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PROSPECTIVE STUDY TO ANALYZE CALCIUM CREATININE RATIO IN A SPOT SAMPLE OF URINE FOR EARLY PREDICTION OF HYPERTENSIVE DISORDER IN PREGNANCY

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Abstract
Hypertension in pregnancy is a big threat to the mother as well as the fetus. Predi[33]ction of preeclampsia with reasonable accuracy is one of the essential prerequisites for its prevention. Various biological markers are available for the prediction of preeclampsia but none of those is reasonably reliable, valid and economical. In this present study, the predictive value of the urinary calcium-creatinine ratio (CCR) for the prediction of preeclampsia was studied. This study was conducted at department of Obstetrics and Gynaecology, Sir T Hospital, Government Medical College, Bhavnagar. 500 Primigravida patients attending the antenatal outpatient department at Sir T Hospital between 18 to 24 weeks of gestation were registered in this study. Single voided urine sample was collected from all the patients in calcium free vial for estimation of urine calcium and creatinine. After initial workup, all patients were followed in the antenatal clinic till the time of delivery and 15 days post partum. The number of patients who develop the hypertensive disorder in pregnancy was noted and the correlation studied. Out of 500 patients, 120 patients (24%) developed preeclampsia,4 patients(0.8%)developed eclampsia,10 patients (2%) developed gestational hypertension. Out of 500 patients, 84 patients (16.8%) showed UCCR<0.04.The remaining 416 patients (83.2%) showed UCCR>0.04. Out of 84 patients with UCCR<0.04, 2 patients (2.38%) developed Gestational Hypertension: A single estimation of calcium to creatinine ratio in asymptomatic pregnant women between 18-24 week of gestation is a simple and cost-effective test. A value of less than or equal to 0.04, in a spot urine sample, has a good predictive value for preeclampsia
Keywords: Calcium creatinine ratio, Gestational hypertension, Preeclampsia, Preeclampsia prediction

Introduction

Hypertension can occur in normotensive pregnant women or can aggravate already existing hypertension. Hypertensive disorders represent the most common medical complications of pregnancy. It has been recognized as a pathological entity since the time of Hippocrates and ancient Greeks. Hypertensive disorders occur in 5–10 % of all pregnancies [1]. They contribute to significant maternal and perinatal morbidity and mortality of which 3.9% is preeclampsia. It is the leading cause of both direct maternal and perinatal mortality. 16% of maternal mortality rate is due to hypertensive disorders in pregnancy[2]. It is said that, pre-eclampsia and eclampsia contributes to death of a woman every 3 minutes worldwide. Infants of women with severe Pregnancy induced hypertension have 5 fold increase in mortality when compared to infants of normotensive women. Primary prevention of pre eclampsia is not possible, as the exact cause remains unclear. Secondary prevention, by identifying the pregnant women who are destined to develop gestational hypertension, in order to avoid dangerous complications is the aim of various researchers and this lead to the interest in screening. Screening is the deliberate examination of substantial segments of the population in search for a disease at its earlier stage, and is a logical extension of the role of preventive medicine. For a screening test to be of value, it should be selective, reliably cheap and easy to perform. It should increase the predictive value and the prophylactic measures must be effective. Preeclampsia is a complex disease process. Several pathological changes have already occured before the development of clinical syndrome of preeclapmsia. One such change occurs in renal function leading to hypocalciuria and microalbuminuria. Several studies have been conducted and various parameters have been evaluated and tested as predictors of pre eclampsia. Calcium-to-creatinine ratio has been suggested by many to be a good screening test for preeclampsia [3].Thus in study, urine calcium creatinine ratio (UCCR) is tested as parameters to predict the development of preeclampsia in asymptomatic normotensive primigravida women. Combining the biochemical markers calcium, creatinine, and microalbuminuria, we can predict the risk of disorder and start preventive therapy at early stages to prevent maternal and feto-neonatal morbidity and mortality.[4,5]An early diagnosis and treatment helps to

reduce it to a minimum, and therefore it is important to identify women at risk at the earliest.

Material and Methods:

This study was conducted at department of Obstetrics and Gynaecology, Sir T Hospital,Government Medical college, Bhavnagar.

•Study Type: Prospective Randomized Observational Study.

•Time of Follow up: 2 weekly up to delivery and 15 days post partum.

•Study design: Prospective.

•Sample size: 500 primigravida patients between 18-24 week of gestation.

•Method: 500 primigravida patients between 18-24 week of gestation attending OPD.

Study Design: Prospective Study

500 Pregnant women attending the antenatal outpatient department at Sir T Hospital between 18 to 24 weeks of gestation were registered in this study.

Inclusion Criteria

Normotensive primigravida with gestational age between 18-24 weeks.

Exclusion Criteria

- Multigravida.
-Previously known and at present diabetic.
- Chronic hypertensive.
- Suffering from major illness like liver and cardiac disease.
- Previous preeclampsia diagnosed women.

From each pregnant women included in the study, a written informed consent was obtained

1. Detailed history was taken.
2. Examination:

I. General examination
II. Systemic examination
a. Cardiovascular system
b. Respiratory system
c. Central nervous system
d. Obstetric examination was done.

3. Blood Pressure

i. In sitting posture is measured
ii. Phase Korotkoff V sound was taken to determine the diastolic component

4. Investigations:

I. Blood-
(1) haemoglobin
(2) Blood group
(3) Complete blood count
(4) Liver function tests
(5) Renal function tests
(6) Others like HIV,HBsAg,VDRL
(7) Blood sugar/RBS

II. URINE-
(a) Urine sugar
(b) Urine albumin
(c) Urinary calcium creatinine ratio

5. Single voided urine sample was collected from all the patients in calcium free vial for estimation of urine calcium and creatinine. Urine sample was sent to the Biochemistry Laboratory.
6. Urinary calcium estimation wad done using commercially available kit by Ortho-cresolphthalein Complexone Method (OCPC) on a semi auto analyser.
7. Urinary creatinine estimation was done by Modified Jaffe's Method on a semi auto analyser.
8. UrinaryCalcium; Creatinine ratio was obtained. If its value is </=0.04, considered as High risk for development of preeclampsia.
9. Patients were followed up with routine antenatal visits for signs and symptoms of pre-eclampsia, routine examination of blood pressure, serial weight, edema, fetal growth, urine albumin by dip stick method and blood investigations for pre eclampsia when and where required, till delivery.
10. Mode of delivery and fetal outcome was noted.

Ortho-cresolphthaleincomplexone method for estimation of calcium in urine.

Calcium in alkaline medium combines with the O-cresolphthaleincomplexone to form a purple coloured complex. Intensity of colour formed is directly proportional to the calcium concentration in the sample. Ortho-cresolphthaleincomplexone reacts with calcium at pH 10. .0 to form a purple coloured complex. Calcium + OCPC purple colour complex. 500micro lit of reagent mixed with 10micro lit of sample incubated for 5 minutes at room temperature (25-30 deg C). Absorbance of standard and sample is read against reagent blank at 578 nm with yellow filter within 30 minutes.

TEST RESULTS

$$\text{Calcium concentration in mg/dl} = \frac{\text{Absorbance of test}}{\text{Absorbance of Standard}} \times 10$$

Creatinine estimation by modified jaffe's method

Creatinine is the carbolic product of creatinine phosphate and it is excreted entirely by the kidneys. Creatinine reacts with picric acid, in alkaline medium to give orange coloured complex – creatinine Picrate (Jaffe's reaction). Intensity of colour formed during the fixed time is directly proportional to the amount of creatinine present in the sample.

Creatinine + Alkaline picrate Orange coloured complex

Procedure:

500micro lit of reagent and 50micro lit of urine sample added after diluted in distilled water in one in 10 dilution,

mixed well and the colour is estimated at 520nm using green filter. The urinary creatinineresults was multiplied by 10.

Results:

Table 1: Various types of hypertensive disorder of pregnancy

Types of hypertensive disorders of pregnancy	No of patients	Percentage
Preeclampsia	120	24%
Eclampsia	4	0.8%
Gestational hypertension	10	2%
Chronic hypertension	Nil	-
Superimposed Preeclampsia on chronic hypertension	Nil	-

Above table shows various types of hypertensive disorder of pregnancy in our study. Out of 500 patients, 120 patients (24%) developed preeclampsia, 4 patients (0.8%) developed eclampsia, 10 patients (2%) developed gestational hypertension.

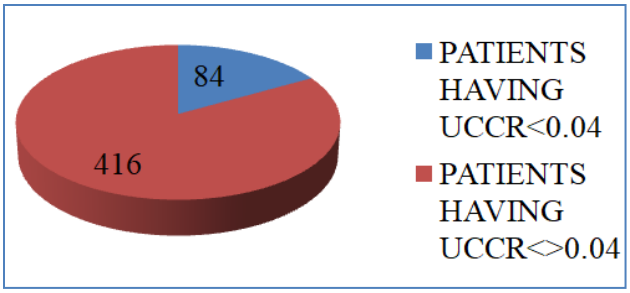

Figure 1: Percentage of patients according to UCCR ratio

Table 2: Relation between uccr and preeclampsia in the present study

UCCR	Positive for preeclampsia	Negative for preeclampsia
Patients having UCCR<0.04 (n= 84)	74 (88.09%)	10 (11.91%)

Out of 84 patients with UCCR<0.04, 74 patients(88.09%) developed preeclampsia, 10 patients(11.91%) didn't develop preeclampsia.

Out of 84 patients with UCCR<0.04, 2 patients (2.38%) developed gestational hypertension.

Out of 84 patients with UCCR<0.04 ,4 patients (4.76%) developed eclampsia.

Table 3: Distribution of patients according to severity of pre-eclampsia in the present study

Severity of PE (n=120)	No of patients	Percentage
Mild (SBP:140-149, DBP:90-99 mmhg)	111	92.5%
Severe (SBP:>=160, DBP>=110 mmhg)	9	7.5%

Above table shows distribution of patients according to severity of preeclampsia. Out of 120 preeclampsia patients 111 patients (92.5%) had mild preeclampsia and 9 patients (7.5%) had severe preeclampsia.

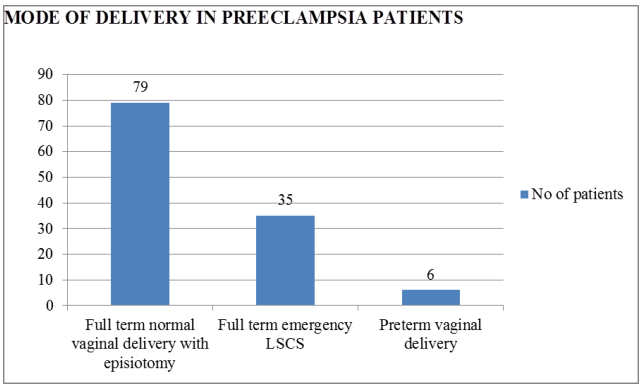

Figure 2:

Regarding the mode of delivery in preeclampsia patients, out of 120 preeclampsia patients, 79 patients (65.83%) had full tern normal vaginal delivery with episiotomy, 35 patients (29.16%) had full term emergency LSCS, 6 patients (5%) had preterm vaginal delivery.

Fetal and neonatal outcome in preeclampsia patients 9 patients (7.5%) developed IUGR, 1 patient (0.8%) delivered stillbirth, 1 patient (0.8%) had IUFD.

Out of 120 neonates, 15 neonates (12.5%) were admitted to NICU, 105 neonates (87.5%) were healthy and kept under observation

Out of 15 neonates (12.5%) admitted to NICU, 3 neonates (2.5%) had low birth weight, 12 neonates(10%) had meconium aspiration syndrome.

Table 4: Maternal complication in preeclampsia patients in present study

Maternal complications (n=120)	No of patients	Percentage
Eclampsia	4	3.33%
Abrupsio placenta	2	1.66%
Placenta praevi	2	1.66%
HELLP syndrome	3	2.5%

Regarding the maternal complications out of 120 preeclampsia patients, 4 patients (3.33%) developed eclampsia, 2 patients (1.66%) developed abruption placenta, 2 patients (1.66%) developed placenta previa , 3 patients (2.5%) developed HELLP syndrome.

Discussion:

This study was conducted at Sir t hospital, Government Medical college, Bhavnagar, in which a total of 500 patients were included. The objective of the study is to analyze the value of UCCR as a predictor of preeclampsia.

Out of 500 patients, 120 patients (24%) developed preeclampsia,4 patients(0.8%)developed eclampsia,10 patients (2%) developed gestational hypertension. Out of 500 patients, 84 patients (16.8%) showed UCCR<0.04.The remaining 416 patients (83.2%) showed UCCR>0.04. Out of 84 patients with UCCR<0.04, 2 patients (2.38%) developed Gestational Hypertension. Out of 84 patients with UCCR<0.04, 4 patients (4.76%) developed eclampsia. Out of 120 preeclampsia patients, 111 patients (92.5%) had mild preeclampsia and 9 patients (7.5%) had severe preeclampsia. Out of 120 preeclampsia patients,92 patients(72.6%) had hypertension after 2 weeks of delivery. The remaining 28 patients (23.33%) were normotensive after 2 weeks of delivery. Hypertensive disorders and their associated morbidity have been haunting obstetricians from time immemorial. Any method to detect the disease early is welcome. Though many screening methods were tried, we are still unable to find an ideal screening test. Calcium-to-creatinine ratio in a spot urine sample seems to be promising. Urinary calcium excretion tends to increase in all pregnant patients, probably because of the increase in effective glomerular filtration rate. Calciuria has been studied to detect hypertension early during pregnancy. Many studies have shown that there is a significantly lower mean urinary calcium level in patients with preeclampsia than in groups with chronic hypertension or normotensive patients [6]. This phenomenon occurs early enough and persists throughout gestation, so it may be useful for early identification of patients at risk of hypertensive disorders of pregnancy. The effectiveness of spot urine calcium-to-creatinine ratio (CCR) in predicting preeclampsia was studied by many groups. Calcium and creatinine estimation in a random urine sample has been found to correlate with a 24-h urinary calcium level. Most of the studies have used 0.04 as the upper limit for calcium-to-creatinine ratio in the prediction of pregnancy hypertension [7]. Rodriguez et al. [8] who investigated the predictive value of decreasing CCR in spot urine sample as early as 1988 reported that it might be an effective marker for preeclampsia. Saudan et al.[9]3 had reported the sensitivity of 85% and specifi city of 91% and Izumi et al. [10] found that it had limited value in prediction of pre-eclampsia. Kazerooni and Hamje-Nezadi [11] evaluating between 20 and 24 weeks of gestation and Kar et al. [12] evaluating the predictive value of CCR at ≤0.04 between 20 and 34 weeks of gestation (similar to our study), have reported that it was satisfactory test for prediction of pre-eclampsia and could be effective method for screening asymptomatic women for pre-eclampsia. Estimation of calcium and creatinine in a spot urine sample is simple test, noninvasive, and is easy to perform and hence assures good patient compliance. It has a good predictive value and hence justifi es the cost and is suited to be adopted as screening test for pre-eclampsia. It can, therefore, recommend as a screening test for pre-eclampsia and could be offered to all asymptomatic pregnant women between 20 and 34 weeks of gestation during their routine antenatal visits. Microalbuminuria, on the other hand, was found to be only fair test in predicting pre-eclampsia. Salako et al. [13] reported that single estimation of microalbuminuria at the time of antenatal booking had a sensitivity of 42% and specifi city of 86%. Pre-eclampsia is a major cause for concern worldwide and there is a constant search for finding the means for predicting pre-eclampsia. An availability of good screening test would initiate more research in this direction and will be useful to decrease maternal mortality and morbidity.

Conclusion:

This study was done among 500 primigravida patients and the study analysis had showed that UCCR is the excellent test for prediction of preclampsia. Primigravida along with low UCCR are the one who are at higher risk of developing preeclampsia. UCCR test is ideal because It is simple and easy to perform, Inexpensive, less time consuming, Non invasive and comfortable for the patient Thus UCCR can be used as routine screening tests in early second trimester for predicting preeclampsia at a much earlier stage like 18weeks to 24 weeks in order to reduce the numerous adverse outcomes and to improve the standards of antenatal, intranatal and postnatal care. Its use can be better accomplished in developing countries where incidence of pre eclampsia is high.

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