REVIEW ARTICLE

Renin–angiotensin system in pre-eclampsia: everything old is new again

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Summary: This review presents an update of the role of the renin–angiotensin system in normal pregnancy and pre-eclampsia. We have known for years that the circulatory renin–angiotensin system in pre-eclampsia is suppressed. We now know that the circulating renin–angiotensin system does not only have a vasoconstrictor arm, but also a vasodilator arm, which is upregulated in normal pregnancy; this balance is probably disturbed in pre-eclampsia. Recent studies show the importance of the local renin–angiotensin system in the uteroplacental unit for early placentation and regulation of placental blood flow. We discuss the possible role of autoantibodies against the AT1-receptor in pre-eclampsia and the suggestion that activation of the AT1-receptor in the placenta may lead to placental dysfunction and the clinical syndrome of pre-eclampsia.

Keywords: hypertension, physiology, pre-eclampsia, renin, angiotensin, placental insufficiency

INTRODUCTION

The renin–angiotensin system primarily regulates blood pressure, fluid and sodium homeostasis. As pregnancy is a state of marked vasodilation and increased plasma volume, it is evident that the renin–angiotensin system plays an important role in the establishment of these adaptations. More than 50 years ago it was noticed that the renin–angiotensin system is upregulated in pregnancy.[1,2] It has been postulated that in pre-eclampsia this system must be further activated, as observations outside pregnancy showed that such activation can lead to hypertension. However, reduced plasma renin levels have been found consistently in pre-eclampsia.[3] This finding has been poorly explained for years, despite extensive research and the realization that understanding this mechanism may give clues to the pathophysiology of pre-eclampsia.

Recently, unraveling of the s-Flt1 pathway, an anti-angiogenic factor leading to endothelial dysfunction, has given new directives for research into the renin–angiotensin system in pre-eclampsia. We now know that stimulation of the angiotensin-1 (AT1) receptor in the placenta may cause the release of s-Flt1 and other pathogenic substances. Moreover, circulating antibodies that stimulate the AT1-receptor have been discovered in pre-eclampsia. The additional new recognition that prorenin may have physiological effects raises new possibilities for a local role of this system in pre-eclampsia. The controversy of a 'suppressed' circulatory renin–angiotensin system in pre-eclampsia now seems to fit with a new model of the renin–angiotensin system in pregnancy.

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IMPORTANCE OF THE RENIN–ANGIOTENSIN SYSTEM IN PREGNANCY

The renin–angiotensin system plays an important role in the maternal haemodynamic adaptations to normal pregnancy. Pregnancy is characterized by an increase in plasma volume and marked vasodilation. The renin–angiotensin system is highly activated in order to increase sodium retention and hence plasma volume and thereby maintain blood pressure in the setting of vasodilation. We will first focus on the role of the traditional renin–angiotensin system in pregnancy, including angiotensin II and aldosterone. Subsequently, we will discuss new peptides of the renin–angiotensin system, such as angiotensin 1–7, that counterbalance the actions of the traditional system. After the role of the circulating renin–angiotensin system in the maternal haemodynamic adaptations to pregnancy, we will focus on the role of the local renin–angiotensin system in the development and function of the placenta. A timeline of the most important findings over the years is given in Figure 1.

The traditional renin–angiotensin system

In pregnancy, all factors of the renin–angiotensin system are upregulated, including angiotensinogen, renin, angiotensin I, angiotensin II and aldosterone.[4] An overview of the components of the renin–angiotensin system is presented in Figure 2. Oestrogens stimulate the production of angiotensinogen by the liver. The kidneys, ovaries and placenta contribute to the production of circulating prorenin, while active renin is mainly produced by the kidneys.[5,6] The levels of circulating prorenin are much higher than levels of active renin in pregnancy. Traditionally, prorenin has been considered as an 'inert' enzyme that only has a role once converted to active renin but it is now known that there are independent actions of prorenin through stimulation of its own (pro)renin

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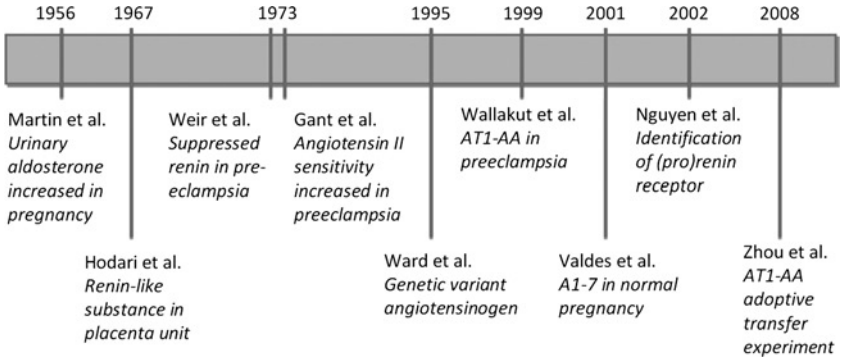

Figure 1 **Timeline of important findings concerning the renin–angiotensin system and pre-eclampsia**

receptor.[7,8] The exact role of prorenin in pregnancy still has to be established, but it seems that binding to the (pro)renin receptor activates intracellular signalling pathways directly and may contribute to angiotensin II formation independent of the circulating active renin concentration.[9–12]

Angiotensin II is a potent vasoconstrictor; however, in pregnancy marked vasodilation is observed despite high angiotensin II levels. Abdul-Karim and Assalin[13] were among the first to notice that pregnancy is a state of relative vascular insensitivity to angiotensin II. Pregnant women require about double the dose of angiotensin II infusion to reach an equal blood pressure increase.[14] This effect is apparent even within the first 12 weeks of pregnancy and there is also some refractoriness to the sodium and urate retaining effects of angiotensin II at this early stage.[15] Recent research shows that the AT1-receptor is usually present in a monomeric form and is partly inactivated in normal pregnancy by, for example, reactive-oxygen species (ROS).[16] Angiotensin II is not only a vasoactive substance, but also has angiogenic, inflammatory and proliferative functions. Angiotensin II has a high affinity to bind the AT1-receptor; however, it can also bind to the AT2-receptor which has counter regulatory actions.

High circulating aldosterone leads to sodium retention in the cortical collecting duct in the kidneys and subsequently an increase in plasma volume.[17] Although the vascular responsiveness to angiotensin II is reduced in pregnancy, the adrenal responsiveness is not. On the contrary, there is a dissociation of the renin and aldosterone levels, in such a way that aldosterone levels are higher than expected for the renin levels compared with that in non-pregnant women.[18,19] This implies that either the adrenal sensitivity to angiotensin II is increased or other factors contribute to the release of aldosterone by the adrenal glands. Earlier studies showed that non-angiotensin factors such as adrenocorticotropic hormone do contribute to the release of aldosterone in pregnancy.[20] Despite the upregulation of the renin–angiotensin system in pregnancy, the system seems to 'reset' and still responds adequately to high- or low-salt diets, saline loading or upright posture.[3,21,22]

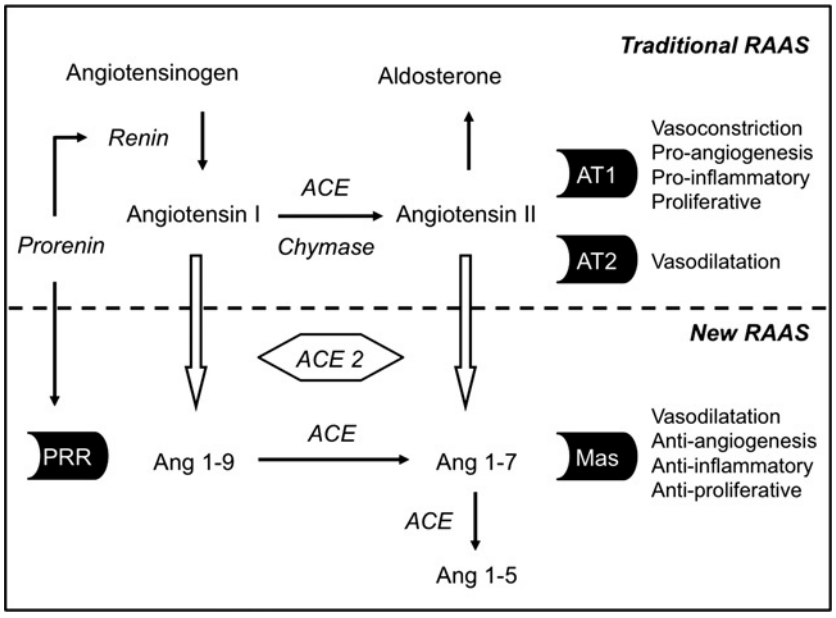

Figure 2 **Overview of the traditional and new renin–angiotensin systems (RAAS)**

The 'new' renin–angiotensin system

Although we have always thought of the renin–angiotensin system as 'defending' the vasodilatory state of normal pregnancy, it is now possible that some newly discovered factors of the renin–angiotensin system may contribute to this vasodilation directly. Angiotensin II, with its main actions through the AT1-receptor, was considered the most important biologically active end-product of the renin–angiotensin system. However, further cleavage of this octapeptide is possible, leading to formation of a heptapeptide called angiotensin 1–7. Angiotensin 1–7 has its own Mas-receptor that exerts actions counterbalancing the traditional renin–angiotensin system.[23,24] The main effects are vasodilation, anti-angiogenesis, anti-inflammation and anti-proliferation. Besides this, angiotensin 1–7 may contribute to the regulation of plasma volume as it possibly serves as an aquaretic, increasing water diuresis.[25]

Recent studies have shown that in pregnancy not only the traditional vasoconstrictor arm, but also the vasodilator arm of the renin–angiotensin system is upregulated. High angiotensin 1–7 levels are found in serum and urine of pregnant compared with non-pregnant women.[26,27] This led to postulate that the balance between these two arms of the renin–angiotensin system is important and, in normal pregnancy, favours vasodilation. Blockade of the vasoconstrictor pathway by an angiotensin-converting enzyme (ACE)-inhibitor in pregnancy leads to a drop in blood pressure that is larger than in non-pregnant women,[28] implying a fair degree of dependence on the vasoconstrictor arm of the renin–angiotensin system in normal pregnancy to 'defend' against the actions of the vasodilator arm.

In summary, both arms of the renin–angiotensin system contribute to the maintenance of blood pressure in pregnancy and the increase in plasma volume. An overview of the effects of the circulating renin–angiotensin system in pregnancy is presented in Figure 3a.

The local uteroplacental renin–angiotensin system

Besides the circulating renin–angiotensin system, there is a complete local renin–angiotensin system in the uteroplacental unit.[29,30] A local renin–angiotensin system can be found in many organs, such as the heart, brain and adipose tissue; we have only begun to discover its role in many regulatory processes such as angiogenesis, inflammation and proliferation.

In the placenta, the renin–angiotensin system is found in cytotrophoblast, decidua and endothelium.[31,32] The renin–angiotensin system has both secretory and vasoactive actions in the placenta. A lot of work to explore the role of the uteroplacental renin–angiotensin system in pregnancy is either done in animal models or *in vitro* using placental material, limiting immediate implications for human pregnancy. Nevertheless, these studies showed that stimulation of the AT1-receptor on trophoblast cells can induce the release of many regulatory factors, such as estradiol, endothelin-1, placental growth factor and ROS.[33–36] AT1-receptors are highly abundant in vessels on the fetal side of the placenta and both angiotensin II and angiotensin 1–7 may directly influence placental blood

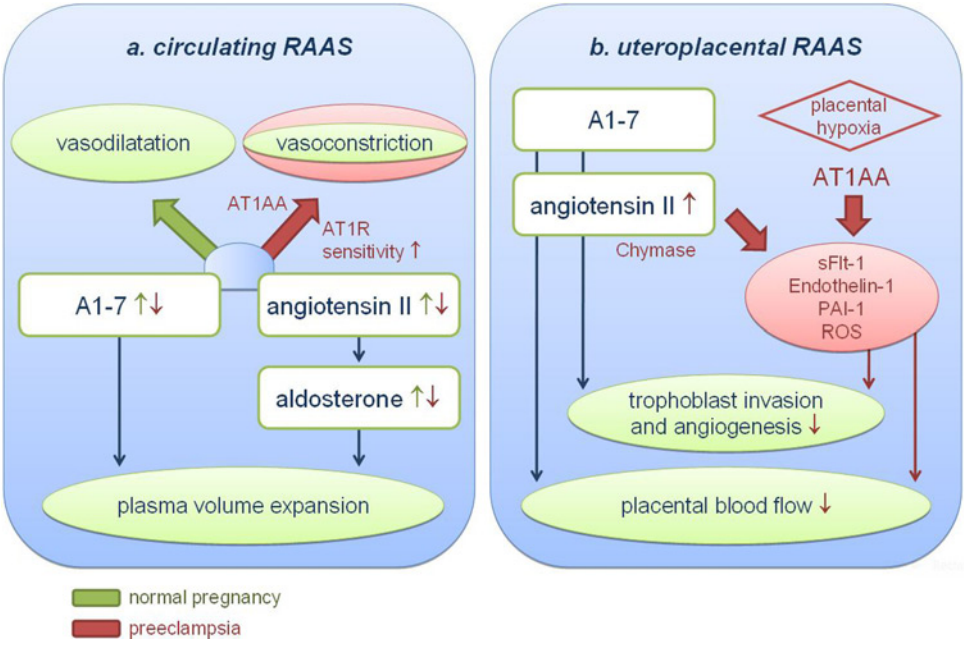

Figure 3 **Main actions of the 'new' renin–angiotensin system (RAAS) during pregnancy and pre-eclampsia in (a) the circulating system and (b) the uteroplacental unit. (a) In normal pregnancy the renin–angiotensin system is up regulated and contributes to the establishment of plasma volume expansion. The balance between circulating A1–7 and angiotensin II favours vasodilation. In pre-eclampsia the renin-angiotensin system is down regulated. Relatively low A1–7 levels in the presence of AT1-AA and increased AT1-receptor sensitivity may result in a shift favouring vasoconstriction.(b) In normal pregnancy both A1–7 and angiotensin II contribute to the regulation of trophoblast invasion and angiogenesis. In pre-eclampsia, over activation of the AT1-receptor in the uteroplacental unit by AT1-AA or angiotensin II may cause the release of pathogenic substances, leading to impaired placentation and reduced placental blood flow**

flow.[37–39] On the maternal side, the invasion of trophoblast cells into spiral arteries is induced at least in part by activation of AT1-receptors.[40] Activation of mineralocorticoid receptors by maternal aldosterone also appears to be required for trophoblast growth and normal placental function.[41] It therefore seems that the uteroplacental renin–angiotensin system plays an important role in trophoblast invasion, angiogenesis and placental blood flow (Figure 3b).

THE RENIN–ANGIOTENSIN SYSTEM IN PRE-ECLAMPSIA

Pre-eclampsia is characterized by vasoconstriction and reduced plasma volume compared with normal pregnancy.[42,43] Contrary to what would be expected in a state of primary volume reduction, the circulating renin–angiotensin system is suppressed in pre-eclampsia almost down to levels seen in non-pregnant women.[44] Plasma active renin, angiotensin II and aldosterone concentrations are all lower in pre-eclampsia.[45] However, total renin concentration (active renin and prorenin together) is similar compared with normal pregnancy, meaning that there is a relatively high prorenin in pre-eclampsia.[46] This was always thought to mean that part of the pathophysiology of pre-eclampsia was the inability to convert prorenin to active renin but now that we know that prorenin has biological actions on its own, this opens up the possibility that there is a direct role for prorenin in pre-eclampsia in stimulating local angiotensin production.

Studies suggest that both urinary and plasma angiotensin 1–7 levels are reduced in pre-eclampsia compared with normal pregnancy and that the balance between angiotensin II and angiotensin 1–7 may be disturbed.[26,27] This would favour the vasoconstrictor arm of the renin–angiotensin system, perhaps leading to hypertension despite 'low' circulating levels of angiotensin II and aldosterone.

Moreover, in pre-eclampsia the vascular responsiveness to angiotensin II is increased.[14] Many explanations have been proposed for this observation, including impaired vasodilation as a consequence of reduced prostacyclin production or enhanced vasoconstriction due to endothelin or thromboxane A2.[47–49] Although these explanations remain plausible, it has been recently found that the monomeric AT1-receptor that is usually present in normal pregnancy is present in an heteromeric form in pre-eclampsia; this receptor appears insensitive to inactivation and highly sensitive to binding by angiotensin II.[16]

Thus, as depicted in Figure 3a, the relatively low angiotensin 1–7 levels in combination with the increased sensitivity to angiotensin II and altered AT-1 receptor conformation means that the renin–angiotensin system favours vasoconstriction in pre-eclampsia.

A few longitudinal studies have observed that the circulating renin–angiotensin system is suppressed mainly during the clinical phase of pre-eclampsia but not in the preclinical phase.[42,50,51] This suggests that the suppressed circulating renin may be secondary somehow to the clinical syndrome of pre-eclampsia. This is the opposite to that expected in the face of volume contraction, but it is possible that there is enhanced intra-renal renin sensitivity to feedback suppression by angiotensin II or that impaired renal prostacyclin production contributes to impaired renin stimulation in pre-eclampsia;[52] this remains conjecture for now. The regulation of renin release by physiological stimulation or suppression (such as salt loading, head-up tilt test and ambulation) is still intact in pre-eclampsia, meaning that renin release has been 'reset' around this new low level.[3,22]

Another possibility is that the low level of angiotensin peptides or aldosterone in pre-eclampsia is caused by a deficiency in enzymatic pathways. Reduced activity of the 18-methyloxidase component of aldosterone synthase has recently been described in pre-eclampsia.[53]

Despite lower active renin and aldosterone levels in pre-eclampsia, the dissociation between plasma renin activity and aldosterone levels remains and may be even larger than in normal pregnancy.[19,54] This relatively enhanced sensitivity of the adrenal cortex did not seem to be explained by non-angiotensin factors.[20,55,56] There must be another factor involved in this regulatory process, perhaps a placental-derived substance which is capable of inhibiting renal active renin release while increasing the vascular and adrenal sensitivity to angiotensin.[4] It is also possible that the newly discovered autoantibodies to the AT1-receptor fulfil this role. Interestingly, a recent study observed that the aldosterone-to-renin ratio correlated with an increase in vascular resistance in the uterine artery.[57]

Autoantibodies to the AT1-receptor

Wallukat *et al.*[58] were among the first in the late 1990s to notice the presence of AT1-receptor autoantibodies (AT1-AA) in pre-eclampsia. They developed a bioassay in which plasma of patients with pre-eclampsia stimulated cardiomyocytes of rats to contract and this action was blocked by an AT1-receptor antagonist. After this, several studies explored the possible role of these autoantibodies in pre-eclampsia. AT1-AA have been reported in as many as 95% of women with pre-eclampsia and seems to correlate with disease severity.[59] Strong evidence supporting a central role for AT1-AA came from an adoptive transfer experiment, in which serum of pre-eclamptic women induced features of the pre-eclampsia syndrome in pregnant mice.[60] Immunization of pregnant rats with AT1-AA induces sensitivity to angiotensin II and high blood pressure, growth restriction and placental dysfunction.[61] AT1-AA can be produced by the placenta in response to placental ischaemia.[62,63] This led to the theory that AT1-AA are capable of inducing features of pre-eclampsia in the mother and placental dysfunction and growth restriction in the fetus. Clearly many more studies are needed before we can be certain about the prevalence, physiological and clinical significance of these antibodies in pre-eclampsia but such studies will be of interest.

AT1-receptor activation and placental dysfunction

In contrast to what is found in the circulation, the uteroplacental renin–angiotensin system is upregulated in pre-eclampsia (Figure 3b). Chymase, the main factor converting AI to angiotensin II in the placenta,[49] is further upregulated in pre-eclampsia.[64] In the placenta, the levels of prorenin, renin and angiotensin II are higher in pre-eclampsia than normal pregnancy.[65,66] This local angiotensin II together with AT1-AA may lead to over activation of AT1-receptors. Animal models and *in vitro* studies show that stimulation of AT1-receptors induces the release of pathogenic factors that have been implicated in the pathogenesis of pre-eclampsia.[67] On trophoblast cells, the AT1-AA stimulate the AT1-receptor to release several pathogenic substances, such as sFlt1, endothelin-1, PAI-1 and ROS/NADPH.[40,68–70] AT1-receptor stimulation by

AT1-AA appears to cause vasoconstriction on the fetal side of the placenta, which may lead to reduced placental blood flow.[71] Angiotensin II-induced sFlt-1 secretion leads to reduced trophoblast invasion *in vitro*.[72]

Further evidence supporting the importance of the renin–angiotensin system in the aetiology of pre-eclampsia was suggested by several genetic variants of components of this system that are found to be associated with pre-eclampsia. After discovery of a molecular variant in angiotensinogen by Ward *et al.*[73] and Procopciuc *et al.*,[74] several polymorphisms in the genes encoding for angiotensinogen, ACE and the AT1-receptor were found in relation to pre-eclampsia and even fetal genetic variations in these genes may play a role. However, these findings have not been consistent and as such a genetic predisposition to pre-eclampsia due to an altered renin angiotensin system seems unlikely. Rather, there is likely to be one or more non-genetic factors that alter the regulation of this system in pre-eclampsia.

Several epidemiological studies have indicated that pre-eclampsia has lifelong cardiovascular implications.[75,76] The plasma values for active renin and aldosterone do not differ from parous controls in the years postpartum,[77] but the increased sensitivity to angiotensin II remains.[78] Moreover, the presence of AT1-AA do not regress completely after pregnancy and have been observed in the postpartum period.[79] Higher levels of soluble Flt-1, although lower than during the clinical phase of pre-eclampsia, are still observed and respond to angiotensin II infusion.[78,79] Thus, alterations in the renin–angiotensin system may contribute to the increased risk of cardiovascular disease in later life in women with a history of pre-eclampsia. Whether these alterations were induced by the pre-eclampsia event or whether they are intrinsic to the woman predisposed to pre-eclampsia will no doubt be a direction of future research.

Table 1 **Summary of the RAAS in normal pregnancy and pre-eclampsia**

Normal pregnancy	Pre-eclampsia
• The RAAS is highly activated in normal pregnancy	• The RAAS is suppressed during the clinical phase of pre-eclampsia
• The RAAS contributes to plasma volume expansion and vasodilation in pregnancy	• The balance between vasodilatory arm (A1–7) and the vasoconstrictor arm (angiotensin II) favours vasoconstriction
• The balance between vasodilatory arm (A1–7) and the vasoconstrictor arm (angiotensin II) favours vasodilation	• The sensitivity to angiotensin II is increased by AT1-AA and dimerization of the AT1-receptor
• The pressor responsiveness to angiotensin II is reduced by inactivation of the monomeric AT1-receptor	• Components of the local uteroplacental RAAS are upregulated in pre-eclampsia
• The adrenal responsiveness to angiotensin II is increased and together with non-angiotensin factors contribute to higher aldosterone for the observed renin levels	• Over activation of the AT1-receptor by angiotensin II and/or AT1-AA induces the release of sFlt-1 and other pathogenic factors by the placenta
• The local uteroplacental RAAS is involved in the regulation of trophoblast invasion, angiogenesis and placental blood flow	• Over activation of the AT1-receptor impairs trophoblast invasion, angiogenesis and placental blood flow

RAAS, renin–angiotensin system

FUTURE PERSPECTIVES

Our knowledge of the renin–angiotensin system in pregnancy and pre-eclampsia has increased substantially as summarized in Table 1. Still, several questions remain for future research. First, although it is tempting to consider the AT1-receptor autoantibodies as the 'missing link' in pre-eclampsia, explaining the suppression of the circulating renin–angiotensin system with at the same time over activation of AT1-receptors, more research is necessary to confirm the importance of this pathway in humans. For example, a study in Mexican women did not support the presence of autoantibodies in pre-eclampsia, suggesting racial differences in the circulating factors involved.[80] AT1-AA are also present in cases of fetal growth restriction without pre-eclampsia and a direct relationship with sFlt-1 levels has not been confirmed in humans.[63,81,82] So far, we do not know what exact epitope causes the production of these agonistic AT1-receptor autoantibodies.

Secondly, the interplay between pre-eclampsia and the fetal circulating renin–angiotensin system has not received as much attention, although the renin–angiotensin system clearly plays a regulatory role in the development of many fetal tissues. The amniotic fluid contains prorenin in high amounts, about 10 times the concentration in plasma from pregnancy,[6] suggesting that there is an important local role for the renin angiotensin system in fetal development and wellbeing. We know from toxicology studies that fetal kidney development is often impaired by the use of ACE- or AT1-receptor blockers in pregnancy.[83] Dysregulation of the fetal renin–angiotensin system, induced by a low protein diet in pregnant rats, leads to smaller kidneys and 30–40% less functional nephrons.[84] AT1 autoantibodies cross the placenta and may have a direct negative influence on fetal growth and the development of the kidneys and liver.[39,85] More research is necessary to explore the role of the fetal renin–angiotensin system in growth restriction and pre-eclampsia.

Finally, postulating that the AT1-receptor plays an important role in the pathophysiology of pre-eclampsia and placental dysfunction, the question arises whether blockage of this receptor or stimulation of its counterbalancing pathway may be of therapeutic benefit. The use of ACE-receptor blockers is strongly discouraged in pregnancy, as it is related to fetal kidney dysfunction and oligo/anhydramnios in the second half of pregnancy and the same observations are made for specific AT1-receptor blockers.[83] New therapeutic options may become available in the future; currently promising is the development of agents that promote the production of angiotensin 1–7, such as ACE2 therapy or A1–7 agonists.[24]

In summary, our thinking around the renin–angiotensin system in pregnancy and pre-eclampsia has changed greatly over the past decade. It now seems likely that overactivation of the AT1-receptor, whether stimulated directly by angiotensin II or AT1-AA or indirectly by prorenin, can cause the release of pathogenic factors by the placenta that probably lead to impaired trophoblast invasion and reduced placental blood flow. Subsequently, this may cause the maternal features of pre-eclampsia and the typical 'suppression' of the circulatory maternal renin–angiotensin system in this condition. Reduced levels of circulating renin, aldosterone and angiotensin II remain among the most consistently observed pathophysiological findings in pre-eclampsia; research that uncovers the mechanism behind these findings is likely to contribute to our understanding of the development of this enigmatic disorder.

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