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Prediction of preeclampsia with routine tests

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Clinical significance of proteinuria determined with dipstick test, edema, and
weekly weight gain \( \geq 500 \text{ g} \) at antenatal visit

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Synopsis: Retrospective analysis indicated that repeated positive dipstick test results in
two successive antenatal visits warrant a need for confirmation test of significant
proteinuria.

Key Words: antenatal care, edema, routine test, preeclampsia, proteinuria

Word counts excluding title page, abstract, references, tables, and figure legends: 2467
Prediction of preeclampsia with routine tests

Abstract

Objective: To determine how urine dipstick test, edema, and/or excessive weight gain (EWG, defined as ≥ 500 g/week) at antenatal visits predict significant proteinuria (defined as a protein-to-creatine ratio [P/Cr, mg/mg] ≥ 0.27) and preeclampsia.

Methods: Data from 3279 antenatal visits between 30 and 36 weeks of gestation were studied in 783 women with singleton pregnancies. In 24 preeclamptic pregnancies, data from 89 antenatal visits at and before diagnosis of preeclampsia were used. Spot P/Cr was determined in women with repeated positive dipstick test results in two successive antenatal visits or in those with a positive dipstick test result test in the presence of hypertension.

Results: Proteinuria on dipstick test, edema, and EWG appeared often in both women with and without preeclampsia; 66.7% vs. 27.7%, 83.3% vs. 44.1%, and 91.7% vs. 81.6%, respectively. However, repeated positive dipstick test results in two successive antenatal visits yielded sensitivity of 45.5%, specificity of 95.2%, and positive and negative predictive values of 30.0% and 97.4%, respectively, for detection of significant proteinuria and corresponding figures of 33.3%, 94.1%, 14.0%, and 98.0% for prediction of preeclampsia.

Conclusion: Repeated positive dipstick test results in two successive antenatal visits warrant a need for confirmation test of significant proteinuria.
INTRODUCTION

Pregnant Japanese women usually have 12–16 antenatal visits before giving birth [1]. Routine work-up includes measurement of body weight, semiquantitative analysis of protein in spot urine samples, and determination of the presence or absence of pitting edema on the anterior tibia at each antenatal visit [1].

As preeclampsia is a life-threatening complication [2,3], assessment of proteinuria is an important constituent of antenatal care for pregnant women. Although the gold standard test for determination of significant proteinuria in pregnancy is currently to confirm protein $\geq 0.3$ g/day in the urine collected for 24 h (24-h urine test), spot urinary protein-to-creatinine ratio of $\geq 0.27$ (mg/mg) (P/Cr test) is a reasonable “rule-out” test for detecting proteinuria of $\geq 0.3$ g/day in pregnancy as an alternative to the 24-h urine test [4–6]. The dipstick test to semiquantitatively determine protein concentration in spot urine samples is widely used as a screening test for detection of significant proteinuria in Japan. However, as our dipstick test has a high false positive rate (low positive predictive value) [7,8] and as we often encounter women who exhibit a negative test result after initially showing a positive test result on the dipstick test, many Japanese obstetricians appear to be insensitive to a positive test result on the dipstick test and do not offer confirmation tests, including 24-h urine test and P/Cr test in women with a positive test result on the dipstick screening test. This may lead to a delayed diagnosis of preeclampsia in some patients. However, it may be overtreatment to give a confirmation test because of the high false positive rate inherent in the dipstick test.
Prediction of preeclampsia with routine tests

test.

There have been no previous studies of how proteinuria determined by the dipstick test, the presence of pitting edema, and/or weekly weight gain $\geq 500$ g predict the subsequent development of preeclampsia. We conducted the present retrospective study to resolve this issue using data routinely recorded at each antenatal visit.

METHODS

This study was approved by the Institutional Review Board of Hokkaido University Hospital, a tertiary teaching hospital managing mainly high-risk pregnant women. The study population consisted of 783 women who received antenatal care and gave birth at the Hokkaido University Hospital during the period between January 2008 and July 2011 (Table 1). Data, including dipstick test results, presence of edema, and weekly weight gain $\geq 500$ g obtained at each antenatal visit from 30 to 36 weeks of gestation, were analyzed with respect to predictive value for detecting women at high risk of developing significant proteinuria and preeclampsia.

Preeclampsia was diagnosed according to the criteria adopted by the Japan Society of Obstetrics and Gynecology in 2005 [9]. Significant proteinuria necessary for the diagnosis of preeclampsia was defined as a positive test result on P/Cr test (protein-to-creatinine ratio $\geq 0.27$ [mg/mg] in spot urine specimens). P/Cr test was performed in women who exhibited proteinuria ($\geq 1+$ on dipstick test) in two successive antenatal visits and/or in those who exhibited a positive dipstick test result test in the presence of hypertension. The dipstick used in this study was designed to be negative,
1+, 2+, and ≥ 3+ on visual judgment at protein concentrations (mg/dl) in the urine < 30, 30 – 99, 100 – 299, and ≥ 300, respectively, according to the manufacturer’s package insert (Siemens, Tokyo, Japan). The screening characteristics of this dipstick were described previously [8]. Protein and creatinine concentrations in spot urine specimens were measured using the pyrogallol red method (Wako, Osaka, Japan) and creatinase sarcosine oxidase peroxidase method (Mitsubishi Chemical Medience, Tokyo, Japan), respectively, at our institution.

A total of 24 (3.1%) of the 783 women developed preeclampsia at 36.0 ± 2.9 weeks of gestation (Table 1). Another 12 women in the control group developed significant proteinuria but not hypertension. Of the 24 women with preeclampsia, 8 developed significant proteinuria first, at least one week prior to the development of hypertension, while 9 women developed hypertension first, at least one week prior to the development of significant proteinuria (Table 2).

The results of routine tests in 3279 antenatal visits, including 89 for the 24 women who subsequently developed preeclampsia and 3190 for the 759 controls during gestational weeks between 30 and 36, were analyzed. Data at antenatal visits after the diagnosis of preeclampsia were not included in this study. Similarly, data at antenatal visits after the diagnosis of significant proteinuria were not included in analysis for prediction of significant proteinuria. These routine tests were conducted by several midwives and included measurement of blood pressure and body weight, semiquantitative determination of proteinuria with a dipstick, and determination of the presence or absence of pitting edema on the anterior tibia at each antenatal visit. When the interval
of weighing was more than 7 days, the gain in maternal weight per day was calculated and multiplied by 7 to estimate the weekly gain. Excessive weight gain (EWG) was defined as ≥ 500 g/week.

All of the data are presented as means or median values. The results were analyzed using the unpaired t test, Kruskal–Wallis test, and Mann–Whitney U test. Fisher’s exact test was used to compare frequencies. In all analyses, $P < 0.05$ was taken to indicate statistical significance. The statistical software package StatView 5.0 for Macintosh (SAS Institute Inc., Cary, NC) was used for all data analyses.

RESULTS

Frequency of proteinuria determined by dipstick test, edema, and excessive weight gain (EWG) (Fig. 1 and Table 3)

Approximately 30% – 40% of women who subsequently developed preeclampsia exhibited proteinuria between gestational weeks 30 and 36, while proteinuria occurred in approximately 10% of women without preeclampsia (Fig. 1). Similarly, edema and EWG were recorded more frequently in women who subsequently developed preeclampsia than in those who did not. As many as 66.7% of women with preeclampsia exhibited proteinuria at least once during the period between gestational weeks 30 and 36, while only 27.7% of controls exhibited proteinuria ($P = 0.0001$) (Table 3). A similar difference was seen regarding edema, but not EWG, between the two groups. The frequencies of simultaneous appearance (coexistence) of proteinuria and edema or of proteinuria and EWG at least once during this period were also
significantly higher in the preeclampsia group than the control group. Only 24 (10.6%) of the 226 women with at least one positive dipstick test result were confirmed later to have significant proteinuria. Thus, a positive result on dipstick test yielded sensitivity of 66.7% (24/36), specificity of 73.0% (545/747), and positive and negative predictive values of 10.5% (24/226) and 97.8% (545/557), respectively, for the detection of significant proteinuria.

Screening characteristics of routine test for prediction of preeclampsia (Table 4)

As positive results on all routine tests, including proteinuria, edema, and EWG, were often seen even in women who did not develop preeclampsia, any single test result appeared not to be clinically useful for prediction of preeclampsia (Table 4). For example, proteinuria yielded a low positive predictive value of 7.1%, which was not markedly different from the value of 3.1% (24/783) for the incidence of preeclampsia in this study population. The coexistence of proteinuria and edema or of proteinuria and EWG enhanced the accuracy for prediction of preeclampsia, yielding positive predictive values of 12.0% and 12.5%, respectively.

How often did repeated positive dipstick test result occur in two successive antenatal visits? (Table 5)

As 3 of the 24 women with preeclampsia and 25 of the 759 controls had only one antenatal visit each, these 28 women were excluded from further analyses. Although a positive dipstick test result occurred frequently even in women who did not develop preeclampsia, a repeated positive test result in two successive antenatal visits was
Prediction of preeclampsia with routine tests

relatively less common in women without preeclampsia; 33.3% and 5.9% of women with and without preeclampsia exhibited this repeated positive test result, respectively (Table 5).

**Screening characteristics of repeated positive dipstick test result on two successive antenatal visits for prediction of significant proteinuria and preeclampsia (Table 6)**

Out of the 755 women with $\geq 2$ antenatal visits, 50 (6.6%) exhibited a repeated positive dipstick test result at two successive antenatal visits (Table 5), and 33 (4.4%) and 21 (2.8%) finally developed significant proteinuria and preeclampsia, respectively. Of the 33 women who were confirmed later to have significant proteinuria, 15 exhibited a repeated positive dipstick test result at two successive antenatal visits. Thus, the repeated positive dipstick test result at two successive antenatal visits yielded a sensitivity of 45.5%, specificity of 95.2%, and positive and negative predictive values of 30.0% and 97.4%, respectively, for prediction of significant proteinuria (Table 6). Of the 21 women later diagnosed with preeclampsia, 7 showed a repeated positive test result. Approximately 1 in 7 women with this repeated positive test result developed preeclampsia (positive predictive value of 14.0% [7/50], Table 6).

**DISCUSSION**

The present study demonstrated that repeated positive dipstick test results in two successive antenatal visits efficiently detected women who developed significant proteinuria and preeclampsia, although single use of each test, such as dipstick test,
Prediction of preeclampsia with routine tests

for the development of preeclampsia.

Assessment of proteinuria on dipstick test, edema, and measurement of body weight has traditionally been a part of routine work-up in antenatal care in Japan. As new onset of proteinuria is a necessary clinical symptom for the diagnosis of preeclampsia [9], and edema and resulting excessive weight gain may be seen frequently in women with preeclampsia [10–13], the aim of these tests has been partly to detect women at higher risk of developing preeclampsia. However, to our knowledge, there have been no systematic studies dealing with this issue. The results of this study may be helpful in interpretation of routine test results in daily obstetric practice.

Screening of proteinuria in pregnancy is usually performed with dipstick test worldwide. However, concerns have been raised regarding the accuracy of dipstick testing [7,14–19]. We previously examined the screening characteristics of the dipstick used in this study in 145 pregnant women, including 35 women with preeclampsia and demonstrated that the dipstick had a low threshold for showing a ≥ 1+ result; 44% of 156 spot urine samples with a ≥ 1+ test result contained protein < 30 mg/dl [8]. Thus, as the dipstick used in this study has a very high false positive rate (low positive predictive value of 56% for the detection of proteinuria ≥ 30 mg/dl [8]), as many as 226 (28.9%) of the 783 subjects in the study population exhibited a positive test result at least once in this study. This resulted in a low positive predictive value of 7.1% for the prediction of preeclampsia.

Generally, patients are recommended to undergo a further detailed test after exhibition of a positive test result on screening. In this case, obstetricians should consider P/Cr test
or 24-h urine test to confirm significant proteinuria [4 – 6]. However, a positive dipstick test result was seen very often and was not a good indicator of elevated risk of preeclampsia in this study. These results suggested that it may be overtreatment to conduct confirmation test for diagnosis of significant proteinuria in women with a positive dipstick test result and explained why most Japanese obstetricians appeared to be reluctant to offer a confirmation test in such cases.

Although a single positive dipstick test result was common and was not a good predictor of significant proteinuria or preeclampsia, a repeated positive test result in two successive antenatal visits was less common; 50 (6.6%) of the 755 women with at least two antenatal visits showed repeated positive test results. As a high percentage (30%) of these 50 women with repeated positive test results subsequently developed significant proteinuria, the repeated test results successfully detected women at high risk for developing significant proteinuria.

As many as 8 (40%) of the 20 women with significant proteinuria in the absence of hypertension subsequently developed hypertension and were diagnosed as proteinuria-preceding preeclampsia (Table 2), consistent with the results of previous studies in which 51% – 61% of women who exhibited new proteinuria in the absence of hypertension progressed to preeclampsia [20,21]. As shown in the present study, the interval until delivery (at 36.7 ± 3.7 weeks) after the development hypertension (at 36.3 ± 3.7 weeks) was only several days in patients who exhibited significant proteinuria at and after 30 weeks of gestation and progressed to proteinuria preceding preeclampsia.

Therefore, early diagnosis of significant proteinuria is clinically important to provide
adequate antenatal care in such patients. Our results demonstrated that approximately
one in three women with repeated positive dipstick test results developed significant
proteinuria, suggesting that obstetricians should recommend a confirmation test of
significant proteinuria in such cases with repeated positive dipstick test results in two
successive antenatal visits at and after 30 weeks of gestation.

Neither single use of edema nor weekly weight gain $\geq 500$ g was predictive of
preeclampsia in this study. However, the coexistence of edema or weight gain $\geq 500$ g
with proteinuria on the dipstick test significantly enhanced the positive predictive value
from 5.6% for edema alone or 3.4% for weekly weight gain $\geq 500$ g alone to 12.0% or
12.5%, respectively, for predicting preeclampsia. These results suggested that 1 in 9
women with simultaneous proteinuria and edema or simultaneous proteinuria and
weekly weight $\geq 500$ g at antenatal visit subsequently developed preeclampsia. This
level of risk for preeclampsia may provide a rationale to consider a confirmation test for
diagnosis of significant proteinuria. Further, these results supported previous reports
that women with preeclampsia often show generalized edema [10,12] and may explain
why women with eclamptic fits are likely to show extraordinary weight gain during the
last two antenatal weeks [13].

In conclusion, positive dipstick test result and weekly weight gain $\geq 500$ g with or
without edema are very common and a single use of any of these tests alone was not
predictive for either the development of significant proteinuria or preeclampsia. The
high rate of false positive results on the dipstick test may explain why many Japanese
obstetricians are reluctant to conduct confirmation tests, such as P/Cr test and 24-h urine
test. However, a positive dipstick test result concomitant with edema or weekly weight gain ≥ 500 g enhanced the accuracy for detection of women at high-risk of developing preeclampsia. Approximately one third of women who showed repeated positive dipstick test results in two successive antenatal visits had significant proteinuria. In women with proteinuria preceding preeclampsia, the time interval until delivery after the development hypertension was only several days. Therefore, early diagnosis of significant proteinuria is clinically important to provide adequate antenatal cares in such cases. Repeated positive dipstick test results on two successive antenatal visits warranted a need for confirmation test for significant proteinuria.

**Conflict of Interest**

All authors declare that they have no financial relationship with a biotechnology manufacturer, a pharmaceutical company, or other commercial entity that has an interest in the subject matter or materials discussed in the manuscript.
Prediction of preeclampsia with routine tests

REFERENCES


doi:10.1136/bmj.39532.543947.BE


Prediction of preeclampsia with routine tests

316 FIGURE LEGEND

317 Fig. 1: Frequencies of proteinuria determined by dipstick test, edema, and weight gain ≥ 500 g/week according to gestational week

319 Data at antenatal visits after diagnosis of preeclampsia were not included in this analysis.

321 ●, 24 women who subsequently developed preeclampsia; ○, 759 control women who did not develop preeclampsia.

323 *, $P < 0.05$ between groups with and without preeclampsia.
Table 1. Demographic characteristics of 783 study subjects

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Preeclampsia</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of women</td>
<td>759</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td>32.0 ± 5.2</td>
<td>31.6 ± 5.3</td>
<td>0.6959</td>
</tr>
<tr>
<td>Primipara</td>
<td>433 (57.1%)</td>
<td>18 (75.0%)</td>
<td>0.0798</td>
</tr>
<tr>
<td><strong>Gestational week</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteinuria†</td>
<td>34.4 ± 3.2‡</td>
<td>35.5 ± 3.1</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>35.3 ± 3.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>36.0 ± 2.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delivery</td>
<td>38.3 ± 1.8</td>
<td>36.8 ± 2.7</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Antenatal care¶</td>
<td>4.2 ± 1.4</td>
<td>3.7 ± 1.8</td>
<td>0.0881</td>
</tr>
<tr>
<td>Infant weight (g)</td>
<td>2850 ± 479</td>
<td>2364 ± 709</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

†, Defined as a protein-to-creatinine ratio ≥ 0.27; ¶, number of antenatal visits between gestational weeks 30 and 36; ‡, 12 women developed proteinuria alone. Data from antenatal visits after diagnosis of preeclampsia were not included.

Table 2. Gestational week at the onset of clinical signs and delivery in three types of preeclampsia

<table>
<thead>
<tr>
<th></th>
<th>Proteinuria*</th>
<th>Hypertension</th>
<th>Delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteinuria-preceding (n = 8)†</td>
<td>34.9 ± 4.3</td>
<td>36.3±3.7</td>
<td>36.7 ±3.7</td>
</tr>
<tr>
<td>Simultaneous (n = 7)</td>
<td>35.5 ± 3.2</td>
<td>35.6±3.2</td>
<td>36.6 ± 2.6</td>
</tr>
<tr>
<td>Hypertension-preceding (n = 9)‡</td>
<td>35.9 ± 1.9</td>
<td>34.1±1.8</td>
<td>37.0 ±1.8</td>
</tr>
</tbody>
</table>

*, Proteinuria (significant proteinuria) defined as a protein-to-creatinine ratio ≥ 0.27; †, Women who exhibited significant proteinuria at least one week prior to the development of hypertension; ‡, Women who exhibited hypertension at least one week prior to the development of significant proteinuria.
Table 3. Frequency of at least one positive test result

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 759)</th>
<th>Preeclampsia (n = 24)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Proteinuria*</td>
<td>210 (27.7%)</td>
<td>16 (66.7%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>2. Edema</td>
<td>335 (44.1%)</td>
<td>20 (83.3%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>3. Weight gain ≥ 0.5 kg/week†</td>
<td>619 (81.6%)</td>
<td>22 (91.7%)</td>
<td>0.1589</td>
</tr>
<tr>
<td>1 and 2 simultaneously</td>
<td>81 (10.7%)</td>
<td>11 (45.8%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>1 and 3 simultaneously</td>
<td>98 (12.9%)</td>
<td>14 (58.3%)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

*, Proteinuria defined as ≥ 1+ on dipstick test; †, Net change in body weight occurring between two antenatal visits was recalculated as the net change per week. Twenty-four of the 226 women with at least one positive dipstick test result were confirmed later to have significant proteinuria.

Table 4. Screening characteristics of routine tests for the prediction of preeclampsia

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Proteinuria*</td>
<td>66.7%</td>
<td>72.3%</td>
<td>7.1%</td>
<td>98.6%</td>
</tr>
<tr>
<td>2. Edema</td>
<td>83.3%</td>
<td>55.9%</td>
<td>5.6%</td>
<td>99.1%</td>
</tr>
<tr>
<td>3. Weight gain ≥ 0.5 kg/week†</td>
<td>91.7%</td>
<td>18.4%</td>
<td>3.4%</td>
<td>98.6%</td>
</tr>
<tr>
<td>1 and 2 simultaneously</td>
<td>45.8%</td>
<td>89.3%</td>
<td>12.0%</td>
<td>98.1%</td>
</tr>
<tr>
<td>1 and 3 simultaneously</td>
<td>58.3%</td>
<td>87.1%</td>
<td>12.5%</td>
<td>98.5%</td>
</tr>
</tbody>
</table>

*, Proteinuria defined as ≥ 1+ on dipstick test; †, Net change in body weight occurring between two antenatal visits was recalculated as the net change per week; PPV, Positive predictive value; NPV, Negative predictive value.
Table 5. Frequency of positive dipstick test result on two successive antenatal visits

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Preeclampsia</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>43/734 (5.9%)</td>
<td>7/21 (33.3%)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Twenty-eight women including 3 with preeclampsia with only one antenatal visit were excluded from the analysis.

Table 6. Screening characteristics of two successive positive dipstick test results for prediction of significant proteinuria and preeclampsia

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Significant proteinuria</td>
<td>45.5% (15/33)</td>
<td>95.2% (687/722)</td>
<td>30.0% (15/50)</td>
<td>97.4% (687/705)</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>33.3% (7/21)</td>
<td>94.1% (691/734)</td>
<td>14.0% (7/50)</td>
<td>98.0% (691/705)</td>
</tr>
</tbody>
</table>

PPV, Positive predictive value; NPV, Negative predictive value.