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Nephrogenous Predictors of Early Preeclampsia

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Abstract

The review of modern scientific researches summarizes the studies of nephrogenous preeclampsia genesis, in particular – the studies of modern biomarkers considering the pathogenesis of kidney damage. We have reviewed the renal markers with respective mechanisms and time terms associated with various levels of nephron damage. Severity and specificity of renal damage and its sensitivity during preeclampsia screening were also reviewed. Attention has been paid to use of preeclampsia screening in clinical practice during all trimesters of pregnancy.

Keywords: *preeclampsia, screening, renal biomarkers, gelatinase-associated lipocalin, CystatinC, podocyturia.*

Introduction

Preeclampsia (PE) is a multi-system inflammatory response of maternal organism usually manifested by renal complications and characterized by hypertension, proteinuria, and edema. Usually it develops during the last trimester of pregnancy. Various studies report different frequencies of PE; however it is found in 3-7% of pregnancies [1]. Multiple contradictory theories were developed to explain this pathologic mechanism.

The leading extra-genital factor resulting PE is renal disease associated with vascular tonus disorders and hypertension. PE diagnosing in pregnant patients with chronic renal disease is complicated due to pre-existing proteinuria. The risk of PE is 5.3% - 8%, while it is only 1.8% in females without chronic renal disease [2]. Renal disease takes the second place among other high risk factors – based on meta-analysis of multi-center studies with risk ratio 7.8 (95% CI 2.2-28.2) [3,4]. According to US Preventive Services Task Force (USPSTF) guidelines (2014) renal disease is the high risk of PE development [5].

Most authors consider endotheliosis (also typical for renal disease) is considered the basic trigger factor of PE. Some authors consider PE as a marginal condition of transient acute renal damage and renal failure [6].

Study Objective

analysis of modern renal markers efficacy for screening of early PE during each trimester.

Materials and Methods

database analysis - PubMed, Scopus, Web of Science, PMC free article и Google Scholar from 2011 to 2018. Totally 43 studies were included, enrolling over 18000 females from Europe, Asia and North America

Results and Discussion

PE diagnosis and definition are usually based on non-specific signs and symptoms, in particular – hypertension and proteinuria [7]. Ah criteria: systolic BP 140 mm Hg and or diastole BP 90 mm Hg for at least 2 measurements on the same arm with 15 minutes interval [8]. Clinically significant proteinuria during pregnancy has been defined as daily proteinuria 0.3 g/l [9]. Stout, Molly J. Et analyzed predictor efficacy of proteinuria in 12 – hours urine fraction sampled in pregnant patients with suspected PE. 12-hours urine sample is significantly different from 24-hours fraction with higher convenience and improved predictor efficacy [10]. Silva RM et al. have conducted a study targeting evaluation of 1-hours urine sampling efficacy for diagnosing of PE and establishment of

sampling time points effect on test efficacy. According to the analysis, the sensitivity level is 85.9% (95% confidence interval 81% -90%), while specificity reaches 91.7% level (95% confidence interval 88% -95%). The authors conclude that test precision level remains acceptable irrespective of urine sampling time [11]. However, complications are frequently associated with significant proteinuria.

Normal pregnancy is associated with various changes that, when disrupted, can result in renal failure and PE. Changes associated with water and electrolytes balance and acid-alkaline balance are reported.

Increase of kidney size by 1-1.5 size usually affecting urine collection system is reported. These changes persist during 12 weeks after labors; they should not be considered a sign of hydronephrosis. Progesterone effect results in dilation and enlargement of ureters by 20-30 cm. The pressure of pregnant uterus on the pelvic section of urethers (especially on the right size) results in dilation of ureters and renal pyelic system, pelvic veins varicose and bladder reflux followed by retention of urine and infection.

Changes of osmosis regulation results in plasma osmolality decrease by 10 mOsm/l starting from gestation trimester I and renin – angiotensin system activation resulting in sodium and water retention. Excessive volume of sodium and water (6-8 l by the end of pregnancy, with 1/3 distributed in maternal organism) is accumulated in extra-cellular space resulting in peripheral edema (at present, edema is not considered a sign of pathologic pregnancy. Orthostatic proteinuria can develop in 20% of pregnancy. Apparent hypervolemia has no effect on volume receptors; however, it contributes to circulating plasma volume (up to 50%), minute circulation volume, uterine circulation, renal circulation and glomerular filtration; 45% renal perfusion increase is reported.

During the second trimester, GFR (glomerular filtration rate) is increased by 50% followed by 20% decrease during the last trimester resulting in significant hyper-filtration. Significant plasma circulation increase is reported during the early stages of pregnancy; therefore, filtration fraction decrease is reported by the median term of pregnancy. Therefore, normal serum creatinine level is lower compared to pre-pregnancy levels. Therefore, values considered normal for non-pregnant patients (1-1.2 mg/dl) can demonstrate renal dysfunction during pregnancy requiring thorough examination [13]. Therefore, normal creatinine levels used in clinical practice can decrease during pregnancy concealing renal failure in pregnant patients [14]. Plasma creatinine level increase can result in increased tubular secretion demonstrating false Roeberg's test and false GFR value in patients with moderate and significant GFR decrease (<50 ml/min). Non-linear dependence of plasma creatinine level and GFR can demonstrate mild decrease of glomerular filtration. GFR values 120 to 50-60 ml/min is considered a blind range for creatinine. However, it is one of the most reliable markers of permanent glomerular filtration disorders [15]. It has been shown that creatinine is a reliable biomarker during pregnancy; however, lower values should be used in non-pregnant patients.

Oya Demirci et al. demonstrated positive correlation (correlation index 0.758) between protein/creatinine ratio and urine protein excretion during 24 hours [16].

InderPalKaur et al. conducted a study enrolling 145 pregnant females at II trimester of pregnancy in order to evaluate the efficacy of micro-albuminuria as PE prediction. Higher micro-albuminuria levels and higher creatinine/albumin ratio were demonstrated in patients compared to pregnant females with normal blood pressure [17].

Among other serum markers of renal excretion function close attention has been paid to Cystatin C – an inhibitor of cysteine proteases. Cystatin C is a 13 kD a protein produced in different cells that enters blood circulation freely, undergoes glomerular filtration and is fully metabolized in distal renal tubules without secretion [18]. Changes of serum Cystatin C levels reflects the function of glomerules and its change throughout the GFR range starting from hyper-filtration to early hypo-filtration; creatinine level decrease usually reflects severe renal dysfunction. Normal creatinine level associated with higher serum Cystatin C level is indicative of pre-clinical renal disease. Urine Cystatin C level reflects tubular dysfunction that usually precedes glomerular dysfunction and micro-albuminuria [19].

Plasma creatinine level and plasma Cystatin C level are the basis for GFR estimation; CKD-EPI 2009 is the most precise and modern calculation formula [20].

Cystatin C level screening specificity and sensitivity for PE prediction were evaluated in pregnant females of different gestation age.

Padma Y et al. have evaluated characteristic changes of creatinine, uric acid and CystatinC levels in females from India. Marker serum levels were evaluated in samples of 69 healthy pregnant females and in 27 patients with pregnancy – induced hypertension and in 20 patients with PE. Higher levels of all three markers were significantly increased in patients with PE compared to control groups with the following means: 1.47 ± 0.9 vs 1.06 ± 0.2 for Cystatin C, 0.95 ± 0.2 vs 0.67 ± 0.1 for creatinine and 6.13 ± 1.8 vs 4.28 ± 1.1 for uric acid respectively [21].

Apeksha Niraula et al. demonstrated higher diagnosing precision of serum Cystatin C level compared to serum creatinine and serum uric acid (sensitivity 88.24%, specificity 98.04%). In some patients with severe PE normal creatinine levels were reported, while Cystatin C level elevation corresponding to pregnancy term occurred. Therefore, Cystatin C reflects renal dysfunction that can result in higher blood pressure and urine albumin excretion. It can be used as a marker demonstrating the transfer of adaptive renal changes to PE. [22].

Dhokikar Gajanan Digambarrao et al. demonstrated that among other markers – urea nitrogen, creatinine and Cystatin C – serum Cystatin C is the earliest and the most reliable marker of renal dysfunction in patients with PE [23]. Gong S. Et al. demonstrated that serum Cystatin C is a reliable marker of renal function in females with severe PE, both at pre- and post-natal periods [24]. Trifonov A.N. demonstrated higher Cystatin C urine level in pregnant females during the I trimester. The reference interval of urine Cystatin C is 0.17—0.25 mg/l. The authors concluded that the hypothesis stating higher urine levels of Cystatin C in pregnant patients with PE failed because no clinically significant difference has been found between different groups of pregnant patients; therefore, this marker is not applicable as a marker of early tubular disorders in PE [25].

Lipocalin associated with gelatinase of neutrophils (NGAL) has been evaluated as an early marker of PE.

NGAL is a 25 kDa protein produced in all cells; synthesis is enhanced under stress conditions. Plasma NGAL is feely filtered by renal glomeruli and undergoes significant re-absorption in proximal tubules through endocytosis followed by destruction. Therefore, urine excretion of plasma NGAL can occur in patients with damaged tubules that results in lower re-absorption of lipocalin and higher level of NGAL synthesis in tubular cells [26]. Evaluation of urine NGAL levels reflects tubular dysfunction while elevated NGAL levels associated with normal creatinine levels reflect acute sub-clinical renal disorder associated with high risk of rapid progression and clinical manifestations onset [19]. Grigorios Karampas et al. studied changes of serum NGAL (s-NGAL) in females with normal pregnancy and with PE. Mean s-NGAL level (ng/ml) in patients with normal blood pressure has been elevated significantly – up to 12.8 during the I trimester, 25.9 during the first trimester ($p = 0.002$) and 48.0 ($p<0.0001$) during the III trimester. In patients with PE significant s-NGAL increase compared to control group during the I trimester (30.9; $p = 0.006$) and II trimester (44.6; $p = 0.015$) were demonstrated [27]. These results support earlier data stating that PE patients have higher s-NGAL levels compared to females with normal pregnancy, with significant difference during each trimester (I trimester – 29.9 (24.1-50.1) ng/ml vs 13.6 (9.1-19.9) ng/ml (normal pregnancy), 59.6 (25.3-82.6) ng/ml vs 6.3 (1.3 – 23.3) ng/ml during II trimester, and 57.2 (18.7-70.9) ng/ml vs 15.8 (9.1-22.5) ng/ml during III pregnancy); 4-fold increase of s-NGAL level during the II trimester is followed by PE and acute renal failure. [28-30]. Sun Min Kim et al. demonstrated significantly higher s-HGAL levels in patients with severe PE compared to patients with mild PE (237.5 ng/ml [67.4-575.4] vs 125.9 ng/ml [66.1-295.7]) [31].

Giuliana Simonazzi demonstrated increase s-NGAL corresponding to PE severity; however, no statistically significant difference of s-NGAL levels for mild and severe disease has been demonstrated [32].

Kasper Pihl et al. conducted a cohort study (2017) evaluating s-NGAL levels in patients with delayed PE onset (≥ 37 weeks + 0 days) (n = 213), and early PE onset (<37 weeks + 0 days) (n = 55) and in control group (n = 449) during the I trimester. The study demonstrated that during the I trimester there has been no correlation between s-NGAl and gestation age; however, significant s-NGAL level increase has been demonstrated in patients with early PE. On the contrary, in patients with delayed PE onset s-NGAL level remains unchanged. Authors conclude that efficacy of s-NGAL level evaluation for screening for early PE is insufficient [33].

Nilgün Tekkeşin and Asena Ayar evaluated change of urine NGAL (uNGAL) during normal pregnancy and in patients with PE. Authors conclude that uNGAL level in patients with PE (n = 30) was higher compared to controls (n = 30), with significant difference during each trimester [34]. However, other studies demonstrated higher uNGAL levels in healthy pregnant females, while no such changes were found in patients with PE [32, 35]. Of note, decreased uNGAL levels were found both in patients with normal blood pressure and in patients with PE at post-natal weeks 6-8 [41]. Moreover, Ødum L et al have shown that uNGAL level does not correlate to urine albumin level [35]. The authors conclude that uNGAL is not an early biomarker of PE [32, 35].

Data demonstrating that significant increase of NGAL level during the II trimester (gestation weeks 20-26) in patients with PE were presented at EuroMedLab conference in 2013; the authors concluded that NGAL is an effective marker for disease prognosis [36].

KIM-1 (Kidney Injury Molecule -1) is a marker of structural kidney damage; It is not found in normal tissues; however, high levels of KIM-1 are expressed by proximal tubules changes after toxic or ischemic damage; serum KIM-1 level elevation occurs before the increase of urea and creatinine levels [37]. Yuping Wang demonstrated similar uNGAL and KIM-1 levels in patients with chronic hypertension, mild PE and in females with normal pregnancy prior to labors; however, significant increase has been reported in patients with severe PE. Urine KIM-1 levels remained unchanged during pregnancy and within 6- weeks after labors in females with normal pregnancy; however, high KIM-1 levels found in patients with severe PE prior to labors had a tendency to significant decrease within 6-8 weeks after labors. High KIM-1 urine levels can also reflect renal ischemia associated with severe PE. Based on these studies results urine KIM-1 is supposed to be a sensible biomarker of renal injury associated with PE severity [38].

Podocyturia can also reflect glomerular injury because endothelium of glomeruli contains podocytes that form a barrier preventing protein loss with urine. Recent studies demonstrate that after injury podocytes can start the mitosis cycle; cell cleavage results in lower adhesion to glomerular basal membrane followed by higher urine excretion of podocytes, both viable cells and cells subject to apoptosis are excreted [39]. Penning ME et al. (2014) reviewed Pathologic registry national database of Netherlands (PALGA) and identified the tissues of renal samples taken from patients from the Netherlands that died of PE since 1990. Kidney tissue samples taken from 11 females that died of PE were compared to 3 control groups that were identified during one time period and included tissues taken from 25 patients with normal blood pressure (death during pregnancy with causes other than PE) and tissues taken from non-pregnant patients with chronic arterial hypertension (n = 14) or without arterial hypertension (n = 13). The study demonstrated typical glomerular damage and glomerular endotheliosis in most PE cases. Total number of podocytes was generally consistent between PE cases and controls; however, more pronounced changes of podocytes were found in PE patients. This finding can be indicative of contribution of podocytes change PE – associated renal disease resulting in proteinuria. However, even during normal pregnancy is associated with activation of inflammation network; low level of glomerular endotheliosis has been found in 12-42% of samples taken from patients with normal blood pressure and normal pregnancy [40]. Craici IM et al. studied podocyturia during II trimester and demonstrated it in 100% of patients that developed PE later and in 0% of healthy patients from the control group. Podocyturia has been suggested as a sensitive and specific PE biomarker during the II trimester [41].

Podocyturia as PE biomarker has been studied by Belinda Jim et al. Podocyturia has been identified in 11 of 29 (38%) patients with PE, 3 of 9 (33%) patients with gestation and chronic hypertension and 3 of 6 (50%) patients with Types I/II gestation diabetes. Podocyturia has not been demonstrated in any of 9 patients (0%) with normal pregnancy. It has been found that sensitivity and specificity of podocyturia evaluation for PE diagnosing are 38% and 70% respectively. The study demonstrated that podocyturia is not a sensitive and specific marker for PE diagnosing [42]. Aita K. et al. demonstrated podocyturia in patients with PE at pregnancy week 35m and at post-partum day 4; however, no podocyturia has been demonstrated within 1 month after labors. Authors conclude that this term includes complete recovery of kidneys after PE-associated damage. Podocyturia has been found in 9 of 45 females with normal blood pressure at post-partum day 4. Therefore, either podocyturia is not a specific sign of PR or it can be found in healthy females also [42,43].

Conclusion

The reviewed studies demonstrate the possibilities of implementation of modern renal biomarkers into practice of PE prognosis at early gestation terms. However, available reliable data are scarce and contradictory. Further research is required to clarify the reliability of nephrogenous predictors for clinical practice.

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