ORIGINAL RESEARCH PAPER

Nephrology

KEY WORDS: Pre-eclampsia, Proteinuria, Outcomes, Perinatal Mortality, Urine Dipsticks

OUTCOMES OF PREGNANCY WITH PROTEINURIC AND NON-PROTEINURIC PRE-ECLAMPSIA

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ABSTRACT

Background: Recent American College of Obstetrics and Gynecology (ACOG) guidelines suggests that pre-eclampsia can be diagnosed even in the absence of proteinuria. The objective of this study was to compare the outcomes of pregnancy in women with pre-eclampsia according to the presence or absence of proteinuria.

Design: This prospective study included all pregnant women enrolled for antenatal care in Mahila chikitshalay, a tertiary care academic hospital in Jaipur, who developed pre-eclampsia during the study period from June 2016 to May 2017. Pre-eclampsia was diagnosed according to ACOG diagnostic criteria for pre-eclampsia. Patients were divided into two groups namely proteinuric and non-proteinuric depending upon presence or absence of proteinuria on urine dipstick test. Patients were followed prospectively to determine the outcome of pregnancy. Epidemiological, clinical and laboratory data were collected in a standard proforma.

Results: Out of 3926 patients enrolled for antenatal care, 181 (4.6%) developed eclampsia. Forty-nine (27.1%) patients had non-proteinuric pre-eclampsia. Women with proteinuric pre-eclampsia had higher systolic (167.19±17.10 vs156.24±9.53, p<0.001) and diastolic blood pressure (108.18±13.3 1vs 103.27±7.43, p= .015) and were more likely to have cerebral symptoms (18.9% vs 6.1%, p=0.034) as compared to non-proteinuric patients. Proteinuric patients were more likely to deliver at earlier gestation (35.7±1.9 vs. 36.7±0.9, p=0.002). , have an infant with small for gestation age (41.7% vs. 20.41%,p=0.008) and had higher perinatal mortality (12.9% vs. 2.0%, p=0.03).

Conclusion: Proteinuric is associated with increased maternal morbidity and perinatal mortality as compared non-proteinuric pre-eclampsia.

Introduction:

Hypertensive disorders of pregnancy are common, affecting up to 10% of pregnancies worldwide [1]. Approximately 3-4% of these hypertensive disorders is attributed to pre-eclampsia [2], a pregnancy-specific syndrome and one of the leading cause of both maternal and perinatal morbidity and mortality. Pre-eclampsia was identified as second leading cause of maternal mortality accounting for 14% of total maternal death worldwide by a recent systemic analysis by World Health Organization [3].

Pre-eclampsia is characterized by the development of hypertension after 20 weeks of gestation in a woman with previously normal blood pressure [1]. While in past proteinuria was considered as a hallmark of pre-eclampsia; the current practice guidelines of American College of Obstetrician and Gynecologist (ACOG) has eliminated the dependence of diagnosis on proteinuria [1]. According to current guidelines, a diagnosis of pre-eclampsia in the absence of proteinuria can still be made in women with new onset of hypertension developing after 20 weeks of gestation and new onset of thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema and cerebral or visual symptoms [1].

Few studies have compared the maternal and fetal outcomes of women having pre-eclampsia with proteinuria and those without proteinuria [4-5]. The objective of this study is to compare the outcomes of women diagnosed with proteinuric pre-eclampsia versus those having non-proteinuric disease.

Materials and methods:

Study Center: This prospective study was carried out in the department of obstetrics and gynecology, Mahila Chikitsalay, Sawai Man Singh Medical College, Jaipur. The hospital is a tertiary care teaching institute providing obstetric care to the pregnant women. The hospital has a level-III Neonatal Intensive Care Unit.

***Study period*:** June 2016 to May 2017.

Study subject: All booked and supervised (at least one visit prior to 20 weeks of gestation) pregnancy who were diagnosed as pre-eclampsia were included in the study. Pre-eclampsia was diagnosed according to criteria given in Table 1 for the purpose of this study. These diagnostic are adapted from the diagnostic criteria of pre-eclampsia given by American College of Obstetrics and Gynecology (ACOG) guidelines [1].

Women with unbooked pregnancy, multiple gestation, urinary tract infections, diabetes mellitus, systemic lupus erythematosus, known renal disorder, those who had no antenatal visit before 20 weeks of gestation and those with hypertension or proteinuria detected before 20 weeks of gestation were excluded from the study.

Methods: Clinical, demographic data and laboratory data were collected and recorded in a standard proforma. Two clean catch urine samples were collected at admission and six hours apart and tested with urine dipstick (Multistix 10 SG, Siemens Ltd.). Proteinuria was diagnosed when a reading of one-plus or more was found on two more occasions. Based on urine dipstick findings patients were divided into proteinuric and non-proteinuric group.

Pregnancies were followed to determine the maternal and fetal outcomes. Severe hypertension was defined as systolic blood pressure of 160 mm Hg or higher, or diastolic blood pressure of 110 mmHg or higher on two occasions at least 4 hours apart.

Preterm delivery was defined as delivery prior to 37 weeks of gestation. Small for gestational age was defined as birth weight less than the 10th percentile.

Statistical analysis: Results were expressed as mean and standard deviation (SD) for continuous variables and values and percentage for categorical variables. Statistical comparison was performed with Student's t test for continuous variable and the Chi-square test for categorical variable. P< 0.05 was considered statistically significant. Statistical analysis was performed using the SPSS software (version 20).

Ethical clearance: Institute ethical committee

Results:

During the study period, 3926 patients were enrolled for antenatal care. One hundred and eighty-one (4.6%) patients developed pre-eclampsia. The mean age of the study population was 25.2+4.2 years. One hundred thirty-four (74%) women were primigravida. The mean completed gestational age at delivery was 36+ 1.7 weeks. (Table 2)

Forty-nine (27.1%) had non-proteinuric pre-eclampsia. The most common feature defining pre-eclampsia among those who had non-proteinuric pre-eclampsia was impaired liver function (n=25, 51.02%) followed by thrombocytopenia (n=19, 38.78%) and renal insufficiency (n=12, 24.49%). (Table 3)

The mean systolic and diastolic blood pressure before 20th week of gestation were similar between those who had proteinuric disease and those who had non-proteinuric disease. Proteinuric patients had higher systolic blood pressure (167.19±17.10 vs156.24±9.53, p<0.001) and diastolic blood pressure (108.18±13.3 1vs 103.27±7.43, p= .015) as compared to non-proteinuric patients. More patients in proteinuric group (n=93, 70.42%), were on antihypertensive drugs as compared to non-proteinuric group n=19, 38.78%, p=0.001). Severe hypertension was seen in 83 (62.88%) patients in the proteinuric group as compared to 15 (30.61%) in the non-proteinuric group (p=0.000). Cerebral symptoms were seen in 25 (18.9%) proteinuric patients as compared to 3 (6.1%) patients in non-proteinuric patients (p=0.034). (Table 2)

Fifty-five (41.67%) neonates born to proteinuric patients were small for gestational age as compared to 10 (20.41%) neonates born to non-proteinuric patients (p=0.008). The perinatal mortality was 12.88% (n=17) among neonates born to proteinuric patients as compared to 2.04% (n=1) neonates born to non-proteinuric patients (p=0.030). (Table 2)

Discussion:

Pre-eclampsia is a pregnancy-specific disease that can affect many organ systems, including the fetus. Historically, proteinuria was a requirement for a diagnosis of pre-eclampsia, but current guidelines and consensus statement by various societies have done away with proteinuria as a 'sine qua non' for the clinical diagnosis of pre-eclampsia [1,6-7]. Pre-eclampsia can be diagnosed in a patient with new onset of hypertension with one/more systemic feature of pre-eclampsia [1,6-7]. This is in recognition of the syndromic nature of pre-eclampsia and to the fact that life-threatening complications, such as acute pulmonary edema, acute renal failure and eclampsia can occur in women with and without proteinuria [4].

Homer et al have used the term 'non-proteinuric pre-eclampsia' to the hypertensive pregnant women with organ dysfunction, e.g. liver dysfunction, renal insufficiency, thrombocytopenia etc who do not have proteinuria [5]. The most common pre-eclampsia defining feature in non-proteinuric patients in our study were impaired liver function and thrombocytopenia, which is similar to those reported by Homer et al and Thornton et al.

While it is well known that outcome of proteinuric pre-eclampsia is worse than gestational hypertension, the outcomes of non-proteinuric pre-eclampsia have scarcely been studied [4,5,8,9]. In this study we have demonstrated that the patients with proteinuric pre-eclampsia have higher morbidity such as higher systolic and diastolic blood pressure, increased frequency of use of anti-hypertensive medications and a higher incidence of cerebral symptoms. We could not evaluate the effect on maternal mortality due to small sample size and because the maternal mortality in our study cohort was just 0.5%. Our finding is similar to the findings of Thornton et al, who have reported higher systolic and diastolic blood pressure, higher incidence of use of anti-hypertensive drugs and magnesium sulfate in proteinuric patient in a cohort of 670 preeclamptic patients [4].

In our study, the proteinuric patients were more likely to deliver at earlier gestation, have an infant with small for gestation age and had higher perinatal mortality. Our findings are similar to those reported by Homer et al [5]. These findings are in contrast to Thornton et al who have in fact reported a better perinatal outcome in patients with proteinuric pre-eclampsia. This finding could well be due to institutional difference and differences in the level of neonatal care.

One of the major strength of our study was its prospective nature and stringent definition of pre-eclampsia as using diagnostic criteria given by ACOG. We have included only those patients who were normotensive at 20 weeks of gestation, thereby excluding patients with preexisting hypertension as well as excluding those patients who had proteinuria before 20 weeks of gestation. One of the major limitation of our study was the use of urine dipstick to define proteinuria, which according to ACOG should be used only if other quantitative methods such as 24-hour protein excretion or spot protein/ creatinine ratio. However urine dipsticks are easily available and dipsticks were used twice, before labeling patient as protienuric. Another major limitation was small sample size, which makes the comparison of rare outcomes like maternal mortality, other maternal morbidity like the development of pulmonary edema, renal dysfunction etc. difficult. Study with larger sample size would be required to compare such outcomes. Another major limitation of our study was that the fetal manifestation of pre-eclampsia such as intrauterine growth retardation was not considered as a diagnostic criterion for pre-eclampsia since we used ACOG criteria [1]. Other guidelines like that of 'Society of Obstetric Medicine of Australia and New Zealand' and 'Society of Obstetricians and Gynaecologists of Canada' include fetal growth restriction as of the diagnostic criteria for pre-eclampsia [10-11].

Despite these obvious limitations, this study shows that proteinuric pre-eclampsia is associated with higher maternal morbidity and adverse perinatal outcome.

Acknowledgment: None
Disclosure: None

Table 1 Diagnostic Criteria for Pre-eclampsia[1]

Blood pressure	≥140 mm Hg systolic or 90 mm Hg diastolic on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure.
And	
Proteinuria	Dipstick reading of 1+ or more
Or in the absence of proteinuria, a new-onset hypertension with the new onset of any of the following	
Thrombocytopenia	Platelet count < 100000/microliter
Renal insufficiency	Serum creatinine concentration > 1.1 mg/dl
Impaired liver function	Elevated blood concentrations of liver transaminases to twice normal concentration
Pulmonary edema	
Cerebral or visual symptoms	

Table 2: Characteristics and outcomes of proteinuric and non-proteinuric pre-eclampsia =

	Total N=181	Proteinuric N=132	Non-proteinuric N=49	P value
Age (years)	25.2±4.2	25.16±4.31	25.45±4.21	0.686
Gestational age (weeks)	36±1.7	35.7±1.9	36.7±0.9	0.002
Primigravida	134 (74.03%)	94 (71.21%)	40 (81.63%)	0.15
SBP before 20 weeks of gestation (mm Hg)	111.91±9.81	112.38±9.71	110.65±10.05	.296
DBP before 20 weeks of gestation (mm Hg)	70.27±8.20	70.98±8.37	68.37±7.47	.057
SBP at admission	164.21±16.14	167.19±17.10	156.24±9.53	.001
DBP at admission	106.85±12.18	108.18±13.31	103.27±7.43	.015
Severe hypertension	98	83	15	0.000
Antihypertensive drugs at admission	112 (61.88%)	93 (70.42%)	19 (38.78%)	0.001
Cerebral symptoms	28 (15.47%)	25 (18.94%)	3 (6.12%)	0.034
Pulmonary edema	3 (1.66%)	2 (1.51%)	1 (2.04%)	0.81
Serum Uric acid (mg/dl)	6.17±1.79	6.17±1.79	6.18±1.78	.985
Serum calcium (mg/dl)	7.45±4.09	7.53±4.84	7.24±0.62	.701
Serum protein (g/dl)	6.58±0.68	6.48±0.66	6.82±0.68	.002
Serum albumin (g/dl)	3.23±o.57	3.17±0.58	3.39±0.52	.018
Serum bilirubin (mg/dl)	0.68±0.29	0.67±0.29	0.68±0.29	0.39
Thrombocytopenia	48 (26.5%)	29 (21.9%)	19 (38.8%)	0.04
SGPT	55.18±57.62	60.60±64.16	40.34±29.80	0.04
Liver impairment	47	22	25	0.000
Serum creatinine (mg/dl)	0.85±0.39	0.87±0.41	0.81±0.36	.427
Renal impairment	33	21	12	0.21
Maternal mortality	1 (0.55%)	1 (0.76%)	0 (0.0%)	0.10
Small for gestational age	65 (35.91%)	55 (41.67%)	10 (20.41%)	0.008
Perinatal mortality	18 (9.94%)	17 (12.88%)	1 (2.04%)	0.030

SBP: Systolic blood pressure, DBP: diastolic blood pressure

Table 3: Diagnostic features defining pre-eclampsia in non-proteinuric patients

Impaired liver function (serum SGPT twice normal concentration)	25 (51.02%)
Thrombocytopenia (platelet count less than 100000/micro liter)	19 (38.78%)
Renal insufficiency (serum creatinine greater than 1.1 mg/dl)	12 (24.49%)
Cerebral symptoms	3 (6.12%)
Pulmonary edema	1 (2.04%)

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