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Early Diagnosis of Preeclampsia by 8 and 12 h Urine Protein

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Present research aim is to determine whether quantitative measurements of 8 and 12 h urine protein vs. 24 h sample are accurate in diagnosing preeclampsia and in differentiating mild from severe disease. The longitudinal-experimental method conducted on 60 preeclamptic women (30 patients with mild preeclampsia and 30 patients with severe preeclampsia). The 8, 12 and 24 h urine protein were compared and results were analyzed by the SPSS-10 statistical software. There was a significant relation between diagnosis of preeclampsia and the amounts of 8, 12 and 24 h urine protein ($p = 0.000$). The relation of systolic ($p = 0.000$) and diastolic ($p = 0.001$) blood pressure with severity of preeclampsia was significant. There was significant relation between gestational age and severity of disease ($p = 0.012$) but the relation of gestational age with parity, gravidity, serum creatinine level, urine volume and urine creatinine level was not significant ($p > 0.05$). Determining total protein of 8 and 12 h urine samples can be a good alternative for 24 h urine protein measurement. This would lead to a faster diagnosis for severe preeclampsia, earlier treatment and consequently reducing morbidity and mortality of mother and fetus/infant.

Key words: Preeclampsia, proteinuria, hypertension, pregnancy, urine sample

INTRODUCTION

Hypertensive disorders of pregnancy (HDP) are important causes of maternal and fetal mortality and morbidity (Leeners *et al.*, 2006). These disorders include chronic hypertension, preeclampsia-eclampsia, preeclampsia superimposed on chronic hypertension and gestational hypertension (Sibai, 2002; Wagner, 2004).

The types of HDP differ primarily in the incidence and not the nature, of maternal and perinatal complications (Ornstein *et al.*, 1999). Preeclampsia is defined as the new onset of hypertension ($>140/90$ mmHg) and proteinuria after 20 weeks of gestation in previously normotensive, nonproteinuric women (Wagner, 2004; Ornstein *et al.*, 1999; Skjaerven *et al.*, 2005; Roberts *et al.*, 2005).

Preeclampsia is a frequent disease with an incidence of 5 to 7% among the general population (Lopez-Jaramillo *et al.*, 2001). Preeclampsia is a pregnancy-associated disease with maternal symptoms, but placental origin (Smets *et al.*, 2006). The signs and symptoms of preeclampsia are usually apparent at a relatively late stage in pregnancy (late second to early third trimester) (Smets *et al.*, 2006). However, the disorder results from abnormal interaction between fetal and maternal tissue much earlier in pregnancy, between 8 and 18 weeks' gestation. There is no clinically useful screening test to predict the development of preeclampsia (Conde-Agudelo *et al.*, 2004).

Diagnostic criteria for preeclampsia include new onset of elevated blood pressure and proteinuria after 20 weeks of gestation. Features such as edema and blood pressure elevation above the patient's baseline no longer are diagnostic criteria (Table 1) (Sibai, 2002; Neithardt *et al.*, 2002). Severe preeclampsia is indicated by more substantial blood pressure elevations and a greater degree of proteinuria (Table 1).

Other features of severe preeclampsia include oliguria, cerebral or visual disturbances and pulmonary edema or cyanosis (Sibai, 2002; Neithardt *et al.*, 2002).

Diagnosis becomes less difficult if physicians understand where preeclampsia fits into the hypertensive disorders of pregnancy (Sibai, 2002).

Proteinuria is used as a criterion in the classification system for hypertensive disorders of pregnancy including preeclampsia (Gangaram *et al.*, 2005).

Urinary protein excretion was usually assessed by collecting urine continuously over 24 h period (Zeller *et al.*, 2005). In spite of repeated efforts for establishment of more rapid method of measurement of urine protein in pregnant women, 24 h urine protein measurement remains the gold standard method

Table 1: Blood pressure and proteinuric criteria for diagnosis of preeclampsia*

Mild preeclampsia

Blood pressure: SBP of ≥ 140 mmHg or DBP of ≥ 90 mmHg after 20 weeks of gestation

(in a woman with previously normal blood pressure)

Proteinuria: 0.3 to 2 g of protein in a 24 h urine collection (usually corresponds with 1+ or greater on a urine dipstick test)

Severe preeclampsia

Blood pressure: SBP of ≥ 160 mmHg or DBP of ≥ 110 mmHg (on two occasions at least 6 h apart in a woman on bed rest)

Proteinuria: ≥ 2 g of protein in a 24 h urine collection (usually corresponds $\geq 3+$ on urine dipstick testing of two random urine samples collected at least 4 h apart)

*For the diagnosis of preeclampsia, both hypertension and proteinuria must be present, SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure. Information from Cunningham *et al.* (2001)

(Cunningham *et al.*, 2001; Waugh *et al.*, 2005; Zeller *et al.*, 2005; Kalilian *et al.*, 2004). However, this method is not only onerous for patients; it is also unreliable if the urine sample is incomplete.

The purpose of this study is to determine if a patient's 8 and/or 12 h urine total protein values correlate with the 24 h value to confirm the diagnosis of preeclampsia.

MATERIALS AND METHODS

This is a longitudinal study performed over preeclamptic pregnant women admitted in Tabriz Al-Zahra and Taleghani Hospitals since Feb. 2003 to Feb. 2004. The inclusion criteria were having mild preeclampsia (DBP <100 mmHg and proteinuria 1+) or severe preeclampsia (DBP ≥ 110 mmHg and proteinuria 2+) and having the age ≤ 35 years.

The exclusion criteria were the history of diabetes mellitus, pyelonephritis, renal disease, chronic hypertension, soft tissue disease and absence of ability to collect the 24 h urine sample for any reason.

A total of 60 patients were selected of which 30 had mild and 30 had severe preeclampsia. Then, the patients asked to collect 8, 12 and 24 h urine, in 3 bottles. The first bottle was contained the first 8 h urine, the second bottle was contained the urine of 8-12 h and the third bottle was contained the urine of 12-24 h. The urine collection was performed in various hours of day and night and under supervision of nurses.

The content of any of bottles was measured quantitatively. One milliliter of urine was sampled from the first and third bottles. Then the content of all 3 bottles were mixed and 1 mL of the mixed urine was sampled. The 3 samples were preserved in refrigerator. The dipstick test was performed over all 3 samples and then all 3 samples were sent within 2-3 h to Tabriz Pashmineh Research Center Biochemical Laboratory, for urine analysis and creatinine and protein measurement.

Protein was measured by Brad Ford Assay which is the most rapid and safe method for protein measurement. Urine contents which are reactive with urine proteins become non-effective in this method (Bollag and Edelsein, 1991). This method is based on maximum optic absorption of protein-attached CBBG (Coomassie Brilliant Blue-G) in 465-595 nm wave-length (Ornstein *et al.*, 1999).

Hundred milligrams of CBBG is solved in 50 CC ethanol 95%. Hundred milliliters of phosphoric acid 85% is added to it and its volume is increased to 1000 CC by addition of water. Then, 5 mL from this solution is added to 100 μ L of urine and 5 min later, the maximum optic absorption in 595 nm wave-length is read and recorded (Bollag and Edelsein, 1991).

The protein content of sample (mg mL^{-1}) is determined by this method and is calculated for collected urine. For confirmation of correctness of urine collection, the creatinine clearance was calculated for all patients by this formula:

$$\text{Creatinine clearance} = \frac{\text{Urine volume (mL)} \times \text{Urine creatinine (mg L}^{-1}\text{)}}{\text{Time (min)} \times \text{Serum creatinine (mg dL}^{-1}\text{)}}$$

The collected data were analyzed by SPSS 10 statistical software and chi-square, t-test and Independent samples. The p-values less than 0.05 were considered significant. The quantitative results were reported as average $\pm$ SE and the qualitative results were reported as percentage.

RESULTS

Sixty hospitalized patients with preeclampsia were studied, of which 50% had mild and 50% had severe preeclampsia. Any of patients had not the prior history of preeclampsia, renal and soft tissue disease, pyelonephritis, diabetes mellitus, or chronic hypertension.

The results show that the relation between DBP and SBP and the severity of preeclampsia was significant ($PV = 0.000$) (Table 2).

There was significant relation between gestational age and the severity of disease (Table 2), but the relation of maternal age and the severity of preeclampsia was not

significant ($PV = 0.08$). Of all patients, 48.3% were gravida 1 and 51.7% were gravida ≥ 2 , of which 8.3% had the history of one abortion and 3.3% had the history of 2 abortions.

Of all patients 53.3% were nulipara and 46.3% were multipara. The relation of parity and severity of disease was not significant ($PV = 0.1$).

Also, the relation of severity of preeclampsia with serum creatinine ($PV = 0.09$), urine volume ($PV = 0.1$) and urine creatinine ($PV = 0.11$) was not significant.

There was significant relation between severity of preeclampsia and the results of dipstick test for 8, 12 and 24 h urine ($PV = 0.000$) (Fig. 1-3).

Present study showed that the relation of protein content of 8, 12 and 24 h urine sample with severity of preeclampsia is significant ($PV = 0.000$) (Table 1).

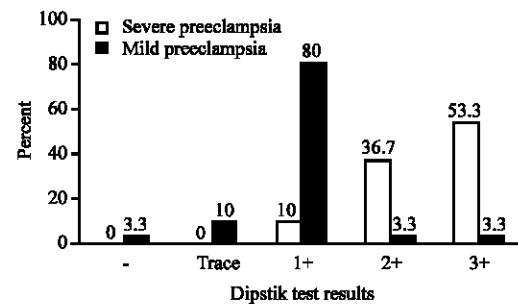


Fig. 1: Comparison of dipstick test results of 24 h urine in patients with mild vs. patients with severe preeclampsia

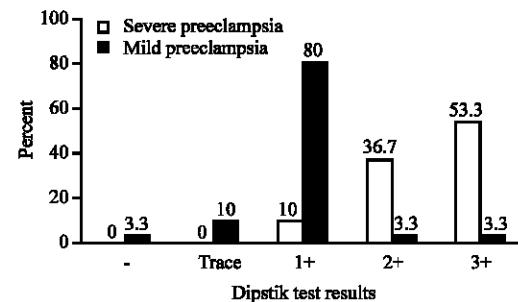


Fig. 2: Comparison of dipstick test results of 12 h urine in patients with mild vs. patients with severe preeclampsia

Table 2: Comparison of variables between patients with mild and severe preeclampsia

Variables	Mild preeclampsia	Severe preeclampsia	p-value
Systolic blood pressure (mmHg)	143.3 $\pm$ 5.47	186.6 $\pm$ 11.9	0.000
Diastolic blood pressure (mmHg)	93.1 $\pm$ 9.3	101 $\pm$ 8.03	0.001
Average gestational age (W)	33.87 $\pm$ 3.28	31.62 $\pm$ 3.46	0.012
Average maternal age (Y)	27.5 $\pm$ 6.5	24.6 $\pm$ 5.9	0.081
Average 8 h urine protein (mg)	53.27 $\pm$ 299.22	2030.97 $\pm$ 740.68	0.000
Average 12 h urine protein (mg)	332.73 $\pm$ 417.59	2565.63 $\pm$ 939.91	0.000
Average 24 h urine protein (mg)	525 $\pm$ 613	3983 $\pm$ 1501	0.000

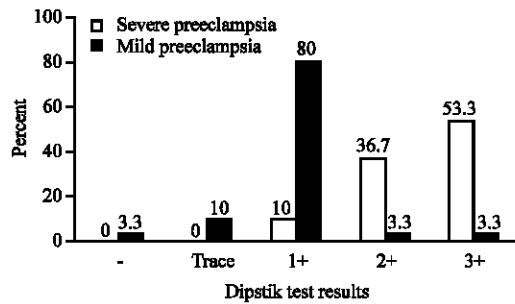


Fig. 3: Comparison of dipstick test results of 8 h urine in patients with mild vs. patients with severe preeclampsia

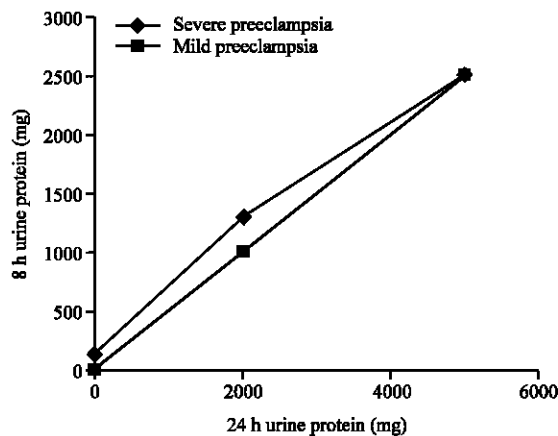


Fig. 4: The comparison of 8 h with 24 h urine protein in mild and severe preeclampsia

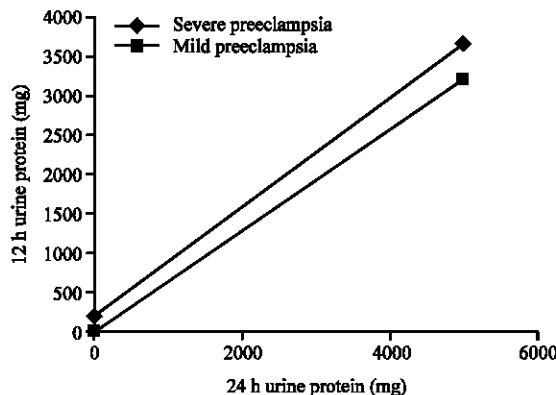


Fig. 5: The comparison of 12 h with 24 h urine protein in mild and severe preeclampsia

The scatter diagram show that protein content of 8 h urine sample is directly related with protein content of 24 h urine sample (Fig. 4).

Also, according to Fig. 5 and 6, protein content of 12 h urine sample is directly related with protein content of 24 and 8 h urine sample, respectively.

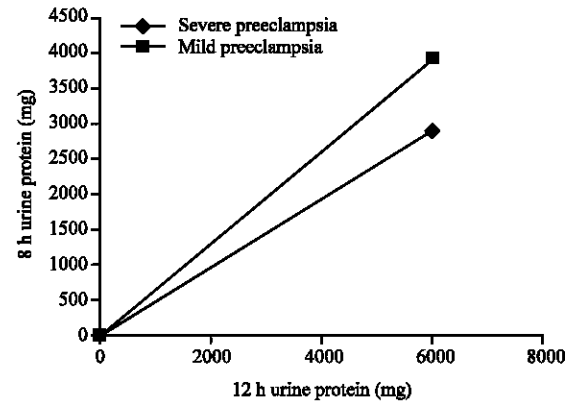


Fig. 6: The comparison of 8 h with 12 h urine protein in mild and severe preeclampsia

Our study suggests that:

- The protein level of ≥ 223 milligram in 8 h urine sample is indicative of mild preeclampsia (PV = 0.000), with sensitivity and specificity of 76.7 and 100%, respectively.
- Urine protein of ≥ 1400 mg/8 h is indicative of severe preeclampsia (PV = 0.000), with sensitivity of 76.7% and specificity of 100%.
- The protein level of ≥ 269 milligram in 12 h urine sample is indicative of mild preeclampsia (PV = 0.000), with sensitivity and specificity of 66.7 and 100%, respectively.
- Urine protein of ≥ 2600 mg/12 h is indicative of severe preeclampsia (PV = 0.000), with sensitivity of 66.7% and specificity of 100%.

DISCUSSION

The signs and symptoms of preeclampsia are usually apparent at a relatively late stage in pregnancy (late second to early third trimester) (Smets *et al.*, 2006) and proteinuria is one of these late onset signs of preeclampsia (Moldenhauer *et al.*, 2003; Mordechai, 1999).

Measurement of total protein content of 24 h urine sample remains the gold standard method for diagnosis of preeclampsia (Cunningham *et al.*, 2001). In most pregnant women, urinary protein excretion is 5 mg dL^{-1} as the upper limit of normal at the first and second trimester; this figure at the third trimester is 15 mg in 100 CC of urine (Higby *et al.*, 1994).

Pregnancies complicated by hypertension are associated with increased risk of adverse fetal, neonatal and maternal outcomes (Roberts *et al.*, 2005; Mordechai, 1999). Although we had not maternal mortality in preeclamptic women, it has been reported that

approximately 18% of maternal mortality since 1987 to 1990 in US was because of hypertensive disorders of pregnancy including preeclampsia (Cunningham *et al.*, 2001). Moreover, the 24 h period for urine collection may result in a delay in diagnosis and treatment. These facts mandate the presence of more rapid diagnostic method with the same or even more accuracy.

Proteinuria is used as a criterion in the classification system for hypertensive disorders of pregnancy including preeclampsia (Gangaram *et al.*, 2005). Proteinuria is affected by factors such as contamination of urine sample with vaginal secretions, blood, or bacteria, as well as by urine specific gravity, pH, exercise and body position (Higby *et al.*, 1994; Moldenhauer *et al.*, 2003). So, urine protein level varies continuously and dipstick urinalysis is not very accurate in prediction of preeclampsia (Mordechai, 1999). Therefore, all women presenting with hypertension during pregnancy should have a 24 h urine protein measurement (Gangaram *et al.*, 2005; Campbell *et al.*, 2006).

Meyer *et al.* (1994) concluded that Urinary protein dipstick values $\geq 1+$ have a positive predictive value of 92% for predicting ≥ 300 mg per 24 h. In contrast, a dipstick of negative to trace should not be used to rule out significant proteinuria because its negative predictive value is only 34% in hypertensive patients. Moreover, urine dipstick values of 3+ to 4+ should not be used to diagnose severe preeclampsia because their positive predictive value is only 36% (Meyer *et al.*, 1994).

In another study by Gangaram *et al.* (2005), the positive predictive value for dipstick urinalysis ranged from 64.9% (single voided urine sample) to 94.2% (24 h urine aliquot). The negative predictive value ranged from 75.2% (single voided urine sample) to 84.2% (24 h urine aliquot). They concluded that the dipstick urinalysis is not very accurate and it can not be alternate method for 24 h urine protein measurement in women presenting with hypertension during pregnancy (Gangaram *et al.*, 2005).

Adelberg *et al.* (2001) conducted the same study to determine if a patient's 8 and/or 12 h urine total protein values correlate with the 24 h value to confirm the diagnosis of preeclampsia. In their study the average diastolic blood pressure in patients with severe and mild preeclampsia was 105 ± 7.4 and 91 ± 207 mmHg, respectively which are compatible with our study.

Also, the average systolic blood pressure in patients with severe and mild preeclampsia was 158 ± 11.9 and 143.3 ± 5.47 mmHg, respectively which are compatible with our study.

As our study, the study of Adelberg *et al.* (2001) suggests that the relation of severity of preeclampsia with gravidity, parity, urine volume and serum creatinine is not statistically significant.

In Adelberg *et al.* (2001) study, the average 24 h urine protein in patients with mild and severe preeclampsia was 902 ± 882 and 10975 ± 5505 mg, respectively. Also, in their study the dipstick test result for patients with mild preeclampsia was negative in 14%, Trace in 52%, 1+ in 14%, 2+ in 9% and 3+ in 9%. The result in patients with severe preeclampsia was 2+ in 20% and 3+ in 80%. They concluded that total protein values for 8 and 12 h urine samples correlate positively with values for 24 h samples for patients with proteinuria (PV = 0.000).

Their study showed that: 8 h urine protein of ≥ 110 mg is indicative of mild preeclampsia with sensitivity and specificity of 84 and 90%, respectively; 12 h urine protein of ≥ 165 mg is indicative of mild preeclampsia with sensitivity of 78% and specificity of 100%; 8 h urine protein of ≥ 1400 mg is indicative of severe preeclampsia with sensitivity and specificity of 100 and 97%, respectively; 12 h urine protein of ≥ 2700 mg is indicative of severe preeclampsia with sensitivity of 100% and specificity of 97% (Adelberg *et al.*, 2001).

Khalilian *et al.* (2001) showed that 6 and 12 h urine total protein is the same valuable as 24 h urine total protein in the diagnosis of mild and severe preeclampsia (Kalilian *et al.*, 2004).

Wongkitisophon *et al.* (2003) suggest that total protein values of 4 h samples positively correlated with values of 24 h samples of patients with hypertensive disorders in pregnancy ($p < 0.001$). This might be modified and used for urine protein collection in outpatients to improve the compliance (Wongkitisophon *et al.*, 2003).

Rinehart *et al.* (1999) suggested that the sensitivity and specificity of the 12 h urine collection was 96 and 100%, respectively and concluded that a 12 h urine collection accurately depicts the amount of proteinuria in hospitalized gravidas being evaluated for preeclampsia.

The urinary protein excretion is different in various hours of day and night probably because of vascular constriction which varies continuously (Moldenhauer *et al.*, 2003).

It seems that protein excretion is increased in upright position because of the increased renal vascular constriction and change in permeability of glomerular barrier. It has been suggested that physiologic factors cause continuous change in protein excretion (Mordechai, 1999).

Protein excretion varies also in preeclamptic patients (Higby *et al.*, 1994; Moldenhauer *et al.*, 2003). However, in our study, the results of 8 and 12 h urine, collected in various hours of day and night, were comparable with results of 24 h urine for protein content.

In the study of Khalilian *et al.* (2001), the samples were collected from 8-morning (8 AM) of the first day to day after 8-morning. The first 6 h sample had the sensitivity and specificity of 100 and 100%, respectively. These figures for the second 6 h sample were 96 and 86.6%, respectively.

The first 12 h sample had the sensitivity and specificity of 100 and 93.2%, respectively. These figures for the second 12 h sample were 80 and 93.3%, respectively.

They concluded that urine protein especially that of pertaining to the first 6 h after waking up is of significant importance in the diagnosis of preeclampsia. There was a circadian rhythm of proteinuria in this study (Kalilian *et al.*, 2004).

CONCLUSIONS

It is concluded from this study that determining total protein of 8 and 12 h urine samples can be a good alternative for 24 h urine protein measurement. This would lead to a faster diagnosis for severe preeclampsia, earlier treatment and consequently reducing morbidity and mortality of mother and fetus/infant.

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