



Title	Clinical significance of proteinuria determined with dipstick test, edema, and weekly weight gain 500g at antenatal visit
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2 **Clinical significance of proteinuria determined with dipstick test, edema, and**
3 **weekly weight gain \geq 500 g at antenatal visit**

4

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15

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

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

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21

22 **Abstract**

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

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

32 **Results:** Proteinuria on dipstick test, edema, and EWG appeared often in both women
33 with and without preeclampsia; 66.7% vs. 27.7%, 83.3% vs. 44.1%, and 91.7% vs.
34 81.6%, respectively. However, repeated positive dipstick test results in two successive
35 antenatal visits yielded sensitivity of 45.5%, specificity of 95.2%, and positive and
36 negative predictive values of 30.0% and 97.4%, respectively, for detection of significant
37 proteinuria and corresponding figures of 33.3%, 94.1%, 14.0%, and 98.0% for
38 prediction of preeclampsia.

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

41

42

43 **INTRODUCTION**

44 Pregnant Japanese women usually have 12 – 16 antenatal visits before giving birth [1].

45 Routine work-up includes measurement of body weight, semiquantitative analysis of

46 protein in spot urine samples, and determination of the presence or absence of pitting

47 edema on the anterior tibia at each antenatal visit [1].

48 As preeclampsia is a life-threatening complication [2,3], assessment of proteinuria is an

49 important constituent of antenatal care for pregnant women. Although the gold standard

50 test for determination of significant proteinuria in pregnancy is currently to confirm

51 protein ≥ 0.3 g/day in the urine collected for 24 h (24-h urine test), spot urinary

52 protein-to-creatinine ratio of ≥ 0.27 (mg/mg) (P/Cr test) is a reasonable “rule-out” test

53 for detecting proteinuria of ≥ 0.3 g/day in pregnancy as an alternative to the 24-h urine

54 test [4 – 6]. The dipstick test to semiquantitatively determine protein concentration in

55 spot urine samples is widely used as a screening test for detection of significant

56 proteinuria in Japan. However, as our dipstick test has a high false positive rate (low

57 positive predictive value) [7,8] and as we often encounter women who exhibit a

58 negative test result after initially showing a positive test result on the dipstick test, many

59 Japanese obstetricians appear to be insensitive to a positive test result on the dipstick

60 test and do not offer confirmation tests, including 24-h urine test and P/Cr test in

61 women with a positive test result on the dipstick screening test. This may lead to a

62 delayed diagnosis of preeclampsia in some patients. However, it may be overtreatment

63 to give a confirmation test because of the high false positive rate inherent in the dipstick

64 test.

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

69 **METHODS**

70 This study was approved by the Institutional Review Board of Hokkaido University
71 Hospital, a tertiary teaching hospital managing mainly high-risk pregnant women. The
72 study population consisted of 783 women who received antenatal care and gave birth at
73 the Hokkaido University Hospital during the period between January 2008 and July
74 2011 (Table 1). Data, including dipstick test results, presence of edema, and weekly
75 weight gain ≥ 500 g obtained at each antenatal visit from 30 to 36 weeks of gestation,
76 were analyzed with respect to predictive value for detecting women at high risk of
77 developing significant proteinuria and preeclampsia.

78 Preeclampsia was diagnosed according to the criteria adopted by the Japan Society of
79 Obstetrics and Gynecology in 2005 [9]. Significant proteinuria necessary for the
80 diagnosis of preeclampsia was defined as a positive test result on P/Cr test
81 (protein-to-creatinine ratio ≥ 0.27 [mg/mg] in spot urine specimens). P/Cr test was
82 performed in women who exhibited proteinuria ($\geq 1+$ on dipstick test) in two successive
83 antenatal visits and/or in those who exhibited a positive dipstick test result test in the
84 presence of hypertension. The dipstick used in this study was designed to be negative,

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85 1+, 2+, and $\geq 3+$ on visual judgment at protein concentrations (mg/dl) in the urine < 30 ,
86 30 – 99, 100 – 299, and ≥ 300 , respectively, according to the manufacturer's package
87 insert (Siemens, Tokyo, Japan). The screening characteristics of this dipstick were
88 described previously [8]. Protein and creatinine concentrations in spot urine specimens
89 were measured using the pyrogallol red method (Wako, Osaka, Japan) and creatinase
90 sarcosine oxidase peroxidase method (Mitsubishi Chemical Medience, Tokyo, Japan),
91 respectively, at our institution.

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

98 The results of routine tests in 3279 antenatal visits, including 89 for the 24 women who
99 subsequently developed preeclampsia and 3190 for the 759 controls during gestational
100 weeks between 30 and 36, were analyzed. Data at antenatal visits after the diagnosis of
101 preeclampsia were not included in this study. Similarly, data at antenatal visits after the
102 diagnosis of significant proteinuria were not included in analysis for prediction of
103 significant proteinuria. These routine tests were conducted by several midwives and
104 included measurement of blood pressure and body weight, semiquantitative
105 determination of proteinuria with a dipstick, and determination of the presence or
106 absence of pitting edema on the anterior tibia at each antenatal visit. When the interval

107 of weighing was more than 7 days, the gain in maternal weight per day was calculated
108 and multiplied by 7 to estimate the weekly gain. Excessive weight gain (EWG) was
109 defined as ≥ 500 g/week.

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

115 **RESULTS**

116 **Frequency of proteinuria determined by dipstick test, edema, and excessive weight** 117 **gain (EWG) (Fig. 1 and Table 3)**

118 Approximately 30% – 40% of women who subsequently developed preeclampsia
119 exhibited proteinuria between gestational weeks 30 and 36, while proteinuria occurred
120 in approximately 10% of women without preeclampsia (Fig. 1). Similarly, edema and
121 EWG were recorded more frequently in women who subsequently developed
122 preeclampsia than in those who did not. As many as 66.7% of women with
123 preeclampsia exhibited proteinuria at least once during the period between gestational
124 weeks 30 and 36, while only 27.7% of controls exhibited proteinuria ($P = 0.0001$)
125 (Table 3). A similar difference was seen regarding edema, but not EWG, between the
126 two groups. The frequencies of simultaneous appearance (coexistence) of proteinuria
127 and edema or of proteinuria and EWG at least once during this period were also

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128 significantly higher in the preeclampsia group than the control group. Only 24 (10.6%)
129 of the 226 women with at least one positive dipstick test result were confirmed later to
130 have significant proteinuria. Thus, a positive result on dipstick test yielded sensitivity of
131 66.7% (24/36), specificity of 73.0% (545/747), and positive and negative predictive
132 values of 10.5% (24/226) and 97.8% (545/557), respectively, for the detection of
133 significant proteinuria.

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

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

143 **How often did repeated positive dipstick test result occur in two successive** 144 **antenatal visits? (Table 5)**

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

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

152 **Screening characteristics of repeated positive dipstick test result on two successive** 153 **antenatal visits for prediction of significant proteinuria and preeclampsia (Table 6)**

154 Out of the 755 women with ≥ 2 antenatal visits, 50 (6.6%) exhibited a repeated positive
155 dipstick test result at two successive antenatal visits (Table 5), and 33 (4.4%) and 21
156 (2.8%) finally developed significant proteinuria and preeclampsia, respectively. Of the
157 33 women who were confirmed later to have significant proteinuria, 15 exhibited a
158 repeated positive dipstick test result at two successive antenatal visits. Thus, the
159 repeated positive dipstick test result at two successive antenatal visits yielded a
160 sensitivity of 45.5%, specificity of 95.2%, and positive and negative predictive values
161 of 30.0% and 97.4%, respectively, for prediction of significant proteinuria (Table 6). Of
162 the 21 women later diagnosed with preeclampsia, 7 showed a repeated positive test
163 result. Approximately 1 in 7 women with this repeated positive test result developed
164 preeclampsia (positive predictive value of 14.0% [7/50], Table 6).

165 **DISCUSSION**

166 The present study demonstrated that repeated positive dipstick test results in two
167 successive antenatal visits efficiently detected women who developed significant
168 proteinuria and preeclampsia, although single use of each test, such as dipstick test,
169 measurement of body weight, and determination of edema, had poor predictive value

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170 for the development of preeclampsia.

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

179 Screening of proteinuria in pregnancy is usually performed with dipstick test worldwide.
180 However, concerns have been raised regarding the accuracy of dipstick testing [7,14 –
181 19]. We previously examined the screening characteristics of the dipstick used in this
182 study in 145 pregnant women, including 35 women with preeclampsia and
183 demonstrated that the dipstick had a low threshold for showing a $\geq 1+$ result; 44% of
184 156 spot urine samples with a $\geq 1+$ test result contained protein < 30 mg/dl [8]. Thus, as
185 the dipstick used in this study has a very high false positive rate (low positive predictive
186 value of 56% for the detection of proteinuria ≥ 30 mg/dl [8]), as many as 226 (28.9%)
187 of the 783 subjects in the study population exhibited a positive test result at least once in
188 this study. This resulted in a low positive predictive value of 7.1% for the prediction of
189 preeclampsia.

190 Generally, patients are recommended to undergo a further detailed test after exhibition
191 of a positive test result on screening. In this case, obstetricians should consider P/Cr test

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192 or 24-h urine test to confirm significant proteinuria [4 – 6]. However, a positive dipstick
193 test result was seen very often and was not a good indicator of elevated risk of
194 preeclampsia in this study. These results suggested that it may be overtreatment to
195 conduct confirmation test for diagnosis of significant proteinuria in women with a
196 positive dipstick test result and explained why most Japanese obstetricians appeared to
197 be reluctant to offer a confirmation test in such cases.

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

205 As many as 8 (40%) of the 20 women with significant proteinuria in the absence of
206 hypertension subsequently developed hypertension and were diagnosed as
207 proteinuria-preceding preeclampsia (Table 2), consistent with the results of previous
208 studies in which 51% – 61% of women who exhibited new proteinuria in the absence of
209 hypertension progressed to preeclampsia [20,21]. As shown in the present study, the
210 interval until delivery (at 36.7 ± 3.7 weeks) after the development hypertension (at 36.3
211 ± 3.7 weeks) was only several days in patients who exhibited significant proteinuria at
212 and after 30 weeks of gestation and progressed to proteinuria preceding preeclampsia.
213 Therefore, early diagnosis of significant proteinuria is clinically important to provide

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214 adequate antenatal care in such patients. Our results demonstrated that approximately
215 one in three women with repeated positive dipstick test results developed significant
216 proteinuria, suggesting that obstetricians should recommend a confirmation test of
217 significant proteinuria in such cases with repeated positive dipstick test results in two
218 successive antenatal visits at and after 30 weeks of gestation.

219 Neither single use of edema nor weekly weight gain ≥ 500 g was predictive of
220 preeclampsia in this study. However, the coexistence of edema or weight gain ≥ 500 g
221 with proteinuria on the dipstick test significantly enhanced the positive predictive value
222 from 5.6% for edema alone or 3.4% for weekly weight gain ≥ 500 g alone to 12.0% or
223 12.5%, respectively, for predicting preeclampsia. These results suggested that 1 in 9
224 women with simultaneous proteinuria and edema or simultaneous proteinuria and
225 weekly weight ≥ 500 g at antenatal visit subsequently developed preeclampsia. This
226 level of risk for preeclampsia may provide a rationale to consider a confirmation test for
227 diagnosis of significant proteinuria. Further, these results supported previous reports
228 that women with preeclampsia often show generalized edema [10,12] and may explain
229 why women with eclamptic fits are likely to show extraordinary weight gain during the
230 last two antenatal weeks [13].

231 In conclusion, positive dipstick test result and weekly weight gain ≥ 500 g with or
232 without edema are very common and a single use of any of these tests alone was not
233 predictive for either the development of significant proteinuria or preeclampsia. The
234 high rate of false positive results on the dipstick test may explain why many Japanese
235 obstetricians are reluctant to conduct confirmation tests, such as P/Cr test and 24-h urine

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236 test. However, a positive dipstick test result concomitant with edema or weekly weight
237 gain ≥ 500 g enhanced the accuracy for detection of women at high-risk of developing
238 preeclampsia. Approximately one third of women who showed repeated positive
239 dipstick test results in two successive antenatal visits had significant proteinuria. In
240 women with proteinuria preceding preeclampsia, the time interval until delivery after
241 the development hypertension was only several days. Therefore, early diagnosis of
242 significant proteinuria is clinically important to provide adequate antenatal cares in such
243 cases. Repeated positive dipstick test results on two successive antenatal visits
244 warranted a need for confirmation test for significant proteinuria.

245

246 **Conflict of Interest**

247 All authors declare that they have no financial relationship with a biotechnology
248 manufacturer, a pharmaceutical company, or other commercial entity that has an interest
249 in the subject matter or materials discussed in the manuscript.

250

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316 **FIGURE LEGEND**

317 Fig. 1: Frequencies of proteinuria determined by dipstick test, edema, and weight gain \geq

318 500 g/week according to gestational week

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

320 analysis.

321 ●, 24 women who subsequently developed preeclampsia; ○, 759 control women who

322 did not develop preeclampsia.

323 *, $P < 0.05$ between groups with and without preeclampsia.

Fig. 1

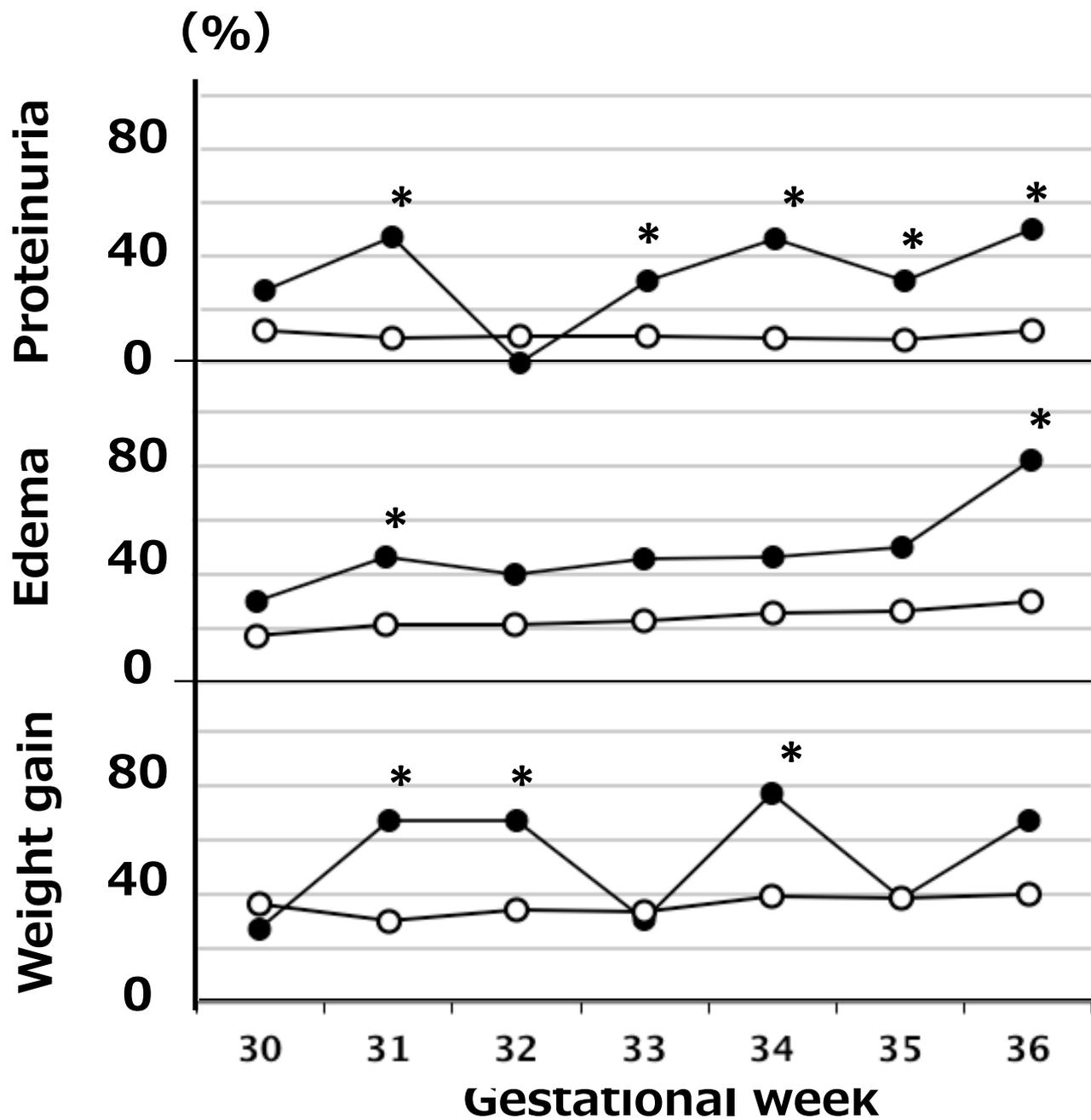


Table 1. Demographic characteristics of 783 study subjects

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

†, 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

	Gestational week when episodes occurred		
	Proteinuria*	Hypertension	Delivery
Proteinuria-preceding (<i>n</i> = 8)†	34.9 ± 4.3	36.3±3.7	36.7 ±3.7
Simultaneous (<i>n</i> = 7)	35.5 ± 3.2	35.6 ±3.2	36.6 ± 2.6
Hypertension-preceding (<i>n</i> = 9)‡	35.9 ± 1.9	34.1±1.8	37.0 ±1.8

*, 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

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

*, Proteinuria defined as \geq 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

	Sensitivity	Specificity	PPV	NPV
1. Proteinuria*	66.7%	72.3%	7.1%	98.6%
2. Edema	83.3%	55.9%	5.6%	99.1%
3. Weight gain \geq 0.5 kg/week	91.7%	18.4%	3.4%	98.6%
1 and 2 simultaneously	45.8%	89.3%	12.0%	98.1%
1 and 3 simultaneously	58.3%	87.1%	12.5%	98.5%

*, Proteinuria defined as \geq 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

	Control	Preeclampsia	<i>P</i> -value
Frequency	43/734 (5.9%)	7/21 (33.3%)	< 0.0001

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

	Sensitivity	Specificity	PPV	NPV
Significant proteinuria	45.5% (15/33)	95.2% (687/722)	30.0% (15/50)	97.4% (687/705)
Preeclampsia	33.3% (7/21)	94.1% (691/734)	14.0% (7/50)	98.0% (691/705)

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