From preeclampsia to renal disease: a role of angiogenic factors and the renin–angiotensin aldosterone system?

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Abstract
Complicating up to 8% of pregnancies, preeclampsia is the most common glomerular disease worldwide and remains a leading cause of infant and maternal morbidity and mortality. Although the exact pathogenesis of this syndrome is still incomplete, a consistent line of evidence has identified an imbalance of proangiogenic and anti-angiogenic proteins as a key factor in the development of preeclampsia. Furthermore, more attention has been recently addressed to the renin–angiotensin aldosterone system (RAAS), to provide understanding on the hypertension of preeclampsia. The imbalance of the RAAS and the imbalance between angiogenic and anti-angiogenic factors, which may be both common to preeclampsia and chronic kidney disease (CKD), might explain why a history of preeclampsia predisposes women to develop CKD. In this review, we briefly describe the characteristics of preeclampsia with a focus on the mechanisms of angiogenesis and the RAAS and its role in the pathogenesis of preeclampsia. Our main focus will be on the intriguing association between preeclampsia and the subsequent increased risk of developing CKD on the potential mechanisms by which the risk of CKD is elevated in women with a history of preeclampsia.

Keywords: angiogenic factors; chronic kidney disease; hypertension; microalbuminuria; preeclampsia; renal haemodynamics; renin–angiotensin-aldosterone system

Preeclampsia
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In this review, we briefly describe the characteristics of preeclampsia with a focus on the mechanisms of angiogenesis and the RAAS and its role in the pathogenesis of preeclampsia. Our main focus will be on the intriguing association between preeclampsia and the subsequent increased risk of developing CKD on the potential mechanisms by which the risk of CKD is elevated in women with a history of preeclampsia.

The diagnosis of preeclampsia is clinical. As defined by the International Society of Studies of Hypertension in Pregnancy, the diagnosis requires blood pressures of ≥140/90 mmHg on two occasions combined with the urinary protein excretion of ≥300 mg/day [5]. Laboratory tests, such as liver function tests, quantification of urinary protein or serum creatinine, may be helpful in characterizing the degree of end-organ damage, but none is specific for preeclampsia [6].

In the pathogenesis of preeclampsia the placenta is the central organ, since the removal of the placenta abolishes the disease [7]. Pathological examination reveals several abnormalities including infarcts, atherosis, thrombosis and chronic inflammation [8]. During normal placentation, the embryo-derived cytotrophoblast cells invade the maternal spiral arteries. As part of this process, the cytotrophoblasts adopt an endothelial phenotype [7, 9]. In preeclampsia, the invasion of the cytotrophoblasts into the spiral arteries is incomplete; they are only present in the superficial layers of the decidua. The abnormal placentation is
thought to lead to a release of secreted factors that enter the mother's circulation, culminating in the clinical signs and symptoms of preeclampsia.

**Kidney**

Renal function undergoes physiological adaptations in pregnancy. Healthy pregnant women show marked glomerular hyperfiltration by 40 to 60% in the second half of pregnancy [4]. This hyperfiltration appears to result primarily from depression of the oncotic pressure [4]. Furthermore, an increased rate of effective renal plasma flow (ERPF) is found during pregnancy, (~80% by 12 weeks' gestation) [4]. In contrast, during preeclampsia these functional changes in renal haemodynamics are different. The GFR in women with preeclampsia is significantly lower when compared with healthy gravid control subjects (91 mL/min/1.73 m² versus 149 mL/min/1.73 m²). Of interest, no differences were found in ERPF between women with preeclampsia and healthy controls [10].

This depression in the GFR during preeclampsia coincides with typical histopathological changes in the kidney, called glomerular endotheliosis, which is characterized by fibrin deposition, endothelial swelling and loss of capillary space [11]. Although these renal histological changes have been considered pathognomonic for preeclampsia, this may not be the case. Several groups have performed antenatal renal biopsies in normal pregnant women and women with gestational hypertension. For instance, Strevens et al. demonstrated that five of twelve normal pregnant women had, albeit very mild, evidence of glomerular endotheliosis [12]. These endotheliosis lesions resolve at variable rates postpartum, but it has been proposed that the characteristic renal changes of preeclampsia can be more long-standing [12]. The mechanism of hyperfiltration during preeclampsia is not elucidated; both (renal) haemodynamic mechanisms and secondary changes to structural renal changes are proposed [4]. Lately, podocyte alterations and podocyturia have been described during preeclampsia [13]. Proteinuria in patients with preeclampsia might not only be mediated by endothelial alterations described classically, but also by disturbances of podocyte biology including impaired survival, enhanced apoptosis and down-regulation of nephrin and other key proteins of the slit diaphragm [14].

**Angiogenic factors**

Recent observations support the hypothesis that altered expressions of placental anti-angiogenic factors are partially responsible for the clinical manifestations of preeclampsia. Soluble Fms-like tyrosine kinase-1 (sFlt1), the soluble form of vascular endothelial growth factor (VEGF) receptor 1 and placenta-derived soluble TGF-B co-receptor endoglin (sEng), secreted by the placenta, are increased in the maternal circulation weeks before the onset of preeclampsia [3]. These elevated factors might lead to endothelial dysfunction and therefore decreased endothelium-dependent vasodilation and proteinuria. Several days after delivery, sFlt1 levels normalize coinciding with decrease in proteinuria and blood pressure. The fact that increasing circulating sFlt1 levels in gravid mice and rats, either by direct infusion of the protein or by injection of adenovirus expressing the sFlt1 mRNA, produce a syndrome resembling human preeclampsia, including hypertension, proteinuria and glomerular endotheliosis, suggests that sFlt1 plays a role in the pathogenesis of preeclampsia [1, 15].

The exact mechanism by which (anti)-angiogenic factors are involved in the development of the typical renal phenotype during preeclampsia is unknown. However, recent evidence shows that the VEGF and its type 2 receptor have a clear role in the podocyte and slit diaphragm [16]. Overexpression of VEGF-A induces glomerular diseases [17]. The VEGF produced by the podocyte regulates the structure and function of the adjacent endothelial cell.

**RAAS**

In normal pregnancy, there are marked changes in the RAAS including considerably elevated angiotensin II (ang II) levels [15]. However, vascular resistance decreases markedly during normal pregnancy, suggesting that pregnant individuals are less sensitive to ang II than non-pregnant individuals [18, 19]. In contrast, during preeclampsia decreased circulating components of the RAAS with enhanced sensitivity of ang II infusion have been reported [5, 19, 20].

There are several possible explanations for this enhanced sensitivity of ang II infusion. First, it may be mediated through increased placental ang II type 1 receptor (AT1-R) expression, which has been specifically observed to be upregulated on the decidual or maternal side of the placenta [21]. Second, angiotensin 1–7 (ang 1–7), a counterregulator of ang II, is decreased during preeclampsia compared with normal pregnancy. Therefore, this decreased ang 1–7 in these women may play a role in the hypertension seen in these patients [22]. A third explanation is that circulating AT1-R autoantibody (AT1-AA) levels are elevated, which may explain the hypersensitivity to the effects of ang II [23]. After injecting AT1-AAs into pregnant mice and rats, hypertension, proteinuria, glomerular endothelial damage and elevated levels of anti-angiogenic factors can be seen, suggesting that AT1-AAs contribute to the pathogenesis of preeclampsia [24, 25]. However, in humans, increases in AT1-AAs are not specifically related to preeclampsia, as this autoantibody is also elevated during intrauterine growth restriction without preeclampsia [26]. Therefore, the AT1-AA could be more related to impairment in placental development (placental ischaemia) rather than mediating the preeclamptic phenotype. This is enforced by the fact that the disappearance of clinical symptoms does not require the loss of the autoantibody [27].

**Interaction between sFlt1 and RAAS**

So far, most studies on preeclampsia have focused on angiogenic factors or on the RAAS, and not on the combination of both and the interaction between the two. Below, we will point out some evidence of interaction between sFlt1 and the RAAS.
A link between the AT1-AA and angiogenic factors has been made by Zhou et al. [28]; circulating AT1-AA and ang II are capable of inducing sFlt1 production via AT1-R activation and downstream calcineurin/nuclear factor of activated T-cell signalling. Therefore, both may be responsible for placental sFlt1 up-regulation in preeclampsia. These observations extend a previous finding from the same group that ang II stimulates sFlt1 production in placental explants [29]. Moreover, Kim et al. have shown that in human proximal tubule cells, ang II induces an increased sFlt1 production of cells, which is significantly blocked by losartan [29].

Furthermore, in pregnant mice, injection of serum from preeclamptic women with AT1-AA increases the sFlt1 concentrations via the AT1-R significantly when compared with pregnant mice injected with serum from normotensive pregnant women [28]. Moreover, another study in mice shows that the AT1-AA induced hypertension, proteinuria and renal abnormalities is reduced by co-injection with losartan or infusion of VEGF_{121} [31]. In contrast, in the transgenic renin overexpression preeclampsia rat model, in which AT1-AAAs are elevated, no increase in sFlt1 concentration was found [32].

Whether a similar relation between AT1-AA and sFlt1 also exists in human pregnancy is unclear. In preeclamptic patients, some studies show no correlation between sFlt1 and AT1-AAAs [33, 34], while another study shows the titre of AT1-AAAs is significantly correlated with sFlt1 level in severe preeclamptic women [35].

In conclusion, although the exact interaction between the RAAS and sFlt is still unknown (especially in humans), the studies described above suggest that during preeclampsia the impairment in the RAAS may influence the sFlt1 production.

**After preeclampsia**

**Long-term vascular risk after preeclampsia**

Long-term vascular risk following a preeclamptic pregnancy has been recognized for many years. Already in the 1960s [35], it was shown that a history of preeclampsia increases the risk of future hypertension. A meta-analysis showed that 1885 of 3658 formerly preeclamptic women developed chronic hypertension in a follow-up time of 5–32 years. Therefore, the relative risk (RR) of a later diagnosis of hypertension in formerly preeclamptic women is 3.7 [36]. Not only the risk of hypertension is increased in formerly preeclamptic women, but they also have a higher risk of hypertension-related diseases, i.e. ischaemic heart disease, in the next 15–19 years [37]. Furthermore, another meta-analysis concluded that formerly preeclamptic women have an approximately double risk of early cardiac, cerebrovascular, and peripheral arterial disease, and cardiovascular mortality [38].

**Kidney disease after preeclampsia**

Preeclampsia is more common in women with an underlying kidney disease. On the other hand, it has been suggested that preeclampsia itself increases the risk of kidney disease later in life. From the early 1960s till 1980s, several renal biopsy studies discussed the occurrence of renal damage in women who had a pregnancy affected by preeclampsia. Zech et al. have studied the occurrence of renal injury in biopsies 3 months to 4 years after pregnancy in a series of 60 formerly preeclamptic women. In many cases, typical glomerular lesions disappeared rapidly within 6 months. However, vascular lesions remained the same or changed only very slowly. Furthermore, these vascular lesions were directly related to an increased blood pressure [39].

Although nowadays postpartum renal biopsy studies in formerly preeclamptic women are uncommon, a recent large cohort study has shown that a history of preeclampsia is a risk factor for undergoing a kidney biopsy later in life [40]. In a cohort of 756 420 women, the RR of undergoing a kidney biopsy was significantly higher in women with a history of preeclampsia {RR 12 [95% CI 3.6–6.1]. Moreover, if women also had preeclampsia during subsequent pregnancies the RR of ESRD was even higher (15.5, 95% CI 7.8–30.8). According to the authors, the association was stronger in preeclamptic women who had given birth to preterm infant or child with low birth weight, which might suggest that women with severe, early-onset preeclampsia have a higher risk of developing ESRD.

**Microalbuminuria after preeclampsia**

A recent meta-analysis concluded that 31% of formerly preeclamptic women had microalbuminuria compared with 7% of women with uncomplicated pregnancies on average 7.1 years postpartum. This prevalence is similar to that found in patients with type 1 diabetes mellitus (28% at 14 years after diagnosis) [42]. Furthermore, women have a 4-fold increased risk of microalbuminuria after mild preeclampsia and an 8-fold increased risk after severe preeclampsia, suggesting a graded relationship according to severity of the preeclamptic episode [42]. The high incidence of microalbuminuria in formerly preeclamptic women found in the meta-analysis might partly be caused by the inclusion of a study that examined women with diabetes mellitus type 1 [43]. Especially since diabetic nephropathy, which is present in 41.9% of the formerly preeclamptic women with diabetes, is associated with elevated blood pressure and endothelial dysfunction. Still, the finding that almost one-third of formerly preeclamptic women have microalbuminuria is important, given the associated risks of ESRD and cardiovascular disease. Several factors may explain the increased risk of microalbuminuria in formerly preeclamptic women: undetected hypertension and microalbuminuria before pregnancy, shared risk factors of preeclampsia and kidney disease and the fact that preeclampsia itself may damage the kidneys with scarring or incomplete healing from the endotheliosis. A potential mechanism of
long-term renal damage might be that renal damage during preeclampsia results in epigenetic changes, therefore leading to permanent kidney damage. It would be interesting to unravel the role of epigenetic changes in the development of kidney damage after preeclampsia.

Renal function parameters after preeclampsia

Although several studies, as described above, have found persistent microalbuminuria in formerly preeclamptic women several years after pregnancy, no differences were found in serum renal function parameters in formerly preeclamptic women [42]. None of these studies have shown a significant difference in serum creatinine values or creatinine clearance between formerly preeclamptic women and healthy parous controls. However, when looking at particular characteristics of renal function and performing renal function measurements in a more accurate way, abnormalities in renal function in formerly preeclamptic women can be seen.

In 1998, van Beek et al. examined renal haemodynamic values (ERPF and GFR) at least 4 months postpartum in primiparous formerly preeclamptic women and healthy parous controls [44]. These renal haemodynamic values were derived from the continuous infusion of para-aminohippurate and inulin. Although the GFR did not differ significantly between the groups, the ERPF appeared to be significantly lower in formerly preeclamptic women (482 ± 88 versus 553 ± 67 mL/min/1.73 m²). Consequently, the filtration fraction was significantly higher in formerly preeclamptic women (0.28% ± 0.04% versus 0.22% ± 0.03%). Likewise, renal vascular resistance (RVR) was also higher.

More recently, Spaan et al. compared formerly preeclamptic women with parous controls at least 20 years after pregnancy, using a similar protocol [45]. They also found a significant difference in ERPF (399 ± 61 versus 463 ± 83 mL/min/1.73m²) in formerly preeclamptic women versus controls respectively) and RVR (122 ± 28 versus 95 ± 20). Furthermore, creatinine clearance appeared to be significantly lower in formerly preeclamptic women (88 ± 15 versus 100 ± 19 mL/min/1.73m²).

According to these results, we can conclude that women who suffered from preeclampsia have abnormalities in renal function later in life. Both after short- and long-term follow-up, an increased RVR and a reduced ERPF are observed, which supports the idea that renal vasoconstriction might play a central role in the development of hypertension and renal impairment in formerly preeclamptic women.

RAAS after preeclampsia

During preeclampsia the plasma levels of ang II are decreased, while the sensitivity for ang II is increased [5, 19,20,21]. In most cases, circulating ang II levels normalize within 3 months after delivery [5, 19,20,21]. However, in one study, up-regulation of ang II was found in hypertensive subgroups of formerly preeclamptic women [5, 19,20,21]. Although there is no clear difference between formerly preeclamptic women and healthy controls in circulating ang II levels, several studies have suggested a difference in ang II sensitivity.

Three studies have examined the ang II sensitivity in formerly preeclamptic women [46,47,48]. One study showed no difference in blood pressure response to ang II between formerly preeclamptic women and healthy controls [49]. However, the two other studies conducted ang II infusion both during low- and high-sodium diet, and showed increased blood pressure responsiveness to ang II during low-sodium intake in women with a history of gestational hypertension or preeclampsia [46, 48]. Furthermore, Hladunewich et al. have shown that after stimulating the RAAS with lower-body negative pressure, a delayed increase in circulating RAAS components was found in formerly preeclamptic women [48].

Differences in results in the studies mentioned above can be explained by the use of different doses of ang II, whether or not using a standardized sodium diet and studying patients at different periods of the menstrual cycle [50]. Sodium intake has a major influence on the RAAS and ang II sensitivity, since the low-sodium diet is a strong activator of the RAAS. From the above studies, it seems that there are differences in the function of the RAAS in formerly preeclamptic women when compared with women who experienced a normal pregnancy. However, this may only be revealed under certain circumstances, such as under low salt diet. In this respect, it is of interest to mention that after pregnancy complicated by hypertension increased pressor response to a high-sodium diet, e.g. sodium sensitivity is reported [46]. This increased sodium sensitivity could lead to renal disease in the long term.

As mentioned above, a different expression of AT1-R may be involved in the enhanced ang II sensitivity found in formerly preeclamptic women. However, Hladunewich et al. could not show differences in AT1-R mRNA expression on the tissue level in skin biopsies [48]. Another explanation for the enhanced ang II sensitivity is elevation of AT1-AA levels in formerly preeclamptic women. Although AT1-AA levels decline by 50% at 1 week after delivery, Hubel et al. concluded that significantly more formerly preeclamptic women were characterized by the presence of AT1-AAs when compared with healthy controls (17.2% versus 2.9%) [51]. Because ang II increases sFlt1 production in the human proximal tubule cell, the existence of AT1-AA and increased levels of sFlt1 may be linked [29].

Concerning other RAAS parameters, no differences in plasma renin concentration and plasma aldosterone concentrations were found between formerly preeclamptic women and control pregnancies at least 4 months postpartum [44, 47, 52, 53]. However, in response to ang II infusion, aldosterone levels in women with a history of new-onset hypertension during pregnancy are significantly increased when compared with normotensive controls [46]. Another study could not confirm this increased aldosterone response [47]. Again, the difference in results might be explained by the differences in concentration and duration of ang II infusion and sodium intake.
sFlt1 after preeclampsia

Even though sFlt1 levels rapidly decrease during the first week after delivery, indicating that the large fraction of sFlt1 is derived from the placenta, increased levels of sFlt1 have been found in formerly preeclamptic women [51, 54, 55]. This persistence of increased levels of sFlt1 in formerly preeclamptic women might be due to a richer extra-placental source of sFlt1 in these women, such as endothelial cells and monocytes. Indeed, 1 year postpartum, formerly preeclamptic women showed an increased expression of sFlt1 in peripheral blood mononuclear cells [56]. This increased sFlt1 may lead to changes in the vascular endothelium which may increase the risk of renovascular diseases in later life. Interestingly, patients with CKD and decreased GFR without a history of preeclampsia present with increased plasma levels of sFlt1, which correlates positively with proteinuria [57].

However, other studies did not find a significant difference in baseline sFlt1 levels between women with a history of new-onset hypertension in pregnancy and women with a history of normotensive pregnancies [2, 46, 58, 59]. Interestingly, in one of these studies it is shown that during low-sodium balance, women with a history of gestational hypertension had a greater sFlt1 response to ang II compared with women with a history of normotensive pregnancies [46]. This not only reinforces an interaction between the RAAS and sFlt1, as described above, but also shows that it is important to take the sodium status into account when studying the interaction between the RAAS and angiogenic factors. It also shows that sodium intake could be a factor of influence in the discrepancy between the human studies on the relationship between the AT1- AA and sFlt1 as described above. This interaction between sFlt1 and the RAAS after preeclampsia is interesting and should be elucidated in future studies.

Conclusive remarks

In summary, preeclampsia is a risk factor for the development of CKD. Why preeclampsia is associated with an increased risk for developing kidney disease is still unclear. One possibility could be that both preeclampsia and CKD are caused by the same risk factors (such as hypertension, obesity, insulin resistance and endothelial dysfunction). Furthermore, the role of angiogenic factors (sFlt1) and the RAAS (AT1-AA and up-regulation of AT1-R) in the pathophysiology of both preeclampsia and CKD reinforces the described association. In regards to well-known cardiovascular risk factors, Romundstad et al. have shown that ~50% of the elevated risk of future hypertension after preeclampsia can be explained by the pre-existing risk factors [60]. Therefore, as it has been described by Sattar et al., pregnancy might be a stress test that can reveal subclinical cardiovascular and renal disease [61].

Moreover, preeclampsia itself induces deleterious effects to the kidney, revealed by persistent microalbuminuria in a subset of formerly preeclamptic women. As described above, during preeclampsia and still after preeclampsia, women have a disturbance in their regulation of the RAAS (increased sensitivity for ang II, possible by up-regulation of the AT1-R and increased AT1-AAs). This might induce persistent increased ang II sensitivity, increased salt sensitivity and altered renal haemodynamics. In addition, preeclampsia-induced endothelial dysfunction appears to remain after preeclampsia in a lot of patients [62] and is an independent risk factor for future cardiovascular and renal health. The reason for the remaining endothelial dysfunction is unknown; however, it may be suggested that preeclampsia induces epigenetic changes in endothelial cells. Endothelial cell dysfunction may also be enhanced by increased levels of sFlt1 in formerly preeclamptic women. Ultimately, these disturbances in formerly preeclamptic women lead to an increased risk of CKD (Figure 1). Future research should attempt to elucidate the exact mechanisms that underlie the complex interaction between preeclampsia and kidney disease.

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References


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