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Mini Review

Preeclampsia- Emphasis away from Proteinuria

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Abstract

American College of Obstetricians and Gynecologists' (ACOG) Task Force on Hypertension in Pregnancy has modified the diagnosis of preeclampsia (PE) by eliminating the dependence of PE diagnosis on proteinuria. Proteinuria in PE may be a late marker of renal injury; and podoctyuria which appears much before proteinuria may serve as an early marker of renal injury. Thus biomarkers influencing endothelial dysfunction and renal damage in PE may need to be looked into and compared with internationally accepted risk stratification model. These women experience a 2-fold increased risk of long-term cardiovascular disease (CVD) and an approximate 5–12-fold increased risk of end-stage renal disease (ESRD). Hence, the objectives of screening tests for PE should be such that it can help in predicting and reducing the prevalence of the disease through early pharmacological intervention along with measures to minimize maternal and perinatal morbidity and mortality.

INTRODUCTION

Preeclampsia (PE) is a hypertensive pregnancy disorder complicating up to 1–5% of pregnancies associated with increased maternal and perinatal morbidity and mortality [1]. This multisystem disorder is classically described as hypertension and proteinuria beyond 20 weeks of gestation [2]. The renal abnormality in PE is due to "endotheliosis" (endothelial cell swelling and disruption of fenestrae) leading to endothelial dysfunction resulting in proteinuria as its clinical presentation. Over the years literature evidences have suggested the role of endothelial dysfunction as the integral part which results in the imbalance between a decrease in pro-angiogenic factors, such as vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), and an increase in anti-angiogenic factors, including the soluble VEGF receptor fms-like tyrosine kinase receptor-1 (sFlt-1) and endoglin [3]. This endothelial dysfunction, which is a pathogenetic mechanism in PE and is also evident among renal proteinuric disease, could be a triggering force to incite a critical loss of viable podocytes causing glomerular destabilization. The ongoing podocyte loss would lead to focal segmental glomerulosclerosis, chronic kidney injury, and finally, end stage renal disease (ESRD). Studies have suggested that podocyte shedding in the urine may occur long before overt proteinuria among glomerular diseases and that podocyturia can be detected in urine samples before overt proteinuria develops and, therefore, may serve as a harbinger of proteinuria and the subsequent diagnosis of preeclampsia [4]. Animal models of chronic kidney disease (CKD) have shown shedding of nephrin from podocytes in the glomerulus resulting in podocyturia leading to chronicity in the kidney, thus indicating that the degree of nephrinuria might predict degree of proteinuria and kidney injury [5].

Literature evidences have shown an increased risk for cardiovascular and renal disease later in life among females who had preeclampsia during pregnancy. Such women were observed to experience a 2-fold increased risk of long-term cardiovascular disease (CVD) and an approximate 5–12-fold increased risk of end-stage renal disease (ESRD) [6]. Hence it seems essential to recognize PE as a risk factor for renal disease and CVD. However due to low level of evidence in research and gap in current knowledge regarding optimal screening and prevention strategies it seems worthwhile emphasizing on the need for developing screening measures among these pregnant females with the aim of reducing the late disease burden.

In contrast to ACOG Committee on Obstetric Practice 2002, ACOG Task Force on Hypertension in Pregnancy 2013 has modified the diagnosis of PE by eliminating its dependence on proteinuria [2,7]. Task force rules out the absolute requirement of proteinuria for diagnosis of preeclampsia. In non-proteinuric patients, presence of end organ damage like new onset renal failure (doubling of serum creatinine or serum creatinine >1.1mg/dl); impaired liver function test (transaminase more than two times of normal); pulmonary edema; cerebral or visual disturbances and thrombocytopenia (<100,000/ml) suggests PE according to Task Force recommended diagnostic criteria. It has practically broadened the term PE helping the physician

in identifying high risk pregnant populations that can be given institutional obstetric care. Thornton et al in 2010 concluded in his study, that all patients who developed eclampsia were non-proteinuric and perinatal mortality in non-proteinuric PE was not lesser than proteinuric PE [8].

But eliminating degree of proteinuria from diagnosis of severe PE by the Task Force may underestimate a substantial number of severe preeclamptic patients those may need termination of pregnancy. The Task Force believes that there is no significant correlation between severity of proteinuria and pregnancy outcome in PE, which is supported by a number of studies [7-13]. Systemic review by Thangaratinam et al., in 2009 suggests that proteinuria is a poor predictor maternal and fetal complication [14]. But many studies have been built up over time that also clearly suggests that both maternal and fetal outcome inversely proportional to severity of proteinuria [15-22]. Massive proteinuria is a marker of early onset disease and progression to severe disease [23]. Higher the proteinuria more chance of developing severe hypertension, eclampsia and need of caesarean section [17]. Small for gestational age (SGA) and perinatal mortality also increases in incidence with increase in proteinuria [16,17]. Severe proteinuria in PE is not only important to predict maternal complication but also an independent risk factors for fetal hypoxia [24].

While forming guideline, authors have not focused on long term maternal renal health. Many studies have clearly indicated that preeclampsia is a risk factor for proteinuria and chronic kidney disease (CKD) in later life [25,26]. Histological finding of preeclampsia similar to focal segmental glomerulosclerosis characterized by endotheliosis and segmental sclerosis [27]. Like other glomerular disease degree of proteinuria might predict progression to CKD in preeclamptic women. Women with massive proteinuria have higher serum creatinine than those with mild to moderate serum proteinuria indicating higher incidence of acute kidney injury (AKI) in former [28]. Now it is also clear that AKI is a risk factor for progression to CKD [29].

Most studies evaluating impact of proteinuria in preeclamptic women were retrospective study and had intervened pregnancy based on proteinuria. Hence, outcome of these studies can't be conclusive in telling that severity of proteinuria doesn't predict maternal and fetal outcome. These studies also had not mention criteria for termination of pregnancy and time between onset of proteinuria and termination of pregnancy. These studies only focused on short term goal like maternal and fetal health, but not on long term effect on maternal renal health. Hence prior to making such concrete opinion, it needs a large randomized multicenter control trial evaluating both short and long term outcome. Albuminuria rather than proteinuria is a marker of glomerular endothelial injury. Hence rather than 24 hour urinary protein, it would be wise to introduces 24 hour urinary albumin. But few literatures are available correlating albuminuria with maternal and fetal outcome.

Proteinuria which is thought to be a late manifestation of renal injury, and renal damage if picked up at subclinical stage could prevent long-term renal outcomes. Whether immediate (at delivery) and ongoing (postpartum onward) podocyte loss could cause irreversible structural changes and increase risk of future kidney disease after preeclamptic pregnancies, remains to be determined. As even a single episode of podocyte injury is known to cause permanent renal injury in mouse models by selective podocyte depletion using diphtheria toxin [30]. Thus critical loss of viable podocytes during PE could cause glomerular destabilization and ongoing podocyte loss leading to FSGS, chronic kidney injury, and finally, end stage renal disease (ESRD).

The major challenge in modern obstetrics is early identification of pregnancies at high-risk of preterm PE and undertaking of the necessary measures to improve placentation and reduce the prevalence of the disease. There is now evidence that a combination of maternal demographic characteristics, including medical and obstetric history, uterine artery pulsatility index (PI), mean arterial pressure (MAP) and maternal serum pregnancy associated plasma protein-A (PAPP-A) and placental growth factor (PlGF) at 11-13 weeks' gestation can identify a high proportion of pregnancies at high-risk for PE [31]. Such early identification of the high-risk group for PE is important because the risk may be substantially reduced by the prophylactic use of low-dose aspirin starting from 11-13 weeks [32].

The association of renal disease with preeclampsia makes one wonder if efforts are not made in picking them early it could lead to irreversible renal damage in later life. Authors have demonstrated a clear dose-dependent relationship with increased risk to CKD and RR of ESRD of 4.7 more episodes of preeclampsia [25]. In women with multiple pregnancies, having preeclampsia in a later pregnancy was worse than having preeclampsia in an earlier pregnancy. This makes one wonder as to develop such non-invasive biomarkers looking into preeclampsia and renal diseases that could help in detecting preeclampsia in its subclinical stage especially for early renal injury and help the obstetrician in careful management of the maternal and fetal outcomes with subsequent follow up under a physician of such patients in terms of long-term renal outcomes

The objectives of such screening for preeclampsia can help first in reducing the prevalence of the disease thus minimizing adverse perinatal events for those that develop PE by determining the appropriate time and place for delivery. It seems likely to reconsider in looking for subclinical markers for proteinuria i.e. selected podocyte-specific proteins such as podocin, nephrin, synaptopodin and GLEPP-1 in early stage of pregnancy which could be used as an marker for subsequent development of preeclampsia and renal damage and a preventive means for prediction and prognosis [33].

In conclusion, we would like to emphasize that preeclampsia carries a long term risk of CKD. Hence, guideline and research should focus on both short term outcome like maternal and fetal outcome and long term risk of CKD.

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