)	85.8 ± 16.1	84.7 ± 17.8	87.3 ± 14.0	0.623
Weight (Kg)	86.5 ± 21.6	85.7 ± 19.7	87.6 ± 24.5	0.787
Pulse rate (bpm)	98.9 ± 13.2	98.7 ± 14.8	99.2 ± 11.2	0.907
Maternal risk factors				
Hypertension, n (%)	23 (58.9)	12 (54.5)	11 (64.7)	0.522
Diabetes mellitus, n (%)	6 (15.4)	3 (13.6)	3 (17.6)	0.731
Lab findings				
24-h urine protein (mg/day)	412.8 ± 2.1	176.1 ± 1.5	486.0 ± 2.0	< 0.001
Urine protein dipstick positive	12 (30.8)	4 (18.2)	8 (47.1)	0.053

Note: Data are expressed as mean ± SD or numbers (%) as appropriate, except geometric mean ± geometric SD for 24-h urine protein. bpm = beat per minute, kg = kilograms, mg = milligrams, mmHg = millimeters of mercury.

Table 2 A univariate analysis for proteinuria in the study subjects

Variable	Crude OR (95% CI)	*P*-value
Age (years)	1.0 (0.91, 1.11)	0.905
Blood pressure		
Systolic blood pressure (mmHg)	1.0 (0.98, 1.04)	0.717
Diastolic blood pressure (mmHg)	1.0 (0.97, 1.05)	0.613
Weight (Kg)	1.0 (0.98, 1.04)	0.780
Pulse rate (bpm)	1.0 (0.96, 1.05)	0.904
Maternal risk factors		
Hypertension	1.5 (0.42, 5.61)	0.523
Diabetes mellitus	1.4 (0.24, 7.75)	0.731
Lab findings		
Urine protein dipstick positive	4.0 (0.95, 16.93)	0.060

Note: bpm = beat per minute, CI = confidence interval, kg = kilograms, mmHg = millimeters of mercury, OR = odds ratio.

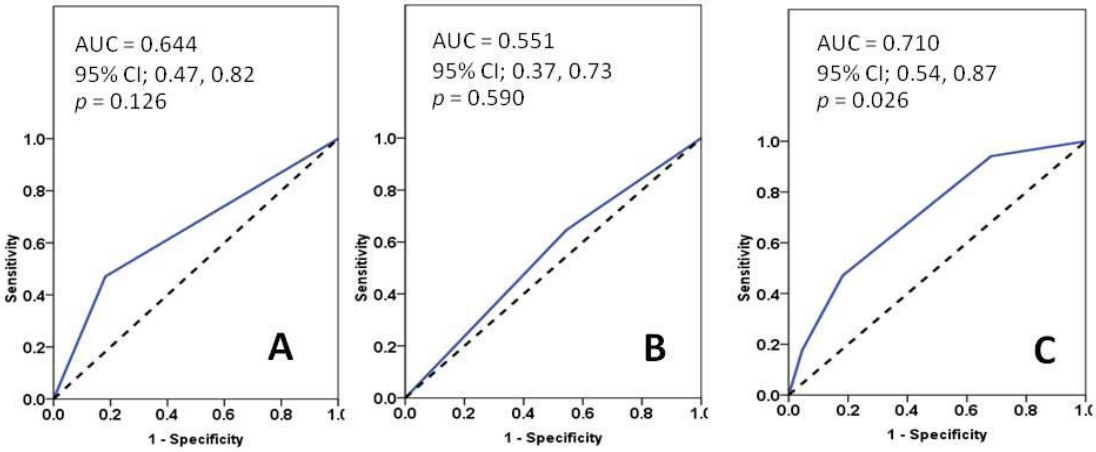

Figure 1. Receiver operating characteristic (ROC) curve for determining area under curves (AUCs) of urine protein dipstick positive (A), hypertension (B), and combination of urine protein dipstick positive and hypertension (C) in proteinuria. Highest AUC was found when urine protein dipstick positive was combined with hypertension.

Discussion

This study demonstrated that among high-risk pregnancies from ANC clinic, Saraburi Hospital, the main findings of this study including 1) approximately one third pregnant have a dipstick test positive at some time during their pregnancy 2) the individual effect of the urine protein dipstick positive and hypertension on significant proteinuria was not observed and 3) an additive effect of urine protein dipstick positive with hypertension on proteinuria was greater than their individual effects [AUC (95% CI), *P*-value] values of [0.710 (0.54 to 0.87), 0.011]. Previous study reported that routine testing for proteinuria is useless in predicting a pre-eclampsia and should be confined to women with hypertension or sudden weight gain (Lowe et al 2015). Thus far, this study confirmed the previous finding that the urine protein dipstick positive was not helpful determinant of proteinuria. Although current practice guidelines do not recommend routine use of urine protein dipstick test to guide for predicting of proteinuria, A recently reported that trace albumin with low specific gravity in urine dipstick test was associated with higher all-cause mortality in Korean adults (Han, E. N., Lee, K. B., Kim, H., & Hyun, Y. Y. (2018). Concerning this study current findings, a combination between urine protein dipstick positive and hypertension enhances may be used for predicting a significant proteinuria in high-risk pregnancy.

However, the current study has a numbers of limitations including, false positive and false negative results are common in urine protein dipstick testing, inaccuracy due to incomplete 24-h urine collection, and the main limitation is a single-center study with a small sample size, which may have led to weak statistical significance and enormous confidence intervals when estimating

odds ratio. To confirm these findings, studies with greater numbers of subjects and others testing such as urine protein/creatinine index or urine albumin/creatinine ratio are required.

In conclusion, the combination of urine protein dipstick positive and hypertension increases the risk of proteinuria assessment among high-risk pregnancies in Saraburi Hospital of Thailand. Therefore, determining the presence of the urine protein dipstick and hypertension may be a useful in proteinuria and pre-ecclampsia evaluation as a clinical benefit aspect in high-risk pregnancies.

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