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New aspects of pre-eclampsia: lessons for the nephrologist

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Pre-eclampsia was first described in 1843 when John Lever from Guy's hospital in London discovered proteinuria in women with puerperal convulsions. Today, this pregnancy syndrome is defined by new onset of hypertension and proteinuria during the last trimester. From population-based studies, pre-eclampsia is reported to affect 3–5% of all pregnancies [1], resulting in substantial maternal and foetal morbidity and mortality worldwide. The exact aetiology is still unknown, but our understanding of pre-eclampsia has improved in recent years. The pathophysiologic changes include disturbances in the vascular development of placenta resulting in placental hypoperfusion and ischaemia. The damaged placenta, in turn, secretes a wide range of anti-angiogenic factors into the maternal circulation that is believed to cause a systemic endothelial cell dysfunction and microangiopathy [2]. In the kidneys, these endothelial damages result in glomerular capillary endotheliosis and proteinuria. Glomerular endotheliosis is characterized by

deposition of fibrin and fibrinogen material in and beneath the endothelial cells as well as endothelial swelling, resulting in obliteration of the endothelial fenestrae and loss of the capillary space [3]. Although these renal changes in general are believed to resolve completely after delivery, recent evidence suggests that pre-eclampsia may leave a permanent renal damage.

Kidney disease as a risk factor for pre-eclampsia

The literature on pregnancies in women with renal impairment is dominated by small, uncontrolled studies with a heterogeneous definition of kidney disease. Pregnancy in women with diagnosed kidney disease is relatively uncommon and prevalence estimates range from 0.03% to 0.12% [4–6]. However, compared to the general population, the fertility is substantially reduced and early pregnancy losses occur frequently [7]. Even though the majority who become pregnant bring forth surviving infants, the risk for pre-eclampsia and other pregnancy complications is substantially increased in women with chronic kidney disease (CKD) stages 3–5 [4–6,8,9]; Cunningham *et al.* evaluated 37 pregnancies in women with moderate or severe renal insufficiency and reported pre-eclampsia in 58% and 64% of the pregnancies, respectively [4]. Fink *et al.* evaluated 169 women with renal disease in a case-control study, and found an odds ratio of 7.3 for pre-eclampsia in those with diagnosed kidney disease. The histopathological origin differs widely in these studies, but diabetic nephropathy is the most common cause of CKD in pregnancy affecting around 10% of pregnant women with diabetes mellitus [6]. Other frequent diagnoses include lupus- and IgA nephropathy, chronic glomerulonephritis and polycystic kidney disease.

Are women with CKD stages 1–3 at increased risk of pre-eclampsia? In a large population-based study from Norway, estimated glomerular filtration rate (eGFR) measurements were available on almost 3500 women who later became pregnant [8]. During an 11-year follow-up, only 0.1% of the women with CKD stage 3 gave birth, and no women with CKD stage 4 or 5 gave birth. The prevalence of pre-pregnancy eGFR in the range 60–89 ml/min per 1.73 m^2 was considerable (18.8%), but these women were not at increased risk for pre-eclampsia. However, there was a significant biological interaction between eGFR and hypertension making eGFR 60–89 ml/min per 1.73 m^2 a risk factor for pre-eclampsia if the women were also hypertensive.

Pre-eclampsia as a predictor of later kidney disease

Several studies during the last decade have shown that women who have had a pre-eclamptic pregnancy have a significantly increased risk of later cardiovascular disease [9,10]. Risk factors for cardiovascular and renal disease are often the same and two recent studies documented a strong relationship also between pre-eclampsia and CKD [11,12], possibly even stronger than that for cardiovascular disease. In the first study, women with pre-eclampsia in their first pregnancy had a considerably increased risk of developing kidney disease that needed investigation with a kidney biopsy [11]. Pre-eclampsia seemed to be similarly associated with the different diagnoses at kidney biopsy and the increased risk was strongest during the first 5 years after giving birth, but remained significant also after this period. In the second study, women who previously had pre-eclampsia had a four to five times increased risk of later end-stage renal disease, independent of primary renal disease [12]. Women with recurrent pre-eclamptic pregnancies and women who gave birth to offspring with low birth weight had an even higher risk. The increased risk remained significant throughout the follow-up period of nearly 40 years.

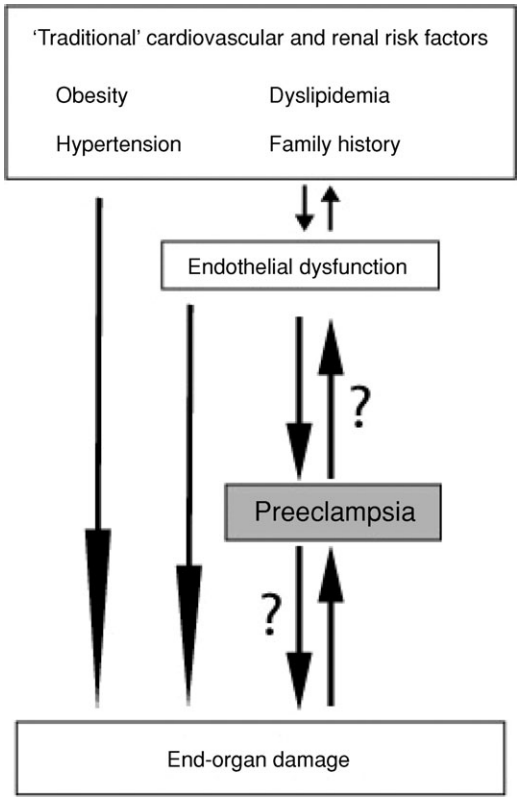

Fig. 1. Pre-eclampsia may be an intermediate factor in the development of end-organ damage.

Several mechanisms might explain the observed association between pre-eclampsia and subsequent renal disease. As hypertension, endothelial dysfunction, obesity and other cardiovascular risk factors are important risk factors for both pre-eclampsia and CKD [1,13–18], these shared risk factors can explain at least parts of the association between pre-eclampsia and kidney disease. However, pre-eclampsia seems to be associated with a four to five times increased risk of later CKD and microalbuminuria [11,12,16–18], a risk that seems to be significantly higher than the increased risk of later obesity, dyslipidaemia and cardiovascular disease [9,19,20]. This might suggest a possible direct renal damage from pre-eclampsia (Figure 1).

A possible renal damaging effect of pre-eclampsia could be mediated either directly by leaving permanent renal damage or indirectly by causing permanent hypertension or endothelial dysfunction that could lead to progressive renal dysfunction. Studies have shown that women with a history of pre-eclampsia have higher blood pressure, endothelial dysfunction, obesity and other signs of an unfavourable cardiovascular risk profile both before and after the pre-eclamptic pregnancy [1,10,18–20]. To our knowledge, however, no studies have investigated whether pre-eclampsia itself has a negative effect on blood pressure and microalbuminuria, although the currently available studies leave an impression of a worse cardiovascular risk profile after pregnancy than that before pregnancy in women with pre-eclampsia. In support of this, one study demonstrated a larger weight gain from before pregnancy to 1 year after birth in women who developed pre-eclampsia than in women who did not [19]. It is important to note that irrespective of whether pre-eclampsia itself worsens the cardiovascular risk profile, or whether pre-eclampsia merely is a clinically significant marker of an asymptomatic adverse cardiovascular risk profile that would be present anyway, a negative cardiovascular risk profile is a risk factor both for development and progression of CKD. It should also be kept in mind that although the extensive glomerular changes during pre-eclampsia are believed to completely resolve after pregnancy [3], no studies have routinely performed a kidney biopsy months after the pre-eclamptic pregnancy. The fact that as many as 20–40% have microalbuminuria after a pre-eclamptic pregnancy may argue for a permanent glomerular damage in a great proportion of these women [17,18]. Furthermore, several investigators argue that proteinuria itself causes progressive renal dysfunction via increased interstitial inflammation [21], and the same might be true for microalbuminuria.

In the last few years, there has also been increased focus on the central role of anti-angiogenic factors in the pathogenesis of pre-eclampsia. Placental soluble fms-like tyrosine kinase (sFlt1) and soluble endoglin (sEng) are both antagonists to vascular endothelial growth factor (VEGF) and placental growth factor (PlGF). VEGF is important for maintaining normal glomerular endothelial cell function, and its absence can result in proteinuria and trombotic microangiopathy [22]. Whether these factors related to angiogenesis remain altered also after the pre-eclamptic pregnancy and contribute in the pathogenesis of CKD remains unknown. It remains to be investigated whether anti-angiogenic factors could be associated with future renal disease in women with pre-eclampsia.

When interpreting the studies of pre-eclampsia and later kidney disease, it should be remembered that pre-eclampsia might unmask asymptomatic or undiagnosed CKD, a disease that might have been present also before pregnancy. A pre-pregnancy eGFR >60 ml/min per 1.73 m^2 measured at screening was in a population-based sample associated with future pre-eclampsia risk in hypertensive women [8]. Furthermore, previous studies have shown that as many as 5–20% of women with severe pre-eclampsia have signs of CKD shortly after pregnancy, a disease that might have been present also before pregnancy [23,24], leaving the question whether these women had true pre-eclampsia or merely a mild exacerbation of their kidney disease.

Opportunity for prevention of kidney disease?

Even though there are still many questions to answer before the mystery of pre-eclampsia is completely understood, evidence from both epidemiological and pathophysiological studies suggests a central role of pre-eclampsia in the development of CKD. A pregnancy complicated by pre-eclampsia seems to provide a unique window into the future regarding cardiovascular and renal risk. We therefore suggest that all women with a history of pre-eclampsia should be followed up by their general practitioners, in the most complicated cases also in collaboration with a nephrologist. Besides evaluation for a possible primary renal or urinary tract disease, the focus should be hypertension, obesity, microalbuminuria and cardiovascular risk profile. Early lifestyle intervention and/or pharmacological treatment of hypertension and microalbuminuria are likely to be highly cost-effective in a public health perspective.

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Renal involvement in AL amyloidosis: the facts, the promise and the hope*

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*Comment on Gertz *et al*. Clinical outcome of immunoglobulin light chain amyloidosis affecting the kidney. *Nephrol Dial Transplant* 2009; 24: 3132–3137.

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AL amyloidosis is a devastating, multisystem disorder that often affects the kidney, with proteinuria and elevated serum creatinine being detected in 55% and 45% of patients at presentation [1]. Many patients will develop end-stage renal failure (ESRF). However, there is little information on the predictors of ESRF and the outcome of dialysis, although it is generally considered that the quality of life under dialysis is poor with a high rate of mortality.

The paper by Gertz *et al*. from the Mayo Clinic examines the long-term outcomes of 145 patients with biopsy-proven AL amyloidosis [2]. Eighty-four had renal amyloidosis and 35 were ultimately dialysis dependent. This is the largest series of patients with renal AL amyloidosis, with an Italian collaborative study that included 198 patients with AL amyloidosis [3]. The Mayo Clinic study provides three pieces of information (1) λ light chain predicts increased likelihood of renal involvement, (2) high serum creatinine and daily proteinuria are predictors for dialysis, (3) median survival for patients starting dialysis is <1 year. These findings have important pathophysiological and therapeutic implications.

Pathophysiology of amyloid deposition: still unresolved issues!

Determinant factors of amyloid are borne by the precursor light chain (LC), as suggested by recurrence in the renal graft and by induction of amyloid deposits in mice injected with LCs from patients with AL amyloidosis [4]. Pathophysiological studies are made difficult by the unique structural heterogeneity of the precursor, each monoclonal LC being different from all others (Figure 1).

Several LC characteristics are considered amyloidogenic. In AL amyloidosis, the λ isotype is approximately 3- to 6-fold more frequent than the κ isotype. A rarely expressed homology family of LC variable regions, the $V_{\lambda VI}$ variability subgroup, is found only in amyloid-associated monoclonal immunoglobulins and represents 41% of amyloid LCs [5]. The essential role of the variable domain is further supported by analyses of extracted fibrils, which showed it to be the main amyloid constituent. This finding suggests a role of proteolysis in fibrillogenesis, and may partly account for the weak reactivity of anti-LC antibodies in some patients.

The search for primary sequence peculiarities of the LC variable domains led to disappointing conclusions,