Correlation of Urinary Protein Creatinine Ratio Versus Urinary Tract Infection in Assessment of Severity of Pre-Eclampsia

Prof. Dr. Suzan Samir Elsharkawy
Assistant Professor of Obstetrics and Gynecology, Faculty of Medicine, University of Alexandria.
Prof. Dr. Abdelmoneim Aly Fawzy
Professor of Obstetrics and Gynecology, Faculty of Medicine, University of Alexandria.
Nora Abdelhamid Hasanin Hasanin
Ministry of health, Alexandria, Egypt
Dr. Dina Aly Kholeif
Lecturer of Medical Microbiology and Immunology, Faculty of Medicine, University of Alexandria. .

Abstract

Background: Preeclampsia is a pregnancy specific syndrome that can affect every system in the body. Preeclampsia can be categorized into severe" and "non-severe." According to the blood pressure measurement and presence of proteinuria. Urinary tract infections are the most common medical complication of pregnancy with an estimated incidence of approximately 20%. UTIs in pregnancy have been associated with increased risks of chorioamnionitis and endometritis. About the fetus, it has been shown that UTI is associated with fetal growth restriction, stillbirth, preterm labor, and delivery, increased perinatal mortality, mental retardation, and developmental delay.

Methods: This was a prospective cross-sectional study conducted on 50 patients whom were diagnosed with preeclampsia and were admitted to El Shatby university hospital. Based on Urinary tract infection, two groups were enrolled; Group A (25 cases) included preeclamptic patients without urinary tract infection and Group B (25 cases) included preeclamptic patients with urinary tract infection.

Results: Urine culture and Bacterial identification were performed in preeclamptic patients with UTI (group B=25). E. coli was responsible for 68 % of the cases, Klebsiella was found in 12 % of the cases, Pseudomonas was found in 12 % of the cases, Methicillin-resistant Staphylococcus aureus (MRSA) was found in 4 % of the cases and Methicillin-resistant coagulase-negative staphylococci (MR-CONS) was found in 4 % of the cases. Protein creatinine ratio has been correlated statistically with the total number of signs of severity in each group and the total sample. There was no significant correlation between them in group A ($r = 0.064$, $P = 0.763$) while there was positive significant correlation between them in group B ($r = 0.501$, $P = 0.011$) and the total sample ($r = 0.734$, $P < 0.001$)

Conclusion: Protein creatinine ratio positively correlates with the severity of preeclampsia. Urinary tract infection

Corresponding author:
Prof. Dr. Suzan Samir Elsharkawy
Assistant Professor of Obstetrics and Gynecology, Faculty of Medicine, University of Alexandria.
E-mail: S_AbdelRahim00@alexmed.edu.eg
Orcid number:
0000-0001-9046-3460

(UTI) during gestation is associated with increased severity of preeclampsia. Escherichia coli was found to be the most prevalent organism isolated in preeclamptic patients with UTI.

Keywords: Preeclampsia, Proteinuria, Urinary tract infections, urinary protein creatinine ratio, asymptomatic bacteriuria, pyelonephritis.

Introduction

Preeclampsia is a pregnancy specific syndrome that can affect every organ system in the body. It is diagnosed by high blood pressure above 140 mm Hg systolic or 90 mm Hg diastolic and proteinuria.[1]

Proteinuria is one of the diagnostic criteria of the preeclampsia syndrome and it reflects the endothelial leakage. Proteinuria is described by 24-hour urinary excretion exceeding 300 mg; a urine protein: creatinine ratio ≥ 0.3; or persistent 30 mg/dL (1+ dipstick) protein in random urine samples. [2] Overt proteinuria may not present in some preeclamptic pregnant women so another diagnostic criteria were added like thrombocytopenia, renal or liver dysfunction, cerebral symptoms, or pulmonary edema. [3,4]

Preeclampsia can be categorized into "severe" and "non-severe." According to the blood pressure measurement, presence of proteinuria, symptoms like headache, visual disturbances, upper abdominal pain or epigastric pain, signs like decreased urine output, seizures, elevated serum creatinine level, elevated liver transaminases, thrombocytopenia, pulmonary oedema and fetal growth restriction. [5]

It affects Young females more than older females, but the older women are at high risk for chronic hypertension with superimposed preeclampsia. It affects nulliparous women more than multiparous women. There are several other risk factors associated with preeclampsia. These include obesity, multifetal gestation, maternal age, hyperhomocysteinemia, and metabolic syndrome. [6-8] Preeclampsia is more common in the first pregnancy and the risk of having preeclampsia in next pregnancy is much lower. [9]

The exact cause is unknown abut there are many mechanisms are described to explain preeclampsia; Abnormal trophoblastic invasion of maternal spiral vessels, production of blocking antibodies to different placental antigenic sites, Maternal maladaptation to inflammatory changes of normal pregnancy, Genetic factors including inherited predisposing genes and epigenetic influences, Endothelial dysfunction and vasospasm because of imbalance of prostaglandins production and increased sensitivity to angiotensin II. [10]

Normally renal blood flow and glomerular filtration rate are increased during pregnancy but with preeclampsia renal perfusion and glomerular filtration are reduced due to increased renal afferent arteriolar resistance. [11,12]

There are also morphological changes characterized by glomerular endotheliosis blocking the filtration barrier. Diminished filtration causes serum creatinine levels to rise to values seen in nonpregnant individuals, that is, 1 mg/mL, and sometimes even higher. [13] Abnormal values usually begin to normalize 10 days or later after delivery. [14] In most preeclamptic women, urine sodium concentration is elevated. Urine osmolality, urine: plasma creatinine ratio, and fractional excretion of sodium also indicate that a prerenal mechanism is involved. Also, Plasma uric acid concentration is elevated in preeclampsia because the elevation exceeds the reduction in glomerular filtration rate, enhanced tubular reabsorption and increased placental urate production in response to increased oxidative stress. [15]

Oliguria is a sign of severity in preeclampsia, but intensive intravenous fluid therapy is not indicated as a treatment unless decreased

urine output is due to hemorrhage or fluid loss. Proteinuria is one of the diagnostic criteria of preeclampsia syndrome. Proteinuria may develop late, and some women may already be delivered or have had an eclamptic convulsion before it appears. [16] For a 24-hour quantitative specimen, the threshold value used is > 300 mg/24 hr. Determination of urinary protein: creatinine ratio may replace the 24-hour quantification. [17-19]

Urinary tract infections are the most common medical complication of pregnancy with an estimated incidence of approximately 20%. [20] Urinary tract infection ranges from asymptomatic bacteriuria to severe pyelonephritis. There are different classifications for UTI, and these can be divided into lower UTI which is infection involving the urethra and bladder, or upper UTI, mainly involving the kidneys. [21]

The most significant factor predisposing women to UTI in pregnancy is asymptomatic bacteriuria and due to the high rate and potential seriousness of pyelonephritis, it is recommended that all pregnant women be screened for ASB at the first prenatal visit. Asymptomatic bacteriuria is seen more frequently in parous women and women of low socioeconomic status. [22]

The increased susceptibility in pregnancy is due to several physiological changes that make asymptomatic bacteriuria progress to symptomatic UTI. These include changes in bladder volume, decreased bladder tone and ureteric dilatation secondary to an increased level of progesterone. This will lead to urinary stasis and chronic residual urine with subsequent UTI. Uropathogens responsible for UTI in pregnancy are like those in non-pregnant women, with E. coli responsible for over 80 percent of the cases. [23]

UTIs in pregnancy have been associated with increased risks of chorioamnionitis and endometritis. About the fetus, it has been shown that UTI is associated with fetal growth restriction, stillbirth, preterm labor, and delivery, increased perinatal mortality, mental retardation, and developmental delay. [24] Christensen et al hypothesized that UTI played a role in preeclampsia by serving to enhance maternal systemic inflammatory response. UTI can potentially lead to activation of systemic inflammatory response and endothelial injury; this in turn can lead to placental hypoxia and uteroplacental atherosis, and eventual development of preeclampsia. [25]

The aim of this study was to correlate between urinary protein creatinine ratio and urinary tract infection in assessment of severity of preeclampsia.

Methods

This was a prospective cross-sectional study conducted on 50 patients whom were diagnosed with preeclampsia and were admitted to El Shatby university hospital during the period of case recruitment, from March 2020 to January 2021. Sample size was calculated using AUC (Area under the ROC Curve) power Analysis in Medcalc program that achieve 80% power with a significance level 0.05 by the Department of Community Medicine and Biostatistics at Alexandria University. The study was approved by the ethical committee of Faculty of Medicine, Alexandria University.

Based on Urinary tract infection, two groups were enrolled; Group A (25 cases) included preeclamptic patients without urinary tract infection and Group B (25 cases) included preeclamptic patients with urinary tract infection. Inclusion criteria were: Pregnant female in the third trimester, Hypertension plus proteinuria (Proteinuria >300 mg/24 hours or Protein: creatinine ratio ≥ 0.3 or Dipstick > 1+ persistent proteinuria), and Pregnant pre-eclamptic females with signs and symptoms of urinary tract infection. Exclusion criteria were: Known chronic kidney disease patients, Known nephrotic syndrome patients or Known Lupus nephritis patients.

Informed consent was obtained from each woman involved in the study. All cases were subjected to: Complete history taking (Age, obstetrical history in terms of gravidity, parity , previous abortion, mode of delivery and gestational age in weeks), Complete general examination, Regular two-hourly blood pressure monitoring, Ultrasonographic examination for assessment of fetal wellbeing (mean gestational age, estimated fetal weight, amniotic fluid index and doppler indices using Mindray DC 30 machine), Full laboratory investigations including complete blood picture, coagulation profile, liver functions tests, kidney functions tests and proteinuria via Urinary protein: Creatinine ratio.

A clean catch midstream urine sample was collected for each case and immediately delivered to the microbiology lab of Alexandria main university hospital. A wet film was performed to detect pyuria and bacteriuria and urine culture was done. Bacterial identification using the standard microbiological techniques and antimicrobial susceptibility using disk diffusion method were done. The two groups were compared as regard to the severity symptoms and signs of PET [26]:

Abnormality	Non severe	Severe
1.Diastolic BP	< 110 mm Hg	≥ 110 mm Hg
2.Systolic BP	< 160 mm Hg	≥ 160 mm Hg
3.Proteinuria	None to positive	None to positive
4.Headache	Absent	Present
5.Visual disturbances	Absent	Present
6.Oliguria	Absent	Present
7.Convulsion (eclampsia)	Absent	Present
8.Upper abdominal pain	Absent	Present
9.Serum creatinine	Normal	Elevated
10.Thrombocytopenia (< 100,000/μL)	Absent	Present
11.Serum transaminase elevation	Minimal	Marked
12.Fetal-growth restriction	Absent	Obvious
13.Pulmonary edema	Absent	Present

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) (27, 28) Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR). Significance of the obtained results was judged at the 5% level.

Results

This study was carried out at Shatby university hospital for 10 months on 50 patients who were pregnant at third trimester with confirmed preeclampsia. The patients were categorized into 2 groups according to the presence of Urinary tract infection: **Group (A):** 25 preeclamptic patients without urinary tract infection, and **Group (B):** 25 preeclamptic patients with urinary tract infection. There were no statistically significant differences between the two groups as regard age, Obstetrical History (Gravidity, Parity, Previous Abortions, mode of delivery and patients' gestational age in weeks)

I) Blood pressure and urinary parameters

Systolic blood pressure in group (A) ranged between 150 – 180 while in group (B) ranged between 160 – 180. Diastolic blood pressure In group (A) ranged between 100 – 120 while in group (B) ranged between 100 – 130. There were statistically significant differences between groups as regards Systolic blood pressure only (P=0.019). **Table 1**

In addition to the blood pressure criteria, a protein (mg/dL)/creatinine (mg/dL) ratio of 0.3 or higher is required to diagnose preeclampsia. In group (A) it ranged between 0.34 – 5.7 while in group (B) ranged between 3.7 – 16.6. Group (B) was found to have elevated protein creatinine ratio in a statistically significant difference (P<0.001). **Table 1**

Table (1): Comparison between the two studied groups according to blood pressure and Protein creatinine ratio

Blood pressure	Group A (n=25)	Group B (n=25)	p
Systolic			
Min. – Max.	150.0 – 180.0	160.0 – 180.0	0.019*
Mean ± SD.	163.6 ± 9.95	170.0 ± 8.66	
Median (IQR)	160.0(160.0 – 170.0)	170.0(160.0 – 180.0)	
Diastolic			
Min. – Max.	100.0 – 120.0	100.0 – 130.0	0.259
Mean ± SD.	108.0 ± 6.45	110.4 ± 7.35	
Median (IQR)	110.0(100.0 – 110.0)	110.0(110.0 – 110.0)	
Protein creatinine ratio			
Min. – Max.	0.34 – 5.70	3.70 – 16.60	<0.001*
Median (IQR)	2.30(1.7 – 3.1)	7.88(6.0 – 9.4)	

Urine culture and Bacterial identification were performed in preeclamptic patients with UTI (group B=25). E. coli was responsible for 68 % of the cases, Klebsiella was found in 12 % of the cases, Pseudomonas was found in 12 % of the cases, Methicillin-resistant Staphylococcus aureus (MRSA) was found in 4 % of the cases and Methicillin-resistant coagulase-negative staphylococci (MR-CONS) was found in 4 % of the cases.

Preeclamptic patients with UTI caused by E–coli showed highest sensitivity to imipenem and meropenem (100%) followed by piperacillin tazobactam and gentamycin (88.2%) then ampicillin sulbactam (82.4%) then nitrofurantoin, ciprofloxacin and cefotaxime (76.5%), while 41.2% of cases were resistant to amoxicillin clavulanate. As for Klebsiella strains, (33.3%) were sensitive to imipenem, meropenem, ampicillin-sulbactam, cefotaxime and ceftriaxone while all strains were resistant to amoxicillin clavulanate, piperacillin tazobactam and aminoglycosides. Pseudomonas strains showed highest sensitivity to imipenem, aminoglycosides and quinolones (100%). Both strains of MRSA and MR-CONS were sensitive to linezolid and vancomycin.

II) Signs of severity of preeclampsia

Signs of severity were assessed in all patients in both groups A and B. Cases in group A showed from 2 to 8 sign of severity while in group B showed from 6 to 12 sign of severity. There were statistically significant differences between the 2 groups where P <0. 001.Also in Group A only 6 cases (24%) had more than 5 signs of severity but in Group B the 25 cases (100%) had more than 5 signs of severity. There were statistically significant differences between the 2 groups where P <0.001which indicates that signs of severity present more with preeclamptic patients with UTI. **Table 2**

Table (2): Comparison between the two studied groups according to signs of severity

	Group A (n=25)		Group B (n=25)		P
	No.	%	No.	%	
indicators of severity					
>5	6	24.0	25	100.0	<0.001*
≤5	19	76.0	0	0.0	
Total no. of indicators of severity					
Min. – Max.	2.0 – 8.0		6.0 – 12.0		<0.001*
Mean ± SD.	4.76 ± 1.59		8.64 ± 1.85		
Median (IQR)	5.0 (4.0–5.0)		8.0 (7.0–10.0)		

Protein creatinine ratio has been correlated statistically with the total number of signs of severity in each group and the total sample. There was no significant correlation between them in group A (r = 0.064, P = 0.763) while there was positive significant correlation between them in group B (r = 0.501, P = 0.011) and the total sample (r = 0.734, P <0.001) which means that protein creatinine ratio increases with increase signs of severity. Table 3

Table (3): Correlation between total no. of indicators of severity with protein creatinine ratio and in each group and total sample

Protein creatinine ratio	Total No. of indicators of severity	
	R	**P**
Group A (n=25)	0.064	0.763
Group B (n=25)	0.501*	0.011*
Total (n=50)	0.734*	<0.001*

Discussion

Preeclampsia is a major cause of maternal morbidity, although its precise etiology remains elusive. A variety of risk factors have been associated with increased probability of preeclampsia like nulliparity and maternal age above 35 years. [29] Several studies suggest that urinary tract infection (UTI) during gestation is associated with elevated risk for preeclampsia, while others have failed to prove such an association.[30]

This study correlated protein creatinine ratio and urinary tract infection to the severity of preeclampsia. Features of severity of preeclampsia have been compared between two groups. It was found that all the cases (100%) in group B had more than 5 signs of severity but in Group A only 6 cases (24%) had more than 5 signs of severity. There were statistically significant differences between the 2 groups which indicates that signs of severity present more with preeclamptic patients with UTI. In 2008 in Soroka University Medical Center, Anatte Karmon and Eyal Sheiner performed a retrospective study on pregnant women between years 1988 and 2006 who were exposed to at least one UTI episode during gestation were 1.3 times more likely to have mild preeclampsia and 1.8 times more likely to have severe preeclampsia as compared to unexposed women. [30] Such results coincide with Izadi et al data who concluded that UTI is a risk factor for developing severe preeclampsia. [31]

In our study, Escherichia coli species was the most prevalent organism isolated in 68% of cases followed by Klebsiella in 12% and pseudomonas in 12 %. Also, Preeclamptic

patients with UTI in group B showed highest sensitivity to imipenem (84 %) followed by meropenem (80 %) then ciprofloxacin and gentamycin (72 %). Kaduma J et al conducted a 1:2 matched case-control study on pregnant women with preeclampsia (cases) and without preeclampsia (control). Pregnant women with preeclampsia had 7.7 odds of having significant bacteriuria than those without preeclampsia [OR=7.7, 95% CI (4.11-14.49); p-value <0.001]. Escherichia coli (45.5%), and Klebsiella spp. (23.6%) predominated, and resistance to gentamicin, ceftriaxone, and piperacillin-tazobactam ranged from 9.0% to 29.0% in these dominant species. [32]

Proteinuria has been assessed in all the cases of both groups using protein creatinine ratio. Protein creatinine ratio has been correlated statistically with the total number of signs of severity in each group and the total sample. There was no significant correlation between them in group A (r = 0.064, P = 0.763) while there was positive significant correlation between them in group B (r = 0.501, P = 0.011) and the total sample (r = 0.734, P <0.001) which means that protein creatinine ratio increases with increase signs of severity.

A meta-analysis was performed by Yan et al aimed to examine the relationship between UTI during pregnancy and preeclampsia. It was found that the ratio of UTI to non-UTI in Preeclampsia is 1.31 times than that of non-Preeclampsia which indicates that UTI during pregnancy may be a risk factor for development of Preeclampsia.[33]

It is hypothesized that UTI played a role in preeclampsia by serving to enhance maternal systemic inflammatory response. One mechanism by which UTI could hypothetically cause preeclampsia might be related to arterial damage triggered by infection, resulting in relative uteroplacental ischemia.[34,35]

In a study by LaMarca et al, inflammatory responses in preeclamptic pregnancies were found to be excessive as compared to that in normal pregnancies. UTI which is one of the most common maternal infections, can potentially lead to activation of systemic inflammatory response and endothelial injury; this in turn can lead to placental hypoxia and uteroplacental atherosis, and eventual development of Preeclampsia.[36]

Conclusion

In addition to revealing a statistically significant increased values in preeclamptic patients with UTI, Protein creatinine ratio positively correlates with the severity of preeclampsia. Urinary tract infection (UTI) during gestation is associated with increased severity of preeclampsia. Escherichia coli was found to be the most prevalent organism isolated in preeclamptic patients with UTI.

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