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PREECLAMPSIA (V GAROVIC, SECTION EDITOR)

The Role of the Renin-Angiotensin-Aldosterone System in Preeclampsia: a Review

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Abstract

Purpose of Review Preeclampsia (PE) is a complex human pregnancy-specific condition and is clinically characterized by new onset hypertension and proteinuria in the second half of pregnancy. The precise etiology of PE is unknown, but much of the pathophysiology has been elucidated, and it is accepted that the disorder is multifactorial in nature. Historically, because of the presence of proteinuria, the role of the renin-angiotensin-aldosterone system (RAAS) has been considered in the etiology of PE. However, the results of studies (including maternal circulatory angiotensin II, urinary angiotensinogen, plasma renin and prorenin, AT1 receptor antibodies, and gene polymorphisms) on the role of the RAAS in the etiology of PE have proved controversial. The purpose of this narrative review was to evaluate the contemporary literature on the RAAS and its role in the pathophysiology of pregnancy.

Recent Findings The current review shows that although the RAAS has a role in the development of normal pregnancy, it does not have a significant role in the pathophysiology of PE except for the AT1-AA components. Despite many researchers having measured increases in s[P}RR and [P]RR, this may be independent of the RAAS.

Summary Our view is in keeping with contemporary thinking that the placenta rather than the RAAS plays a central role in elaborating pro-inflammatory factors (antiangiogenic and angiogenic) into the maternal circulation resulting in widespread endothelial dysfunction in all organ systems including the renal system.

Keywords Renin · Angiotensin · Aldosterone · Preeclampsia · Renin · Prorenin

Abbreviations

ACE	Angiotensin converting enzyme
ANG II	Angiotensin II
AGT	Angiotensinogen
AT1	Angiotensin 1
AT1R	Angiotensin 1 receptors
AT2R	Angiotensin 2 receptors
AT1-AA	AT1 receptor autoantibodies
Eng	Endoglin
EOPE	Early-onset preeclampsia
FGR	Fetal growth restriction
IUGR	Intrauterine growth restriction
JGC	Juxtaglomerular cells
LOPE	Late-onset preeclampsia
mRNA	Messenger ribonucleic acid
PE	Preeclampsia
PlGF	Placental growth factors
P(RR)	Prorenin receptors
RAAS	Renin-angiotensin-aldosterone system
RAS	Renin-angiotensin system
RGSG2	Regulator G protein signaling 2 gene
sFlt-1	Soluble fms-like tyrosine kinase-1
s(P)RR	Soluble pro-renin receptors
VEGF	Vascular endothelial growth factor

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Introduction

Preeclampsia (PE) is a unique condition that may occur in some women during pregnancy and is characterized by sudden onset of hypertension after 20-week gestational age which may or may not be accompanied by proteinuria (≥ 300 mg/24 h urine collection or 1+ urine dipstick in the absence of any quantitative method) in an otherwise healthy normotensive woman [1]. In the absence of the latter (proteinuria), hypertension may be accompanied by one of the following: thrombocytopenia (platelet count of < 100,000/μl), impaired liver function (abnormally elevated blood concentrations of liver enzymes—to doubling of normal concentration, severe persistent right upper quadrant abdominal, or epigastric pain which is unresponsive to medication), progressive renal insufficiency (serum creatinine level > 1.1 mg/dl or a doubling of serum creatinine concentration in the absence of other renal disease), pulmonary edema, new-onset cerebral, or visual disturbances [1, 2]. Hypertension that develops in PE is defined as systolic blood pressure ≥ 140 mmHg or diastolic pressure ≥ 90 mmHg or both, measured on two occasions at least 4 h apart. In severe cases, the systolic blood pressure may be ≥ 160 mmHg or diastolic pressure ≥ 110 mmHg which require emergency antihypertensive treatment [1].

Classification of Preeclampsia

Depending on the onset of hypertension, preeclampsia may be classified into two main types: early-onset type (EOPE) where the clinical signs occur before 34 gestational weeks and the late-onset type (term preeclampsia) where the clinical signs appear at or after 34 gestational weeks [3–5]. The late-onset type (LOPE) seems to be less dangerous, occurs in the majority (80%) of PE, and has better fetal and maternal outcomes, while the early-onset type is more serious and is responsible for high rates of maternal and fetal morbidity and mortality [3, 4, 6]. It, therefore, has been suggested that these two types have different pathological and pathophysiological features [4, 7]. It is believed that the EOPE is mainly due to incomplete transformation of the uterine spiral arterioles and hypoperfusion of the placenta with reduced nutrient supply to the fetus, resulting in signs of fetal growth restriction (FGR) [5, 8], while in the LOPE there is either no changes in spiral arteriolar remodeling resulting in overcrowding of microvilli or the diameter of the spiral arterioles is slightly modified causing overcrowding of microvilli and fetal growth may not be effected [7, 9, 10]. However, preeclampsia is also associated with changes in placental weights. It has been found that placental weights from EOPE were smaller than that of LOPE or from normal pregnant women [6]. Similar findings were observed by others [11]. Dahlstrom et al. also found that preterm or EOPE placentae were of lower weight when compared with placentas from normotensive women, while term placentas or from LOPE were of similar weight or bit lighter than placenta from normal pregnancies [12]. In addition, pathological infarcts were more common in placentas from EOPE than in LOPE or from normotensive women [6].

Despite many years of research, the pathogenesis of PE is still not clear [3]. Of interest is that recent investigators have identified vascular angiogenic biomarkers such as vascular endothelial growth factor (VEGF) and placental growth factors (PlGF) and antiangiogenic factors such as soluble fms-like tyrosine kinase-1 (sFlt-1) and endoglin (Eng) which are associated with the development of PE [3–15].

It has, nevertheless, been known that the renin-angiotensin-aldosterone system (RAAS) plays an important role in the development of non-pregnancy hypertension and there is an agreement that in EOPE there is an increased sensitivity to circulating angiotensin II (ANG II) [16]. However, its exact role in PE is known poorly or is not well established. Many researchers think the renin-angiotensin plays a role in PE. However, there is agreement that the pathogenesis of PE is multifactorial [3]. The authors further believe that RAAS plays an insignificant role in the pathogenesis of PE.

Role of RAAS in Preeclampsia

Maternal Circulatory RAAS

The etiology and pathogenesis of PE, at least in the early-onset type, is believed to be initiated by a defective spiral arteriolar remodeling which leads to reduced placental blood flow causing increased placental oxidative stress [3, 17, 18]. This then sets up the production and release of various factors/proteins from the placenta, such as sFlt-1, sEng, PlGF, and VEGF into the maternal circulation, leading to endothelial dysfunction and maternal inflammatory response, causing the maternal blood pressure to rise and proteinuria to occur [18]. In addition, several other organs and systems are affected other than the kidney [1, 2].

Circulatory Angiotensin II

In a normal pregnancy, the peripheral vascular resistance and total blood volume decrease resulting in a decrease in blood pressures (both systolic and diastolic) early in pregnancy which normalizes later on or even rises slightly whereas in PE both the peripheral vascular resistance and blood pressure (systolic and diastolic) are increased [19]. A recent study has shown that non-pregnant women require a lower dose of angiotensin II (ANG II) infusion to cause a given rise in blood pressure, compared with normal pregnant women, i.e., pregnant women appear to be resistant to ANG II administration compared with the non-pregnant state [20]. Although the maternal circulatory levels of ANG II decline after 39 weeks of

pregnancy in normal women, nevertheless, the levels were still higher than in the non-pregnant state [21••]. Women who develop PE on the other hand, at 7–10 weeks of pregnancy, require even a higher dose of ANG II infusion than normal pregnant women for a given pressor response, and thereafter the infusion levels fall below the levels in normal pregnancy [20]. It also has been found that in PE, after 10 weeks of pregnancy, the infusion levels of ANG II begin to rise, but the levels are still below that of normal pregnancy. This happens until 18th gestational week. Thereafter, there is a steady decline in infusion level of ANG II and after 32 weeks of pregnancy; however, the infusion levels are even lower than that in the non-pregnant state [20]. It has, therefore, been hypothesized that preeclamptics are more sensitive to ANG II compared with normal pregnant women [20]. Furthermore, it has been shown that the activities and plasma levels of most components of the RAAS are decreased in PE compared with normal pregnancies [22, 23, 24••].

In an excellent review on RAAS in PE, Irani and Xia indicated that a number of researchers found that most of the components of RAS are not increased but are at a lower concentration than normal pregnant women. Laskowska et al. observed that in preeclamptics, with and without intrauterine growth restriction (IUGR) compared with normal pregnancies, maternal blood angiotensin I, II, and aldosterone levels and plasma renin activity are reduced, while serum angiotensin converting enzyme activity are higher in PE without IUGR compared with normotensive pregnant women and PE with IUGR [25•].

In a recent study, using a more valid method, a bioassay method to determine ANG II concentration, it was revealed that ANG II levels are lower in PE without severe features and even lower with severe features [16]. Yet other studies have reported no differences in the level of ANG II between preeclamptics and normal pregnant women [26•], while others have reported lower levels in PE than in normal pregnant women [27]. We agree with Shah, who in his review of the role of the renin-angiotensin system in the pathogenesis of PE seems to believe that RAS especially renin and ANG II is not implicated in the development of PE [28••]. However, we do not believe that the different experiments which he proposes will be able to show that the RAS is involved in the pathogenesis of PE [28••].

Urine Angiotensinogen

Yilmaz et al. reported that urine samples of women around 35 gestational weeks had significantly higher levels of AGT (ng/ml) in normal pregnancies compared with preeclamptic and non-pregnant women [29]. Chen at al. observed a significantly lower level of urinary angiotensinogen in PE compared with women with normal pregnancies and that the urinary angiotensinogen was inversely proportional to BP levels [30]. In addition, these researchers also identified three proteins: AGT, albumin, and SERPINA1 which could be interactive and stated that further work was needed in identifying their role in PE; they nevertheless concluded that some of these could also be used in the diagnosis of PE [30]. As angiotensinogen is not able to pass through the glomerular filtration mechanism, it was concluded that the kidney tubules produce components of RAS including AGT [31]. Kobori and Urushihara in a review on intrarenal or urinary AGT in hypertension stated in their conclusion that the assessment of urinary AGT as an indicator of its use as an early biomarker for hypertension may be of importance [32]. It does appear that further research is essential on the role of urinary AGT and other related proteins such as albumin and SERPINA1 especially in identification markers for preeclampsia.

Plasma Prorenin and Renin

The initial, those prior to discovery of the prorenin receptors (P)RR and soluble prorenin receptors s(P)RR, we do not think it is relevant to review this section completely. This is because it was initially thought that prorenin was an inactive molecule with the sole purpose of giving rise to renin which was only thought to be synthesized in the juxtaglomerular cells (JGC) of the kidney [33]. It was initially thought that renin is formed from its inactive precursor, prorenin in the kidney, and renin is then secreted into the circulation when the systemic arterial blood pressure fell below normal levels or when intravascular blood volume fell [34]. Since it is an enzyme, sole function is to covert angiotensinogen, which is produced in the liver,into angiotensin I. The latter is converted to angiotensin II (ANG II) by angiotensin-converting enzyme (ACE) which is produced by endothelial cells mainly in the lungs. Angiotensin II is a powerful vasoconstrictor. Angiotensin II also acts on the sympathetic outflow to the heart and increases the heart rate and force of cardiac contractility. In addition, ANG II is also partly responsible for the formation of aldosterone which acts on the kidney tubules to conserve water. Therefore, in the presence of ANG II, the arterioles constrict, the heart rate and force of cardiac contraction increases, and water conservation by the kidney increases. Renin continues to be secreted until the normal systemic arterial blood pressure is attained at which point renin secretion ceases. Furthermore, many researchers reported varying amounts of prorenin or renin in PE versus normotensive pregnancies: with some researchers reporting no differences between PE and normotensive pregnant women [22, 35, 36], some researchers reported higher levels in PE than normotensives [37], while other researchers have reported lower levels in PE compared with normotensive pregnancies [24••, 38••, 39]. Verdonk et al. found that the level of plasma renin activity and the concentrations of plasma renin and prorenin depended on the ratio between plasma sFlt-

1 and PlGF levels; in those PE who had a ratio of ≥ 85, plasma renin activity and concentration were higher than those whose ratio was < 85, whereas plasma prorenin concentrations were not significantly different in these two groups [40]. de Leon et al. also reported that in preeclamptic women compared with normal pregnant women, plasma renin levels were significantly less during the 1st and 2nd trimester in the superimposed groups only, while the level of plasma prorenin concentration was significantly elevated during all three trimesters in the mild group only [34].

Prorenin Receptors (P)RR

However, (P)RR has been discovered to which prorenin and renin bind and are activated [41, 42]. A recent study found significantly increased plasma levels of prorenin in PE women and in rats compared with normal pregnant women and rats, respectively [43]. In the rat model of PE, the placental tissue also had elevated prorenin levels compared with normal pregnant rats [43]. In addition, the study also showed that the expression levels of P(RR) in placental tissue of PE were higher than normal pregnant rats whereas in the kidney tissue, the expression levels were similar in the two groups of rats [43]. Another study by Watanabe et al. found significantly elevated levels of plasma s(P)RR) at delivery in PE compared with normal pregnant women, but the sample size was too small to give an adequate explanation for the findings [44]. In addition, these researchers also found that the elevated plasma levels of s(P)RR in early pregnancy (before 16 gestational week) was associated with raised blood pressure levels during all stages of pregnancy [44]. However, these researchers in their conclusion could not explain whether PE increased the concentration of plasma s(P)RR or whether increased plasma s(P)RR levels affected women who later became preeclamptic. On the other hand, a recent research by other workers also showed that renin, (P)RR, and s(P)RR do not play a role in pathogenesis of PE [45••]. Sugulle et al. showed that plasma s(P)RR levels in maternal circulation in PE were below the levels found in normal pregnancies [21••].

In a recent study, Narita et al. observed that placental expression of (P)RR and maternal plasma concentration of s(P)RR are elevated in PE compared with normal pregnant women [45••]. However, these workers could not detect any correlation between plasma s(P)RR and placental (P)RR activity in all the pregnant women including PE [45••]. These researchers concluded that because placental expression of (P)RR were correlated with systolic blood pressure and not with renal function and that plasma s(P)RR levels were negatively correlated with renal function and not with plasma (P)RR, therefore, s(P)RR was produced independently from (P)RR [45••]. Newer research implicates (P)RRs and s(P)RRs as having other functions such as hypertension and increased absorption of water, etc. [41, 42, 46••].

AT1 Receptor Autoantibodies (AT1-AA)

It was first identified by Wallukat in 1999 that maternal plasma levels of AT1 receptor autoantibodies are found in PE women [47]. Purification of and identification of the antibodies showed that it belonged to the IgG fraction [47]. These workers observed that serum from preeclamptic women when applied to rat-isolated cardiomyocytes increased the beating rate, similar to the application of ANG II, and the beating rate was blocked by using losartan (is a class of drugs called angiotensin receptor blockers); these led them to the view that the IgG fraction was an AT1-AA. These researchers concluded that PE women could be treated by removal of the autoantibody [47, 48]. Dechend et al. confirmed the findings of these workers [48]. However, in 2008, Yang et al. observed that 31 of 49 pregnant women were preeclamptic and 80.6% had increased levels of AT1-AA in their sera [49]. On the other hand, only one of the 18 normotensive women had AT1-AA in their sera. These findings may mean that in the PE women, there were some with no or very little AT1-AA in their sera although the BP was raised, and in one normotensive woman, although she was positive for AT1-AA, yet she had her BP within the normal range. These researchers posited that sera from positive PE women caused significant vasoconstriction which is blocked by ANG II and therefore proving that the antibodies act on AT1 receptors. They concluded by stating that the AT1-AA isolated from PE women caused significant vasoconstriction of isolated coronary and other smaller arteries [49]. Similar findings were recently obtained by Bian et al. where isolated AT1-AA from PE women caused sustained contraction of aortic ring whereas negative AT1-AA obtained from normal pregnant women had no such effects [50]. They further showed that AT1-AA combine directly with AT-1R, and to prevent overactivation of the receptor, they presumed that a process of internalization occurs during which AT1Rs combine with ß-arrestin1/2. However, they were of the view that further studies were warranted [50].

Zhou et al. observed PE-like symptoms in mice which were administered with AT1-AA isolated from preeclamptic women [51]. These researchers further found that IgG purified from women with PE when incubated with trophoblast cells resulted in the formation of sFlt-1 and formation of the latter was suppressed by the presence of losartan in the incubation medium [51]. They also observed that purified antibodies from normotensive pregnant women had no such effect on the synthesis of sFlt-1 [51]. These finding led them to conclude that AT1-AA are formed by trophoblasts cells secrete sFlt-1 in PE [51].

Siddiqui et al. observed that administration of AT1-AA obtained from PE women to pregnant mice caused the blood pressure to rise and proteinuria to occur [52]. However, these researchers showed that continuous infusion of $VEGF_{121}$ blocked the action of AT1-AA-induced hypertension and

proteinuria [52]. Xia et al. in their review of the subject were of the view that women with PE have antibodies (AT1-AA) which are implicated in the pathogenesis of PE and that PE can be regarded as an autoimmune disease [53]. Many years later, Kobayashi et al. showed that sera isolated from PE women caused a significant increase in sEng production and mRNA expression levels from isolated trophoblast cells from PE women compared with those from normal pregnant women and that the use of losartan blocked these process thus concluding from their findings that since the use of losartan blocked the formation of sEng and its messenger RNA expression levels by trophoblasts cells that sera of PE women had AT1-AA [54]. On the other hand, Stepan et al., in an earlier investigation, were unable to correlate AT1-AA and sFlt-1 in PE [55] Siddiqui et al. showed that > 95% of women with PE have significantly raised AT1-AA in their blood, the levels of AT1-AA are raised with severity of PE, and in severe PE, they found a strong correlation among AT1-AA activity and hypertension, proteinuria, and sFlt-1 levels. What is worrying is that they also found elevated levels of AT1-AA in women with gestational hypertension and that normotensive pregnant women have AT1-AAs levels ranging from low to undetectable levels [56]. We are, therefore, of the view that in all cases, PE is not accompanied by AT1-AA as demonstrated by Stephan et al. in 2006 [55].

Gene Polymorphism of the Renin-Angiotensin-Aldosterone System

Yang et al. in an excellent review of the literature stated that they found many studies to be controversial in the findings on the role of gene polymorphism of RAAS and the risk of development of PE, and while many studies showed a positive correlation between gene polymorphism and the risk of developing PE, they nevertheless suggested that more meticulously and large-scale studies are needed to prevent interference from various factors to show a positive correlation between gene polymorphism and the risk of developing PE [57]. In their review, Yang et al. alluded to the fact that daughters and sisters of preeclamptic mothers had a much higher incidence of the disease than daughters or sisters of normotensive mothers. In addition, these researchers also mentioned paternal contributions to the disorder; e.g., fathering a preeclamptic child was seen among fathers who had previously fathered a preeclamptic person with another partner. In addition, these reviewers also drew to the attention of their readers that polymorphism of the genes concerned with RAAS also plays a role in preeclampsia [57]. Readers interested in reading early research work done in the 1990s and early 2000s are advised to read this review.

In the association of gene polymorphism and essential hypertension in Han Chinese population, Ji et al. studied 41 SNPs of the RAAS [58]. Of these 41 SNPSs, they found 6 SNPs—rs3789678 and rs2493132 within AGT, rs4305 within ACE, rs275645 within AT1R, and rs3802230 and rs10086846 within CYP11B2— to be significantly associated with development of essential hypertension. Li et al. recently (2016) studied six SNPs of the RAAS also in a Chinese population for gene polymorphism and the risk of development of PE and found that gene polymorphism of ATRI rs275645 GG may reduce the risk of developing PE [59]. They then looked at age categories and possible effect on DNA methylation. For the < 30 age group, these researchers observed that for only AT1R (3q24) rs275645 GG genotype, gene polymorphism was negatively associated with PE development while those > 30 years old and carrying a GA OR AA genotypes increased the risk of developing PE [59]. In addition, these researchers also concluded that ACE D/I polymorphism was associated with increased proteinuria, but they felt that gene-gene interaction was possibly responsible for their findings, but they nevertheless felt that a larger sample size was warranted [59].

In a study by Rahimi et al., it was reported that the presence of G allele of AT2R-1332 G:A polymorphism increased the risk of development of PE [60]. In addition, it was also observed that the presence of both alleles of AT1R 1166C and AT2R-1332 G was associated with the development of mild PE. These researchers also observed increased risk of PE in the presence of both ACE D and AT2R alleles that gave rise to the risk of severe PE and in the presence of both MMP-9 and AT2R G alleles; however, they were of the view that this finding remains to be proven and concluded that their findings suggest that RAS together with gene-gene interactions would play a role in the pathogenesis of PE [60]. Akbar et al. conducted a similar study in three groups of women: Afro-Caribbean, Asian, and Caucasian in origin, and their sample consisted of 236 women with PE or eclampsia and 426 normal pregnancies [61]. They observed a significant association between GG genotype of AT2R at position 1667 and PE only in Afro-Caribbean population but no association of gene polymorphism of AT1R (A1166C) and PE in any of the population groups [61]. They speculated that gene-gene interactions could have been the cause of the differences [61].

A metanalysis by Chen et al. found that that a number of publications showed a significant association between the risk of development of PE and DD variant of ACE polymorphism especially among Caucasians and Asians [62]. Bogacz et al. in their study of gene polymorphism of CYP11B2, though they showed in a table that there was no significant difference in the frequency of TT genotype between the PE and normal control women, yet these workers in the discussion section stated that there was a significant difference [63].

Kvehaugen et al., in a Norwegian study, studied three SNPs: rs5433, rs5186 of ATR1 system, and rs4606 of regulator G protein signaling 2 gene (RGSG2) polymorphism and the risk of developing PE and found that women carrying

rs4606 CG or GG genotypes were more susceptible [64]. They found no association with other two SNPs. They concluded that further research on regulator G protein signaling pathway should be undertaken to show that it plays a role in preeclampsia development [64]. Bouba et al. studied gene polymorphism of the three most common components of RAS: M235T polymorphism of AGT gene, insertion/deletion polymorphism of ACE gene, and A1166C polymorphism of the AT1R gene [65]. They found that the frequency distribution of homozygotes for T allele of M235T was significantly higher in preeclampsia compared with control pregnancies; however, for other two genotypes, they did not find any significant differences [65]. However, no significant differences in gene polymorphisms of AGT and ACE genes were observed by Kim et al. in Korean women [66] nor in Japanese women [67] nor of ACE I/D gene polymorphism in PE by Kaur et al. [68]. Salimi et al. studied Iranian women for ACE I/D and AT1R AC1166 polymorphism and their associations with development of PE [69]. The study found that there was a significant association in genetic and allelic frequency of ACE I/D polymorphism between PE and normal pregnant women but no association of gene polymorphism of AT1R AC1166 between PE and normal pregnancies [69].

Another metanalysis of 23 studies looked at I/D of ACE gene polymorphisms. Overall, 1620 cases of PE and 2158 control participants were analyzed for intron 16 insertion/deletion ACE polymorphism [70]. The analysis showed that no clinical significance was observed with ACE gene, and they concluded that further studies were warranted [70]. Knyrim et al. investigated German women and found that there was no influence of AGT gene polymorphism on the risk of developing PE [71]. Li et al. also did not find in any association in ACE I/D and in AT1R gene polymorphism and development of PE in Chinese women [72]. In a metanalysis consisting of 22 studies, Ne at al. analyzed 2367 PE and 5167 controls and concluded that TT genotype of AGT M235T polymorphism was associated with increased risk of developing PE [73].

In another metanalysis of ACE insertion/deletion polymorphism in a Chinese population, Zhong et al. searched 11 publications on the risk of developing PE [74]. Their analyses consisted of 800 PEs and 949 controls. They showed that Chinese women having D allele of ACE gene made them to be significantly associated with the risk of developing PE [74]. In a separate study, Miskovic et al. observed a positive association between D allele of ACE gene and the risk of developing recurrent PE [75]. These researchers concluded that the D allele of ACE gene could be an important factor in the development of early-onset and recurrent PE [75]. Another metanalysis was conducted by Zafarmand et al. (2008) on the role of angiotensinogen gene M235T polymorphism and the risk of developing PE [76]. Their analyses showed that individuals who were homozygous T allele of angiotensinogen gene were significantly associated with development of PE [76].

A recent study was done in our laboratory on the role of gene polymorphism of the components of RAAS. The sample size was 433 in PE and 246 in the normotensive control groups. We showed that T allele of TT genotype of AGT (M235T) plays a role in the risk of development of PE [77], while polymorphism of genotype TT of CYP11B2 protected pregnant females from developing a risk for PE [78].We found that polymorphism of the other genes of the components of RAAS (ACE, renin, AT1R, and AT2R) did not play a role in the development of PE. In addition, our laboratory has also shown that maternal plasma level of s(P)RR is higher in PE compared with control normotensive pregnancies either in the early-onset or late-onset groups [79].

Seki believes that the RAS system could be playing an important role in the development of hypertension in PE and dwells upon the role being played by AT1-AA in generating hypertension but forgets about the role played by the anti-angiogenic and angiogenic factors produced by the placenta which enter the maternal circulation and cause endothelial dysfunction which in turn cause hypertension and proteinuria and affect the functioning of other systems and organs [80, 81, 82••, 83, 84].

Conclusion

We believe that particularly in early-onset PE, the elaboration of proteins or factors by the placental tissue enter into maternal circulation and, in turn,these substances cause maternal endothelial dysfunction which then result in hypertension, elaboration of proteins in the urine, liver abnormalities, CNS problems etc. Thus, the RAAS is not affected. In fact, maternal plasma levels of renin, angiotensinogen, angiotensin-converting enzyme, AT1R, AT2R, and aldosterone will not be expected to change. We support the view of Shah who believes that RAS, especially renin and ANG II, does not play a role in PE [28••]. Nevertheless, many researchers have measured an increase in s(P)RR l and (P)RR levels. We tend to agree with Sugulle et al. that s(P)RR and (P)RR may not be related to plasma pro-renin or renin to PE but may be related to diabetic pregnancies and independent of RAS [21••]. We also tend to agree with others who have stated that the placenta plays a pivotal role in elaborating factors which enter the maternal circulation where they lead to the pathophysiology of PE [8, 81, 82••, 83, 84]. We also believe that the RAAS, except for the role of AT1-AA, plays an insignificant role in PE.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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