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Relation of protein excretion during conservative management of eclampsia and severe pre-eclampsia with maternal and perinatal outcome.

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ABSTRACT

Objectives: *The aim of our study was to determine the amount and natural course of urinary protein excretion during conservative management of eclampsia and severe pre-eclampsia and to observe whether changes in urinary protein excretion can predict maternal and perinatal outcome.*

Study design: *Retrospective study*

Setting: *Department of Obstetrics and Gynaecology, Dhaka Medical College and Hospital.*

Patient population: *Fifty one patients with pregnancy induced hypertension (PIH) (31 women eclampsia and 20 with severe pre-eclampsia) who were managed conservatively before 36 weeks of gestation.*

Methods: *Twenty four hour urinary protein excretion of all patients was measured after admission and at weekly intervals. Maternal complications and perinatal outcome were correlated with amount of proteinuria.*

Main outcome Measured: *Maternal complications, days gained during management, still birth and low birth weight.*

Results: *Out of 51 patients only 4 (7.84%) patients excreted > 5gm protein per 24 hours. But in all cases there was fetal death in utero. In 14 cases the 24 hour protein excretion was 2–5gm. The birth weight of babies born to these women were 2.23 $\pm$ 0.25kg and the perinatal death rate was 21.43%. The total protein excretion was 1–1.99 gm in 17 women and the birth weight of delivered babies were 1.83 $\pm$0.47kg and perinatal death rate was 47.08%. The total protein excretion was < 1gm in 16 women. Birth weight of babies delivered by this group was 2.03 $\pm$0.53kg and perinatal death rate was 25%. There was no serious maternal complications recorded. Only one patient developed abruptio placenta with total protein of 1.5gm. Pregnancy could be continued up to 35days in patients whose 24 hours protein excretion was 1–5gm. But mean duration was maximum (17.05 days) in group whose 24 hours protein excretion was 1–1.99 gm. Although there is a negative correlation between proteinuria and birth weight r = –0.34 p = .47, and still birth r = –0.17p, p = .21, it was not statistically significant, although a negative correlation of proteinuria and days gained during conservative management is significant r = –0.31, p = 0.02.*

Conclusion: *Proteinuria increases in a few patients with PIH who were managed conservatively. No significant differences in maternal and foetal outcomes were found between pregnancies with marked increases in proteinuria and in those women with moderate or no increase in urinary protein excretion.*

Key words: *Proteinuria, eclampsia, severe pre-eclampsia, conservative management perinatal outcome, maternal outcome.*

INTRODUCTION

Preeclampsia (PE) and eclampsia is a multisytem disorder and characterized by endothelial damage and acute atherosis[1]. Pre-eclampsia is a major contributor to maternal and fetal mortality and morbidity[2]. The incidence of pre-eclampsia ranges from two to ten percent between studies, depending on the population studied and the criteria used to diagnose pre-eclampsia[3,4]. The basis for the diagnosis is an increase in blood pressure during pregnancy, but the extent of increase that is required for diagnosis varies between studies. For the most often used diagnostic criteria proteinuria should also be present, but in some studies this has not been a requirement. The fact that several classification systems for pre-eclampsia are in current international use[5] complicates comparisons between different studies.

Shallow endovascular cytotrophoblast invasion in the spiral arteries and generalised maternal endothelial dysfunction are characteristics of pre-eclampsia, but its aetiology remains obscure[6]. Genetic, immunologic, environmental and vascular-mediated factors are all thought to play an important role in the development of pre-eclampsia[7,8], and several risk factors have been identified. Among those, nulliparity, previous pre-eclampsia, high maternal weight, hypertension, diabetes and twin pregnancy[9–11] have shown a consistent association wtih increased risk. In most analyses cases have encompassed all clinical manifestations of pre-eclampsia, failing to distinguish between cases of dramatic early onset and cases with mild symptoms gradually developing towards term.

Pre-eclampsia is often distinguished from gestational hypertension by the presence of significant proteinuria[12,13]. The 24-hour urine collection has been the gold standard for making the diagnosis of significant proteinuria in patients with pregnancy-induced hypertension[12–14]. The test is cumbersome and takes 24 hours to complete, which leads to delay in diagnosis and inaccurate results as the result of incomplete collections. Noncompliant patients are often admitted to the hospital to ensure a proper collection. In addition, for patients who are diagnosed with hypertension while in labor, the clinician is unable to complete a 24-hour collection. A rapid method for diagnosing significant proteinuria could help clinicians make more timely decisions regarding delivery and the use of magnesium for seizure prophylaxis. The dipstick has been shwon to be inaccurate with 1 study that shows that 66% of the patients with negative or trace protein had significant proteinuria when the sample was compared with the 24-hour urine collection[15].

The important diagnostic criteria among the three parameters (Hypertension, Oedema, Proteinuria) for pregnancy induced hypertension, heavy proteinuria (≥ 5gm/24hrs) has traditionally served as a criteria of severe disease. It is an indicator of damage to the glomerular endothelium. Termination of pregnancy irrespective of gestational age is believed to be the definitive treatment for pregnancy induced hypertension (PIH). Since the only cure for these conditions is delivery, there is universal agreement that patients should be delivered if severe pre-eclampsia develops after 34 weeks of gestation or if convulsion occurs anytime during the gestational period[16,17]. Current evidence however, indicates little risk to the mother when a conservative approach to management in well selected cases of severe pre-eclampsia is conducted[18,19]. In this study, an attempt is made to investigate the relationship between increased proteinuria and adverse maternal and perinatal outcome.

MATERIALS AND METHODS

This retrospective study was conducted at Dhaka Medical College and Hospital between January 1998 and October 2000. Fifty one patients with pregnancy induced hypertension (30 eclampsia and 21 severe pre-eclampsia with blurred vision and headache) with gestational age < 36 weeks were treated conservatively. We selected 36 weeks as a cut off point for gestational age because of the high neonatal morbidity and mortality among babies born before this cutoff point. All patients had a live fetus at the time of inclusion and all had documented evidence of the disease i.e. proteinuria, oedema, high blood pressure, and convulsion. All patients underwent 24-hour urine collection for measurement of urinary total protein (UTP). Serum urea, creatinine, uric acid, SGOT, SGPT and platelet count were determined in all cases. Ultrasonography was performed for estimation of gestational age. Laboratory evaluations

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of UTP, urea, uric acid, platelet count, SGOT,SGPT were repeated weekly when initial concentrations were higher than normal levels.

Termination of pregnancy was based on both maternal and fetal indications. Maternal indications for delivery were the following: uncontrolled severe hypertension in spite of the adequate antihypertensive therapy, onset of persistent headache, epigastric pain, vaginal bleeding (abruptio placenta), and ruptured membranes. Fetal indications for delivery included fetal distress (or, nonreassuring fetal status, as determined by ausculating fetal heart sound and in some cases by biophysical profile) fetal deaths, static growth, and attainment of 36 weeks pregnancy. All patients were discharged with stable blood pressure levels with 1+ or absent urinary albumin.

Analysis of data included assessment of maternal complications, laboratory findings, days gained during management, and perinatal outcome and its correlation with proteinuria. Results were expressed as mean ± SD and correlation coefficient was computed.

RESULTS

Of the 51 patients, 21 were diagnosed with severe pre-eclampsia, and 30 were diagnosed with eclampsia. The average age of the patients was 25.21 ± 4.64 years (range, 17-35 years). Most of the patients were primigravid (68.63%) and no patients had antenatal check-up before admission to the hospital. Average gestational age was 30.65 ± 2.38 weeks (range, 24-34 weeks) (Table 1).

Table 2 shows the patient's conditions at admission. Patients had diastolic blood pressure levels ranging from 90-140 mm Hg with a mean value of 109.05 ± 11.61 mm Hg. All patients were fully conscious at admission.

The laboratory investigations are given in Table 2. Urea, SGOT, SGPT, and platelet count were within normal limits. The mean UTP was 2.25g/24 hours (range, 0.12-6.53 g/24 h;serum uric acid was 5.5mg/dl, (range, 3.6-8.7mg/dL; and serum creatinine was 1.31 mg/dL (range, 0.7-3.6mg/dL).

Table 3 shows the relation of proteinuria with maternal and fetal outcomes. Those women with > 5gm proteinuria in 24 hrs gave birth to stillborn babies in all cases. Average birth weight was 2.23 kg in patients whose 24 hrs protein excretion was 2-5gm. There was no significant difference in birth weight between the groups who had proteinuria < 1gm or 2-5 gm in 24 hrs. Pregnancy can be continued up to 35 days in patients whose 24-hrs protein excretion was 1-5gm. The mean duration was maximum (17.05 days) in the group with proteinuria between 1 and 1.99g/24hr. These appeared a negative correlation between proteinuria and birth weight $r = -0.34$, $p = 0.47$, and still birth $r = -0.17$ $p = 0.21$ which was not statistically significant. Besides, a negative correlation was observed between proteinuria and days gained during conservative management which was significant ($r = -0.31$, $p = 0.02$).

DISCUSSION

There is a strong debate on the expectant management of severe eclampsia and pre-eclampsia as the clinical course of these conditions may lead to a progressive deterioration of both mother and foetus. Proteinuria is predominant among the three important (Hypertension, proteinuria, oedema) diagnostic criteria in PIH. As with other types of proteinuria of glomerular origin, the proteinuria of PIH invloves predominantly high molecular weight protein such as albumin. It is caused by reversible structural alterations of the glomerular filter resulting from injury of endothelial cells in the glomerular capillaries.

TABLE 1
Patients characteristics

Characteristics	**Range**	**Mean ± SD**
Age of the patients (Yrs)	17–35	25.21 ± 4.69
G/A at admission (Weeks)	24–34	30.27 ± 2.59
Parity	**No**	**%**
Nulliparous	35	68.63
1–2	11	21.57
3–4	5	9.80
Total	51	100

TABLE 2
Patients condition at admission

Parameters	**Range**	**Mean ± SD**
DBP (mmHg)	90–140	109.05 ± 11.61
24 hour UTP (g/24h)	0.12–6.53	2.25 ± 7.32
Urea (mg/dl)	22–65	41.25 ± 7.32
Creatinine (mg/dl)	0.7–3.6	1.31 ± .56
Uric acid (mg/dl)	3.0–8.7	5.5 ± 1.12
SGOT (IU/L)	7–42	17.85 ± 8.06
SGPT (IU/L)	10–42	20.0 ± 11.57
Platelet count (n/mm3)	100–300	202.81 ± 49.82
GCS 15	Number 51	Percentage 100

TABLE 3
Relationship of 24 hour urinary total protein with maternal and foetal outcome

Outcome	<1g	1-1.99g	2-5g	> 5g	r	p
Birth weight (Kg) Mean+SD	2.03 ± 0.53	1.83 ± 0.47	2.23 ± 0.25	0	-0.34	.47
Still birth (%)	25	41.17	28.57	100	-0.17	.21
Preg. continued (Days) Mean ± SD	3-28 17 ± 7	3-35 17.05 ± 11.22	3-35 11.29 ± 10.36	3-7 11.29 ±	-0.31	.02

Since the renal glomeruli are frequently affected, showing a typical pathologic picture of glomerular endotheliosis[2], the consequent clinical manifestation is the appearance of proteinuria, one of three fundamental criteria for the clinical diagnosis of preeclampsia. Heavy proteinuria (≥ 5gm/24 hours) has traditionally served as one criterion in the definition of severe disease. The traditional management of severe preeclampsia has been expeditious delivery, regardless of gestational age and of the criteria by which the disease was defined as severe. In two randomized trials[23,24], conservative management in well-selected cases of severe preeclampsia remote from term (prolongation of pregnancy until specific maternal or fetal indications necessitated delivery) was shown to benefit the fetus with little risk to the mother. The natural history of renal protein excretion during pregnancy prolongation with severe preeclampsia and the association of increased proteinuria with maternal and perinatal outcomes are unknown. This study was designed to investigate the natural course of urinary protein excretion during conservative management of severe preeclampsia and to explore the relationship between increasing proteinuria and adverse maternal or perinatal outcome.

Although massive proteinuria has long been considered as important indicator of maternal and foetal outcome, Schiff et al[6] described that amount of proteinuria is not important predictors of perinatal outcome. The quantity of protein excretion and the quantity of urine production are associated with several haemodynamic factors in addition to basic renal function[7].

The aim of this report was to explore the natural course of renal protein excretion during conservative management of PIH and to investigate whether a marked increase in protein excretion during conservative management period is associated with a poorer prognosis for the mother and foetus. Our results show that 90% patients had proteinuria > 300mg (Upper limit of normal value) at the time of recruitment. Out of 51 patients 16 (31.37%) had > 300-900 mg/24hrs, 17(33.33%) had 1-1.99gm/24hrs, 14 (27.45%) had 2-5gm/24hrs and 4(7.84%) had > 5gm/24hrs.

We did not repeat the test where the baseline value was ≤ 300mg/24hrs as it is a relatively inconvenient test. In some cases tests were repeated weekly when initial value exceeeds 2gm (4 cases), in other cases it was done twice weekly (6 needed once and 7 needed

twice). In 12 cases we could not repeat UTP estimations which were > 1gm as they delivered within 7 days. We found that excretion of protein increment was not significant. Only in three patients (5.88%) protein excretion increased by 1.9 gm, in 2 cases (3. 92%) it reduced by 1 gm and in other cases it remained static. In 4 cases protein excretion was > 5 gm at the time of recruitment whose test could not be repeated as in all cases IUD occurred within 7 days.

The three patients in whom protein excretion increased gave birth to live infants after 10, 14 and 14 days of admission at gestational age of 34, 34 and 35 weeks with birth weight of 2, 2 and 2.2 kg respectively. So during conservative management increment of protein excretion was not significant and which did not affect the foetal outcome significantly. But in cases where UTP was > 5gm/24hrs at recruitment all babies died in utero. Schiff et al[20] described that patients whose 24 hrs protein excretion was > 5gm and in several patients it was 10-20gm/24 hours had outcomes and admission – to – delivery interval similar to those for women who had mild proteinuria. So, it is clear that the amount of proteinuria and the rate of increase in protein during conservative management are not important predictors of maternal or perinatal outcome.

In this series increment of protein excretion did not affect the foetal or maternal outcome. But patients whose protein excretion was ≥ 5gm/24 hours had IUD within 1st 7 days of admission. But in other few cases whose protein excretion was between .09 – 2 gm/24 hours had IUD though admission to delivery interval was longer (up-to 21 days). So it is difficult to determine whether amount of protein excretion is predictor of foetal outcome. In this series pregnancy was terminated only in one case due to increment of proteinuria and she gave birth to a alive baby of 2 kg. Schiff et al recommended that during conservative management of PIH pregnancy not to be terminated on the basis of proteinuria or an increment therein as long as other maternal and foetal biochemical and biophysical variables are reassuring[20].

In PIH endothelial cell injuries in the glomerular capillaries causes reversible structural alterations of the glomerular filter. The quantity of protein excretion and the quantity of urine production are associated with several haemodynamic factors in addition to basic renal function. In most pre-eclamptic patients with proteinuria > 5 gm/24 hours, renal function as reflected by serum creatinine concentration or creatinine clearance is within normal range[20]. In this series it is also found that patient whose protein excretion was ≥ 5gm/24 hours urea, creatinine and uric acid levels were either normal slightly increased. Chua and Redman[22] have demonstrated that severe proteinuria in PIH even with conservative management for a median duration of 2 weeks showed no evidence of residual renal function. So, it can be concluded from above findings that proteinuria should not be an indicator for expeditious delivery at any gestational age. The change in urinary protein excretion did not correlate with the admission-to-delivery interval, demonstrating that proteinuria does not portend the appearance of other factors that would necessitate delivery. Other fetomaternal conditions should be judiciously considered against the risk and benefit both for mother and fetus during conservative management.

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