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ORIGINAL ARTICLE

Urine Calcium–Creatinine Ratio in Prediction of Pre-eclampsia

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Abstract

Background Hypertensive disorders of pregnancy are first identified during pregnancy (gestational hypertension, pre-eclampsia, eclampsia, and HELLP syndrome) or may present as a complication of previously existing disease (chronic hypertension, renal disease, and systemic disease). These hypertensive disorders complicate the pregnancy, leading to significant maternal and perinatal morbidity and mortality, especially in low- and middle-income countries (Chappell in Lancet 398(10297):341–354, 2021). These hypertensive disorders are about 5–10% of all pregnancies.

Methods This is a single institutional study, which was conducted among 100 normotensive asymptomatic antenatal women at, 20–28 weeks of gestation attending our OPD. Voluntary participants were selected based on inclusion and exclusion criteria. Spot urine sample was taken for estimation of UCCR by an enzymatic colorimetric method. These patients were followed up throughout the pregnancy and monitored for the development of pre-eclampsia. UCCR is compared in both groups. Pre-eclampsia women were further followed up to observe the perinatal outcomes.

Results Among 100 antenatal women, 25 of them developed pre-eclampsia. UCCR of <0.04 was considered as cutoff and compared between pre-eclampsia and normotensive women. This ratio yielded a sensitivity of 61.54%, specificity 87.84%, positive predictive value 64%, and negative predictive value of 86.67%. It was also observed that primigravida had more sensitivity (83.3%) and specificity (91.7%) in predicting pre-eclampsia compared to multigravida. The mean and median UCCR among pre-eclamptic women was significantly low (0.062 ± 0.076, 0.03) compared to normotensive women (0.15 ± 0.115, 0.12) with a p value of <0.001.

Conclusions Spot UCCR is a good predictor of pre-eclampsia in primigravida women and can be considered as a routine screening test at 20–28 weeks of gestation during regular antenatal visits.

Keywords Pre-eclampsia · UCCR · Hypertension in pregnancy

Introduction

Hypertensive disorders of pregnancy are first identified during pregnancy (gestational hypertension, pre-eclampsia, eclampsia, and HELLP syndrome) or may present as a complication of previously existing disease (chronic hypertension, renal disease, and systemic disease). These hypertensive disorders complicate the pregnancy, leading to significant maternal and perinatal morbidity and mortality, especially in low- and middle-income countries [1]. These hypertensive disorders are about 5–10% of all pregnancies.

Pre-eclampsia is a multisystemic progressive disorder, which is characterized by the new onset of hypertension and proteinuria, or hypertension and significant end-organ dysfunction with or without proteinuria, after 20 weeks of gestation [2]. Incidence of pre-eclampsia is 2–8% worldwide, of all pregnancies [2]. It accounts for 5–8% of maternal

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morbidity and mortality [3]. It usually affects the first pregnancies. It is known to be a composite disease process with multifactorial pathophysiology. It occurs due to the failure of placental trophoblastic invasion into the myometrium and loss of remodeling. It results in placental (hypoperfusion, hypoxia, and ischemia) and maternal vascular dysfunction (release of antiangiogenic factors into the maternal circulation causing hypertension) leading to adverse manifestation in cardiovascular, central nervous system, and hepatic and renal systems. Several changes occur before the development of clinical symptoms. These changes which are occurring in the renal system affect its function resulting in fluctuation of renal parameters.

Excretion of urinary calcium in an antenatal woman is 350–600 mg/day, which is increased when compared with normal women (100–250 mg/day). It depends on various factors like diet and hormonal and renal factors. In pre-eclampsia women, ionized calcium levels were observed to be in the lower limit of normal and due to placental hypoperfusion, absorption of 1,25 dihydroxy vitamin D3 from the intestine is decreased. This results in elevated parathyroid hormone which promotes reabsorption of calcium from kidneys in distal convoluted tubules. Hence, this results in the reduction of urinary calcium excretion and fractional calcium excretion. In addition due to placental ischemia and oxidative stress, urate levels increase, causing further hypocalciuria.

In pregnancy due to raised blood volume, creatinine clearance (amount of creatinine filtered out of the blood and passed into the urine) is increased by 50% compared to normal women. In pre-eclampsia women, due to renal damage, this creatinine clearance decreases leading to low urinary creatinine levels.

Screening is a tool for methodical investigation of large sectors of the population in a community, to identify disease in an earlier stage, and it also helps in the prevention of the development of the disease. There are several biomarkers (beta HCG, PAPP-A, Inhibin A and B, uterine artery Dopplers, PP13, etc.) available. UCCR is considered a screening test to predict pre-eclampsia as it is easy to perform, convenient, non-invasive, cheaper, readily available, and has less time consumption (Table 1).

Table 1 Mean comparison of various parameters between pre-eclampsia and normotensive women

Parameter	Pre-eclampsia	Normotensive	*p* value
Age (years)	30.12 ± 5.349	28.48 ± 4.397	0.17
Gestational age at delivery	33.64 ± 3.053	37.25 ± 1.77	< 0.001
Birth weight of baby	1.66 ± 0.804	2.84 ± 0.66	
UCCR	0.062 ± 0.076	0.15 ± 0.115	

Methods

The present study is approved by an institutional ethical and scientific committee review board.

i. Selection and description of participants

It is a single institutional study that was conducted among 100 antenatal women. The study population was selected depending on inclusion and exclusion criteria. Normotensive asymptomatic women attending our OPD between 20 and 28 weeks of gestation with negative urine albumin, including women who had a positive family history of pre-eclampsia or with a previous history of gestational hypertension or pre-eclampsia, were considered. Women who have had BP > or = 140/90 mmhg at booking visit or a history of chronic hypertension or renal diseases and other chronic illness were excluded. Spot UCCR was performed in the selected group of voluntary participants at 20–28 weeks of gestation after taking informed consent by explaining aims and objectives. Detailed past medical and surgical history was noted. General physical examination and obstetric examination were performed. These women were reviewed during regular antenatal visits. Women diagnosed with pre-eclampsia were identified and followed throughout the pregnancy. Maternal and neonatal outcomes were analyzed during the peripartum period.

Based on the sensitivity of pre-eclampsia in 20–28 weeks of gestation (81%) observed in an earlier publication with 20% allowable error and 95% confidence, the minimum sample size comes to 15 positive cases of pre-eclampsia (18.7% in the previous article) with 83 total sample size (Sinha R, Bhushan I). Here, I had included 100 women with 25 pre-eclampsia women.

ii. Technical information

Spot urine sample was collected and sent to the biochemistry laboratory within 2 h of collection for testing. It was performed by using Roche Cobas machine model number C702. UCCR was calculated by an enzymatic colorimetric method. The result was reported within half an hour time.

iii. Statistics

The information recorded on the data collection forms was uploaded in an excel sheet, and data were analyzed using IBM SPSS version 20. Categorical variables are expressed using frequency and percentage. Continuous variables are presented by mean, SD, median, 25th, and 75th percentile. To test the statistical significance of the association of categorical variables with pre-eclampsia, the chi-square test was used. To test the statistical significance of the difference in the mean and median of UCCR with pre-eclampsia, Mann–Whitney U test was used.

Results

Among 100 antenatal women included in the present study, 25 women developed pre-eclampsia. The mean age of the total study population was 28.89 ± 4.679 years, and pre-eclamptic women were 30.12 ± 5.349. BMI was calculated and found that a total of 23 pre-eclamptic women had a statistically significantly high level in which 43.8% were overweight and 40.9% obese (p value < 0.001).

The mean and median distribution of UCCR was calculated as 0.062 ± 0.076 and 0.03 (0.01–0.1) in pre-eclampsia women and 0.15 ± 0.115 and 0.12 (0.06–0.19) in normotensive women. This difference in the mean is statistically highly significant (p value < 0.001). UCCR < 0.04 was considered a cutoff. Out of 25 women with UCCR<, 0.04 16 (64%) developed pre-eclampsia and the other 9 (36%) were normotensive. This yielded a sensitivity to predict pre-eclampsia of 61.54%, specificity of 87.84%, a positive predictive value of 64%, and a negative predictive value of 86.67% (Table 2, Fig. 1). The association of UCCR was analyzed in primigravida and multigravida women separately. Out of 12 primigravida women with UCCR < 0.04, 10 developed pre-eclampsia with a sensitivity of 83.3% and specificity of 91.7% (Table 2, Fig. 2). This association was statistically significant (p value < 0.001). The mean gestational age between testing (UCCR < 0.04) and development of pre-eclampsia is 4.25 ± 0.86 weeks. Sensitivity and specificity of other predictors like gestosis score (45%, 84%), uterine artery Doppler (58.8%, 81.3%), PAPPA-A (29.6%, 76.7%) were compared to be less than UCCR when analyzed individually.

Pre-eclampsia women were followed up till the delivery, and perinatal outcomes were analyzed. A total of 22 pre-eclamptic women delivered as preterm, in which 2 (66.7%) were extreme preterm (< 28 weeks), 6 (85.7%) were very preterm (< 32 weeks), 7 were moderate (32–< 34 weeks) and late preterm each (34–< 37 weeks). The mean period of gestation of delivery in pre-eclampsia women is 33.64 ± 3.053. This association between preterm delivery and pre-eclampsia was statistically highly significant (p value < 0.001). 23 (92%) women delivered by cesarean section out of 25 pre-eclamptic mothers (p value < 0.001). During delivery, 5 women developed atonic PPH and all of them were pre-eclamptic women. Hence, this association was statistically significant.

Table 2 Association of UCCR with pre-eclampsia

Pre-eclampsia	UCCR		p value
	< 0.04 n (%)	> 0.04 n (%)	
Yes	16 (64)	9 (36)	< 0.001
No	10 (13)	65 (87)	

Parity	UCCR	Pre-eclampsia		p value
		Yes n (%)	No n (%)	
Primi	≤ 0.04 (12)	10 (83.3)	2 (16.7)	< 0.001
	> 0.04 (36)	3 (8.3)	33 (91.7)	
Multi	≤ 0.04 (14)	6 (42.9)	8 (57.1)	0.092
	> 0.04 (38)	6 (15.8)	32 (84.2)	

Pre-eclampsia	Gestosis score	
	= or > 3 n (%)	< 3 n (%)
Gestosis score with pre-eclampsia, Uterine artery Doppler with UCCR, PAPPA-A with pre-eclampsia		
Yes	14 (56)	11 (44)
No	17 (22)	58 (88)

Pre-eclampsia	Uterine artery Doppler	
	High resistance n (%)	Normal n (%)
Gestosis score with pre-eclampsia, Uterine artery Doppler with UCCR, PAPPA-A with pre-eclampsia		
Yes	10 (40)	15 (60)
No	7 (9)	68 (91)

Pre-eclampsia	PAPPA-A	
	= or < 0.4 MOM n (%)	> 0.4 MOM n (%)
Gestosis score with pre-eclampsia, Uterine artery Doppler with UCCR, PAPPA-A with pre-eclampsia		
Yes	8 (32)	17 (68)
No	19 (25)	56 (75)

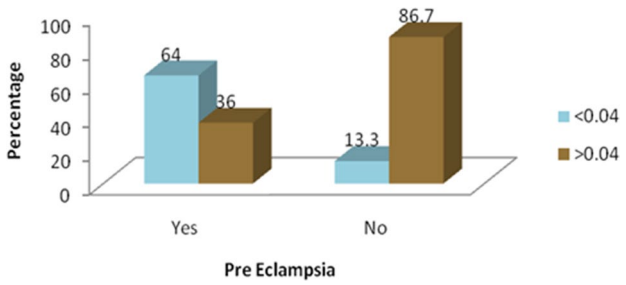

Fig. 1 Association between pre-eclampsia and UCCR

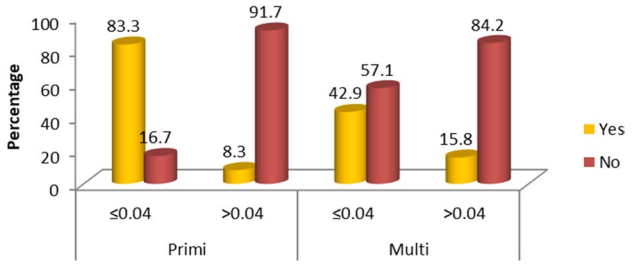

Fig. 2 Association between pre-eclampsia and parity

Neonatal outcomes were analyzed among 30 babies, born to 25 pre-eclamptic women (5 of them being twins). 25 (83%) babies were born with low birthweight, in which 9 (36%)of them weighed between 1–1.5 kg and 1.5–2.5 kg each, and 2 (8%) weighed less than 1 kg (extremely low birth weight). The mean and median birthweight {1.66 ± 0.804, 1.53 (1.16–2.16)} was significantly low compared to newborns of normotensive mothers {2.84 ± 0.66, 2.9 (2.5–3.28)}. About 26 (80%) newborns required a NICU stay. 17 (56.6%) developed respiratory distress syndrome (RDS). 10 (33%) developed sepsis. 16 (53.3%) developed neonatal hyperbilirubinemia. And 13 of them were small for gestational age (SGA). And 2 (6.7%) of them had retinopathy of prematurity. One (3.3%) of them expired (neonatal outcomes mentioned in Table 3).

Discussion

UCCR as a predictor of pre-eclampsia is studied since the 1980s. Several such studies conducted by David A et al., Rodriguez HM et al., Ye Y et al., Ozcan et al. and Suzuki Y et al. reported having a statistically significant decrease in UCCR of pre-eclampsia women compared to normotensive women.

UCCR was tested among 100 women. 25 women developed pre-eclampsia with an incidence of 25%, of which 20 of them belong to the age group 20–35 years (86%). Primigravida who developed pre-eclampsia were 13 which accounts for about 52% with an incidence of 27%. UCCR value of 0.04 is taken as cutoff and 26 of the total study population were below the cutoff, out of which 16 were pre-eclampsia women (64%) and the other 10 (36%) were normotensives.

In the current study, the spot UCCR in the gestational age of 20–28 weeks (even before the onset of clinical symptoms and signs) is low in 16 patients with a sensitivity of (61.54%), specificity (87.84%), PPV (64%), and NPV (86.67%) and showed a statistically significant p value < 0.001. Comparison of sensitivity and specificity with the previous studies is mentioned in Table 4.

A recent study conducted in Kosovo, in which 24 h of UCCR was tested among 200 women at 24–34 weeks of gestation, showed a higher sensitivity rate of 87.9% [4]. Deepti et al. studied UCCR among 256 women, out of which 21 developed pre-eclampsia that showed a sensitivity of 73.8% and specificity of 95.18% [5]. Another case–control study stated low UCCR in pre-eclampsia women with a sensitivity of 100% and specificity of 84% [6]. Rodriquez et al. conducted a similar study which stated low UCCR in pre-eclampsia women with a sensitivity of 70% and specificity of 90% [7]. Another prospective study of UCCR among 174 women at 20–28 weeks of gestation revealed a sensitivity rate of 71.4% and specificity of 98.75% among pre-eclampsia women [8]. Rupa et al. conducted a study among 150 women, and UCCR was tested at 20–28 weeks of gestation and showed a prediction for pre-eclampsia with a sensitivity rate of 83% and specificity rate of 96%. M Vahdat et al. conducted a study among 150 antenatal women, spot urine is collected for CCR between 20 and 24 weeks of gestation, and women were followed up till delivery. Mean UCCR was calculated and observed to be significantly low (0.07 vs. 0.16, $p < 0.001$) with a cutoff of 0.07, a sensitivity of 77%, and a specificity of 78%.

In our study, mean UCCR in the women with pre-eclampsia was observed to be low (0.062), when compared to women without pre-eclampsia (0.15), with a statistically significant p value < 0.001. Anita et al. conducted a study on mean UCCR among 50 pre-eclampsia and 50 normotensive women, which concluded that mean UCCR is comparatively low in pre-eclampsia women than in normotensive women (0.925 vs. 0.125) [7]. Chauhan calculated mean UCCR in

Table 3 Neonatal outcomes

Neonatal parameters	Yes	No
Preterm	22 (73.3)	8 (26.7)
Small for gestational age	14 (46.7)	16 (53.3)
Neonatal intensive care unit	24 (80)	6 (20)
Respiratory distress syndrome	17 (56.6)	13 (43.4)
Early onset sepsis	10 (33.3)	20 (66.7)
Neonatal hyperbilirubinemia	16 (53.3)	14 (46.7)
Asymptomatic hypoglycemia	7 (23.3)	23 (76.7)
Asymptomatic coagulopathy	6 (20)	24 (80)
Symptomatic coagulopathy	4 (13.3)	26 (86.7)
Cyanotic congenital heart disease	3 (10)	27 (90)
OB incompatible	2 (6.7)	28 (93.3)
Transient feed intolerance	2 (6.7)	28 (93.3)
Cardiac anomaly	2 (6.6)	29 (93.4)
Left renal duplex collecting system with mild dilatation of lower moiety	1 (3.3)	29 (96.7)
Retinopathy of prematurity	2 (6.7)	28 (93.3)
Death	1 (3.3)	29 (96.7)

Table 4 Sensitivity and specificity comparison of the previous studies

Previous study	Sensitivity (%)	Specificity (%)
Turkey, T Ozcan et al.	86	75
Anita David et al.	80	98
Gaurang et al.	100	84
Indu Bhushan et al.	81.2	96
Indu Prasad et al.	90.9	76.7
J Kar et al.	75	94.38
Sheela et al.	69.2	98.2
Nikitha et al.	92.85	95.45
Y Ye et al.	81	98.2
Hellen Rodriguez M	70	95
Kamra et al.	71.4	95.5
Lekha et al.	69	98
Ibrahmi et al.	87.9	40.7
Present study	61.54	87.84

pre-eclampsia and normotensive women and observed to have low UCCR levels among pre-eclamptic mothers (0.04 vs. 0.07).

Primigravida has 15 folds higher risk of developing pre-eclampsia compared to multiparous women. In the present study, 12 primigravida patients had UCCR</= 0.04, out of which 10 patients developed pre-eclampsia (83.3%) and about 2 (16.7%) were normotensives. This association was statistically significant with a p value < 0.001 with a sensitivity of 83.3% and a specificity of 91.7%. In a study conducted by Kuntal et al. among 500 antenatal women, spot urine was collected for CCR between 18 and 24 weeks of gestation, out of which 200 women developed pre-eclampsia and 74 women were observed to have UCCR < 0.04 with a sensitivity of 88.09% [9]. Another study conducted by Indu Prasad et al. stated that the primigravida of UCCR< or = 0.04 had a statistically significant p value of < 0–001 compared to multigravida.

Gestosis score above or equal to 3 is considered a predictor for pre-eclampsia with a sensitivity of 45.16% and specificity of 84%. Individual factors like obesity attribute to a 30% increased risk of pre-eclampsia for women with pre-pregnancy BMI > 35 kg/m^2 [10]. A study conducted by Y Shoa was a comparison of pre-pregnancy BMI between normal and pre-eclampsia women, which showed an increased risk of developing the disease in obese patients [11]. In our present study, out of 25 pre-eclampsia women 14 (43.8%) were overweight, and 9 (40.9%) were obese.

Uterine artery high resistance interpreted sensitivity of 58.8% and specificity of 81.9%. A study conducted by Martin et al. on the uterine artery as a predictor showed a sensitivity of 27%. However, uterine artery Doppler is often subjective screening with inter- and intraobserver variation which would require expertise. PAPPA-A levels analyzed during the same visit showed a sensitivity of 29.6% and specificity of 76.1%. PAPPA-A had high false positives as it is used to predict trisomy and fetal anomaly. The individual screening revealed less sensitivity compared to UCCR.

Cesarean section is increased in pre-eclampsia women due to worsening maternal and fetal parameters. The mode of delivery among pre-eclampsia women in our study was cesarean section for 23 (92%) patients due to prematurity and 2 (8%) patients delivered vaginally. A cross-sectional study done among 5166 women interpreted the odds ratio of the cesarean section in pre-eclampsia women as 1.92 times more compared to normotensive women [12].

Postpartum hemorrhage (PPH) is a risk factor for pre-eclampsia; however, the exact mechanism for progression is unknown [13]. In the present study, 5 women developed atonic PPH and all of them had pre-eclampsia. Hence, this association between PPH with pre-eclampsia was statistically significant p value < 0.001. Another study on this relationship conducted by Kristina Arion et al. concluded that 3.2% of pre-eclampsia mothers developed PPH [13]. However, the use of magnesium sulfate in pre-eclamptic women can also act as an indirect cause of the development of PPH [14].

Neonatal outcomes were observed to be critical for babies born to pre-eclamptic mothers. In the present study of 25 pre-eclampsia women, there were 30 babies. The mean birth weight of a newborn is 1.788 ± 0.766 (p value < 0.001) which is statistically significant. In a previous study conducted by Gulnara et al., low mean birth weight of newborns (1.565 g) was observed in the early onset of pre-eclampsia women [15].

Newborns requiring ICU stay in this study were 27 (90%) out of 30 babies of pre-eclampsia women. Out of them, all 27 were preterm, with moderate preterm being 44%, late preterm at 32%, and very preterm term at 8%. Due to prematurity, 53% of pre-eclamptic newborns developed neonatal hyperbilirubinemia. A decrease in gestational age of delivery increases the risk of hyperbilirubinemia in newborns leading to neonatal morbidity and NICU stay [16]. A study on bilirubin levels was conducted by Khan HA et al. among 100 neonates delivering term and preterm. It was observed that the incidence of hyperbilirubinemia among term babies was 64% and preterm babies were 84% (p value < 0.05).

A small for gestational age (SGA) fetus is one of the most common adverse neonatal outcomes of pre-eclampsia. In the present study, SGA was observed in 13 newborns out of 30, in which 5 of them developed asymmetrical SGA (38%) and 8 (62%) of symmetrical SGA. It is also been studied that SGA in normotensive mothers during their first pregnancy is a high-risk factor for the development of pre-eclampsia in further pregnancies [15]. The mortality rate of a newborn in

the present study is 3%. But according to a previous study, it can be as high as 15% in very low birth weight babies [17].

Limitations

The sample size was limited, and there was disproportion between the number of pre-eclampsia women and normotensive women.

Strength

Value error was minimized as the investigation is done in the same standardized laboratory. Assessment of UCCR was done in the definite gestational age 20–28 weeks which is confined to a specific population confined to a specific region.

Conclusions

1. Spot urine calcium–creatinine ratio is easy, affordable, simple, done in a single visit, and requires no expertise, hence making it a good predictor of pre-eclampsia, which is particularly feasible in rural areas and low resource settings.
2. UCCR has higher sensitivity compared to other first trimester markers when analyzed individually, thereby making it superior to the other markers.
3. Urine calcium–creatinine ratio in a primigravida with pre-eclampsia was observed to have a statistically significant low value compared to multigravida with pre-eclampsia.
4. Overweight and obese women were observed to have a strong association with the development of pre-eclampsia.
5. Perinatal outcomes like maternal atonic PPH, prematurity, and NICU stay of the newborn were significantly associated with pre-eclampsia leading to maternal and neonatal morbidity.

Declarations

Conflict of interest No conflict of interest declared.

Ethical Approval This study was approved by the institutional research ethics committee. The study was performed following the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

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