Renal Function Tests in Women with Preeclampsia with and without Intrauterine Growth Restriction

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Abstract

Background: The kidney is the most likely to be affected by endothelial injury in patients with preeclampsia, so assessment of renal function is essential in the evaluation of the pregnant women with preeclampsia. **Aim of the study**: to evaluate which test of renal function in preeclamptic patients with and without intrauterine growth restriction is more useful. **Patients and method**:150 women in third trimester with preeclampsia over period of 14 months diagnosed based on measurement of blood pressure and presence of proteinuria divided into two group : group A those preeclamptic women without feature of intrauterine growth restriction by ultrasound and Doppler study and group B those with features of intrauterine growth restriction. Blood aspirated from each woman and blood urea, serum creatinine, serum uric acid, and serum cystatin-C were measured using spectrophotometer. **Results**: From 150 women with preeclampsia 120 of them had no features of intrauterine growth restriction and 30 had some features. Mean maternal age of patients included was 22±0.3 in group A and 24±0.7 in group B which is not differ statistically while the body mass index should statistically differences between the two group with P value <0.001. the blood urea, serum creatinine and serum uric acid levels found to be higher in group B but not reach statistical differences while serum cystatin C are higher in group B mean 1.23±0.45when compared to group A 1.08±0.97with p value <0.001. **Conclusion**:Renal function may be affected more in patients with intrauterine growth restriction and cystatin C level is more promising marker for renal function in preeeclamptic women.

Keywords: *preeclampsia, renal failure, urea, creatinine*

Introduction

Preeclampsia is a complex syndrome that typically starts after 20 weeks' gestation, with many risk factors and affect 5-10% of all pregnancy[1]. The exact pathophysiology of preeclampsia is poorly understood, but it mainly concentrates on dysfunction of the placenta and maternal vascular endothelium . Microscopic examination of the placenta may range from infarction, arthrosis, thrombus formation, or chronic inflammation[2]. The kidneys may play an important role, both in the adaptive physiological changes of healthy pregnancy and in the pathophysiological process of Preeclampsia [3] and some of changes found in renal function be more common at term pregnancy and Preeclampsia. Pathological lesion in PE is the pathogomonic renal lesion termed glomerular endotheliosis, which is characterized by widely spread endothelial dysfunction in the mother, that may compromise glomerular dynamical function and barrier function [4]. Assessment of renal function is, therefore, important and essential in the evaluation of the pregnant patient with different type of hypertension.

Kidneys slightly increase in size. Early in pregnancy, the glomerular filtration rate [GFR] and renal plasma flow increase. The GFR increases in about 25 percent by the second week after beginning of pregnancy and increased in about 50 percent by the start of the second trimester. Renal plasma flow also elevated. An unusual feature of the pregnancy-induced changes in renal excretion is the

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markedly increased amounts of various substances lost in the urine. There is loss of greater amounts of amino acids and water-soluble vitamins in pregnancy. Serum creatinine levels decrease during normal pregnancy from a mean of 0.7 to 0.5 mg/dL. Creatinine clearance in pregnancy approximates 30 percent higher than the 100 to 115 mL/min in women who are not pregnant. Glucosuria during pregnancy also may be encountered. The remarkable elevation in glomerular filtration, with impaired tubular resorptive ability for filtered glucose, resulted in normal pregnancy there is no proteinuria and albumin excretion is minimal and usually ranges from 5 to 30 mg/day.

Pathophysiology of renal system in preeclampsia

Renal perfusion and glomerular filtration are reduced in pregnancy complicated with preeclampsia as compared with normal pregnancy. Diminished glomerular filtration may be due to a reduced plasma volume which cause serum creatinine values to rise to 1 mg/mL [as in non-pregnant], but sometimes even higher. The level of plasma uric acid is markedly elevated in preeclampsia.The diagnosis of preeclampsia-eclampsiacan be established by presence of some degree of proteinuria. This proteinuria may develop late, and some women may develop eclampsia before the appearance of proteinurea [5].Cystatin C is a non-glycosylated, Low Molecular Weight [LMW] protein. Its reabsorption and catabolism take place by the proximal convoluted tubules. Serum cystatin C risesmarkedly in patients with renal impairemnet, and even small decline in GFR can significantly increase serum cystatin C levels [6,7]. Pre-eclampsia is usually characterised by a decrease in GFR and changed in renal handling of cysteine protease inhibitors [8,9].

Intrauterine growth restriction [IUGR]

It refers to a fetus whose growth has been disrupted by some pathologic mechanisms.Fetal growth can be divided into two phases: before 20 weeks ofgestation, growth is mainly due to cellular hyperplasia [increasing number of cells], and after 20 weeks, which is primarily due to hypertrophy [increasing cell size]. Any insult before 20 weeks of gestation may result in symmetric growth restriction, while after 20 weeks will causeasymmetric growth.Maternal risk factors includeanemia, hypertension, antiphospholipid antibody syndrome,chronic renal disease, severe malnutrition and systemic lupus erythematosus,. Long standing diabetes with vascular disease mayalso lead to IUGR. Placental factors like; placenta previa, velamentous and marginal cord insertion, and placental thrombosis with or without infarction leading to diminished placental blood flow can lead to IUGR [10,11].

Diagnosis of IUGR: Identification of growth-restricted fetus remains a challenge, however; early estimation of gestational age, identification of risk factors, careful measurement of uterine fundal level and good evaluation of maternal weight gain during pregnancy will identify many cases of IUGR in low-risk pregnancy.[5]

Patients and method:

This is cross sectional study from December 2018 till February 2020 in Najaf city, 150 women in reproductive age group included in the study after taking their agreement to participate in this study. All women in the third trimester of pregnancy[based on last menstrual period and dating ultrasound] diagnosed as preeclampsia based on measurement of blood pressure [more than 140/90 on 2 accossion] and presence of proteinuria on urine exam, ultrasound done for each woman to calculate gestational age and compare to early dating ultrasound, measure amniotic fluid index to identify presence of oligohydramnios, then Doppler for umbilical artery done to measure RI, PI, S/D ratio to detect changes in blood flow in order to diagnosed cases of IUGR.

We divide the patients included in the study into two groups, group A those without IUGR and group B those preeclamptic with IUGR, for both groups blood aspirated [5 ml], centerfuged, then serum used to measure blood urea, serum creatinine, and serum cystatin C.

Results

From 150 women with preeclampsia enrolled in the study, 120 of them had no clinical or radiological feature of preeclampsia belong to group A, while 30 women had features of IUGR.

The mean age for both groups showed no statistial differences, for group A the mean age 22±0.3 years and in group B 24±0.7 years. Body mass index[BMI] was measured and there is stastical differences [p value

<0.001] between the two groups in group A the mean BMI was 25±1.1Kg/m² while in group B 27±0.96Kg/m² as shown in table 1

Table1: Comparison between age and body mass index

parameters	Group A	Group B	P value
Age [years]	22±0.3	28±1.2	0.12
Body mass index kg/m²	25±1.1	27±0.96	<0.001

Renal function tests were made and blood urea, serum creatinine, and serum uric acid were higher in group B but statistically not significant between the two group while there is significant difference in level of serum cystatin C, in group A 1.08±0.97 while group B was 1.17±0.4

Table 2: differences in parameter of renal function between the two group

Parameters	Group A	Group B	P value
Blood urea mg/dl	38±2.3	42±1.2	0.04
Serum creatinine mg/dl	1.07±0.85	1.3±0.9	0.05
Serum uric acid mg/dl	6.8±0.95	7.2±0.8	0.04
Serum cystatin C mg/dl	1.08±0.97	1.23±0.45	<0.0005

Discussion

Preeclampsia and intra uterine growth restriction are significant causes of fetal and women morbidity and mortality[12,13].The pathophysiology of both Preeclampsia and IUGR is incompletely clarified, but a process of defective endovascular trophoblastic invasion and changes of spiral artery earlier in pregnancy due to an exaggerated inflammatory response and later on endothelial cell stimulation may plays a vital role in the pathogenesis of this disease [14]. Recent studies focus on screening tests by various maternal serum markers including: serum pregnancy-specific beta-1-glycoprotein [sp1], which is associated mainly with SGA.[15] The preform of eosinophil major basic protein [proMBP], which is associated essentially with PIH, IUGR and PE [16] and glucose regulated protein 78 [grp78] [17], cystatine C [18], matrix metalloproteinase-9 [19], which are also associated with PE.

The limitation of the widely use of serum markers has manifested by the introduction of specific antibody assays, which is a time consuming and more expensive procedure. As PE and IUGR without preeclampsia seem to have genetic basis, understanding their genetics might help to find most useful predictive markers for screening high risk women. Most of maternal serum markers have been identified and their relationship with poor pregnancy outcome has been evaluated [14].

An association was found between preeclampsia and maternal body mass index [BMI], but whether BMI has an effect on preeclampsia of all severities is controversial. Yet, an association between maternal height andpreeclampsia is undetermined. In a study done by Sara Sohlberg, Stephansson, Sven Cnattingius and Anna-Karin Wikström1 et al 2011, they found that not only maternal BMI, but also maternalheight is associated with preeclampsia of all severities. A short

maternal stature was associated with increased risks of the different types of preeclampsia, while overweight and obesity were closely associated with the milder forms of preeclampsia [20].One previous study has shown an association between maternal height and the risk of development of severe preeclampsia, but only in multiparous and not in primiparous women [21]. Infants born small for gestational age may have an increased risk of short final stature, although most of them catch up in height during childhood[22].

Preeclampsia manifests by proteinuria, hypertension, and resulting impaired renal function. Serum creatinine only is an unreliable measure of kidney function in pregnancy. Cystatin C measurment has been proposed as one measure of kidney function in population studies and in pregnancy. Cystatin C in general is an endogenous low molecular weight protein [13kDa] synthesized by nearly all nucleated cells and produced at a constant rate. It is freely filtered in the healthy kidneys and then completely metabolized by the proximal tubular cells. Elevated cystatin C concentrations is mainly associated with cardiovascular outcomes in population studies. Many previous studies have shown increased in cystatin C levels in preeclampsia. However, these studies have not quantified different preeclampsia risk with varying cystatin C levels, nor have they adjusted for any potential confounders. A case control study by Nora Franceschini, ChunfangQiu, David A. Barrow & Michelle AWilliams et al 2009 to evaluate the relation between plasma cystatin C and preeclampsia in pregnant women without pre-pregnancy comorbidities. This study shows an increased risk of developing preeclampsia aassociated with a high cystatin C plasma levels among women without preexisting renal disease, diabetes, and different type of hypertension. The increased risk of preeclampsia was independent of maternal age, pre-pregnancy BMI, and physical inactivity, and remains after adjustments many cofounders like gestational age, maternal smoking, and corticosteroid exposure, which have all been associated with eleveted cystatin C levels. This study had some limitation by its cross-sectional design, and therefore unable to document whether this increased concentrations of cystatin C levels precede the clinical diagnosis of preeclampsia. Finally they conclude that there is an association between high plasma cystatin C levels and preeclampsia, which may reflects the acute kidney dysfunction that associated with preeclampsia. A large prospective cohort studies are needed to clarify the temporal relationship between changes in cystatin C concentrations and the later development of preeclampsia, and to determine whether elevated cystatin C concentrations in early pregnancy can be used as predictive of poor maternal and fetal outcomes in women with preeclampsia.[23]

Another study that was done by Magna Manjareeka, Sitikantha Nanda et al; 2013 to measure and compare the level of serum uric acid, serum creatinine and serum urea in pre-eclamptic and normotensive women. In this study, though the serum uric acid level was higher in pre-eclamptics when compared to the normotensives, the elevated levels of uric acid did not correlate closely with the raised systolic blood pressure or the raised diastolic blood pressure. The differences in each of the mean SUA or SCr concentrations between the preeclamptic and the normotensives respectively were not statistically significant and that these parameters may bo of little value in the prediction of preeclampsia. Few studies[9,16] observe insignificant change in serum creatinine level in the two studied groups. On the other hand, an early study showed increased serum creatinine level but conclude to be of no predictive value in preeclampsia. Certain aspects of this study had few limitations like :Small sample size and a lack of urinary measurements of uric acid level, creatinine and urea. [24]

A study that was done by Cimona Lyn Saldanha*, ShabnumAra, Tabassum Parvez et al 2017 found thatserum creatinine has been routinely used for monitoring of renal functions. In this study, we have found a significant increase in serum creatinine in pre-eclamptic patients in comparison with healthy control group. Same results were found in other studies as well. Kidneys play a important role in the metabolism of uric acid and it is an important predictor to understand the outcome of pregnancy in terms of maternal and fetal morbidity and mortality. Similar results for serum creatinine and uric acid are noticed in all groups. There was significant difference in the mean values of serum uric acid between normal controls women and pre-eclamptic patients. There is conflicting evidence regarding the efficacy of this test but recent data is showing favour for the usefulness of cystatin C assay in the diagnostic armamentarium of renal decline in preeclampsia. Cost is a major obstacle , especially in

the low resource setting and among patients with lower socioeconomic status [25].

Study done in 3rd. trimester of pregnancy, using several tests for measuring renal function including GFR but the substance frequently used to assess renal function impairment is serum creatinine .Cystatin C measurement is more promising ,especially in cases of mild impairment of kidney function compared to the use of serum creatinine. This may be explained as Cystatin C does not pass the placental barrier and there is no significant correlation between maternal and neonatal levels,unlike creatinine level [26].

In a study done by Tam M. Le1, Long H. Nguyen Nam L. Phan Duong D. Le Huy V.Q. Nguye|Vinh Q. Truong Thanh N. Cao1 There were 205 women enrolled in this study. Serum uric acid at a cutoff value of 393 μmol/L can be used as a good predictor for fetal and neonatal complications [AUC 0.752], with 64.4% sensitivity and 79.5% specificity. High uric acid level [≥393 μmol/L] resulted in increased risk of complications like preterm labor [OR 6.367, 95% CI 3.009–13.084], low Apgar scores and intrauterine growth restriction [OR 7.188, 95% CI 3.592–14.382], and even early neonatal death [OR 7.818, 95% CI 1.614–37.867]. There was no significant relationship between uric acid level and fetal death [OR 1.803, 95% CI 0.355–9.168][27].

A German study which describes relationship of maternal serum uric acid level [SUA] and serum cystatin C with maternal and neonatal cardiac and metabolic risk markers and with birth weight and risk of small-for-gestational age [SGA] as well as large-for gestational age [LGA] shows a positive association of cystatin C with birth weight and obvious increased risk for LGA with maternal increased cystatin C values in a population with fairly normal kidney function. In this study, most of the mothers were of German nationality [85%] and were between 26 and 35 years of age [69%]. Maternal SUA changes was associated with maternal age, body mass index, alcohol consumption and history of hypertension as well as with many other maternal and neonate cardiovascular risk markers. Cystatin C was associated with parity. No clear association of SUA with SGA and LGA was observed. However, cystatin C was found to be negatively associated with SGA with an odds ratio [OR] of 0.35 [95% CI: 0.16±0.77]. [28]

Another case–control study was performed by SK Srinivas, AG Edlow, PM Neff, MD Samme, CM Andrela1 and MA Elovitz et al . Cases were patients with preeclampsia. Controls were patients presenting for delivery at term [≥ 37 weeks]. IUGR prevalence by case–control status, or severity of disease was evaluated using Pearson w2 tests. Multivariable logistic regression was used to control for most confounders. In patients with CHTN and superimposed preeclampsia, the pathogenesis of IUGR may be related by various factors including the use of different medications, aggressiveness of treatment of hypertension, or willingness to deliver at a clinically earlier stage of the disease. Their findings conclude that preeclampsia is associated with IUGR independent of CHTN. The lack of synergy between preeclampsia and CHTN in the development of IUGR [as these patients did not have the higher rates of IUGR] suggests that the pathways leading to the development of IUGR may be disparate and not all IUGR develops from the same pathways. IUGR is more frequent in women with lower BMI [29].

Another study has declared that women of advanced maternal age [AMA] develop more preeclampsia [9.4%] than younger women[6.4%]. They had more prior terminations of pregnancy [<0.001], were more likely to have a body mass index [BMI]>25 kg/m2 [<0.001], more with in vitro fertilization [IVF][<0.001] and other fertility treatments [<0.001] and a higher incidence of maternal diseases like diabetes [<0.001] and chronic hypertension [<0.001]. Multivariate logistic regression indicated that women of AMA had higher rates of: preterm labor before 37 weeks 19.2% [OR 1.39 CI 1.24 to 1.56] and before 34 weeks8.7% [OR 1.68 CI 1.43 to 2.00] low Apgar scores at 5 min. 7.1%, Small-for-Gestational Age[SGA] 26.5% [OR 1.42 CI 1.28 to 1.57], birth Asphyxia 12.1% [OR 1.54 CI 1.34 to 1.77], Caesarean delivery 50% [OR 2.02 CI1.84 to 2.20] and the need for admission to a Neonatal Intensive Care Unit [NICU] 31.6%[30].

Other study in India demonstrates the association of serum UA, creatinine and cystatin C with maternal and fetal outcomes. The adjusted odds ratio [OR] was 3.73 [95% CI: 1.18-11.75; P=0.024] for UA; 15.79 [95% CI: 3.04-81.94; P=0.001] for serum creatinine and 2.03 [95% CI: 0.70-5.87; P=0.192] for cystatin C in different hypertensive disorders of pregnancy. All the three renal

parameters were not significantly associated with birth weight, gestational age at delivery and mode of delivery after adjusting for the other confounding factors. They conclude that serum creatinine and uric acid are independent risk factors for hypertensive disorders of pregnancy. High serum uric acid is associated with low birth weight and more delivery by caesarian section whereas high serum creatinine with preterm delivery only before adjustment for confounding factors and not after adjustment. But Serum cystatin C was not significantly associated with the maternal and fetal outcomes[31].

Another study was conducted at 2006 to examine whether preeclampsia, gestational hypertension, and unexplained IUGR [the latter often assumed to be due to placental insufficiency], could be linked together by comparing their different risk factors and perinatal outcome in a large collected data base from 4 distinct ethnic populations. They found similarities between preeclampsia and gestational hypertension, but the results suggest that unexplained IUGR [e.g, those not associated with smoking, under nutrition, secondary to hypertensive conditions, or congenital malformations] is obviously different entity from preeclampsia. Furthermore, we have confirmed that preeclampsia is a major risk factor for severe perinatal morbidity and mortality, but that gestational hypertension without proteinuria also independently may increases perinatal risk. [32].

A study that was done in Egypt has recruited twenty women normal primigravidae with singleton pregnancy and another 40 with severe preeclampsia recruited from preeclamptic unit of El-Shatby Maternity University Hospital, in Egypt in the third trimester of gestation without any medical disease. They are selected and full history taken, complete clinical examination, laboratory investigations including serum uric acid, serum creatinine and serum cystatin C, obstetric abdominal ultrasound and Doppler. The difference in the mean serum uric acid level [3.55±0.58 versus 6.76±1.06mg/dl] was significantly higher in the preeclamptic women [p=0.001], the specificity was 100% and sensitivity was 97.5%, the difference in the mean serum level of creatinine [1.55±0.89 versus 0.66±0.12] was significantly higher in preeclamptic group [p=0.001], the specificity of the test was 100% and the sensitivity was 60%. Serum cystatin C level has a mean value [0.98±0.29 versus 0.70±0.06] which was significantly higher in preeclampsia [p=0.001] with a specificity 100% and sensitivity 72.5%. They found a positive correlation between serum concentration of cystatin, and PI of umbilical artery Doppler [p=0.05]. Also, a significant correlation was found between serum level of cystatin and both PI and RI of middle cerebral artery Doppler [p=0.05]; this may indicates the relation of serum cystatin C level with the severity of preeclampsia , resulting in increasing poor reproductive outcomes [33].

Another study was done to compare between creatinine and cystatin C value in preeclampsia regarding severity and neonatal outcome. In this study, creatinine, cystatin C, and neonatal outcomes were assessed in 17 normotensive pregnant , 17 cases of mild preeclampsia and 17 samples with severe preeclampsia.Analysis of data with statistical tests of ANOVA and t test differences between 2 proportions. The mean levels of creatinine in the normotensive group, mild preeclampsia, severe preeclampsia are 0.56 mg/dL, 0.67 mg/dL, and 0.75 mg/dL respectively, p=0.138; While on cystatin C are 0.82 mg/L,1.03 mg/L and 1.32 mg/L, p=0.000. The adverse neonatal outcome wasn't recognised in the normotensive group. In mild preeclampsia obtained 1 preterm birth and 1 intrauterine fetal death[IUFD], whereas in severe preeclampsia obtained 3 babies born preterm, one IUFD, and 1 intrauterine growth restriction [IUGR]. It was concluded that levels of cystatin C was increased significantly parellel with increased severity of preeclampsia, whereas creatinine was not increased significantly with severity of the disease. Cystatin C is better than creatinine as a marker of renal dysfunction in preeclampsia patients. There was significat increase in adverse neonatal outcomes in the group of preeclampsia. [34].

Conclusion

We conclude that Cystatin C may be promising marker for renal function in patients with preeclampsia complicated by IUGR.

Conflict of Interest: we declare that there is conflict of interest

Ethical Approval: the research approved by scientific and ethical committee at our department

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