CHAPTER 8

GENERAL DISCUSSION
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Historically, medical research has been focused on men, with current medical knowledge and practice mainly based on single-sex studies. However, logically, not all knowledge, gained primarily in males, may be transferable to females. Nowadays, increasing evidence from several biomedical fields reveals that men and women differ in their basic physiology, the susceptibility to and progression of disease, and the response to therapy. Many of these gender differences in medicine have the potential to affect our daily practice of medicine and research. Elucidation of the mechanism behind gender disparities will not only help explain why women or men are more prone to certain diseases, but also may translate into gender specific treatment and subsequently better outcomes in men and women.

In this regard, awareness of gender differences in overall risk and in risk profiles for development of cardiovascular and renal disease is increasing as well. It is well recognized that in general premenopausal women are protected from chronic kidney disease (CKD) and cardiovascular disease (CVD) compared to men. Moreover, men and women face gender specific risk profiles, as it has been shown that the impact of well-established renal and cardiovascular risk factors, like proteinuria and blood pressure, differs between the sexes. Finally, there are risk factors that occur in women only, namely those related to pregnancy and its complications, like preeclampsia. Preeclampsia is a pregnancy-specific disease, characterized by de novo development of hypertension and proteinuria in the second half of pregnancy. Evidence has mounted that women that have suffered preeclampsia, especially early-onset preeclampsia, have an increased risk for cardiovascular- and renal diseases later in life.

The mechanism behind the gender differences in the susceptibility to cardiovascular and renal disease and the increased cardiorenal risk in formerly preeclamptic women is not completely understood. The studies described in this thesis shed new light on the role of the renin-angiotensin aldosterone system (RAAS; chapter 2-4) and alterations in renal hemodynamic function and volume status (chapter 5-7) as possible mechanisms involved in gender differences in the risk for renal and cardiovascular disease, and the increased risk in formerly preeclamptic women.

Gender differences in response to angiotensin II

In the last few years, gender differences in the components and regulation of the RAAS have been recognized to be of functional importance. Although data is limited, it has been shown that men and women respond differently to RAAS inhibition. Furthermore, in several animal studies, it has been shown that females are less sensitive to exogenous stimulation of the RAAS than males. In chapter two we
investigated gender differences in the response to ang II infusion with a translational approach. In healthy humans we showed indeed an increased response of blood pressure to acute ang II infusion in men. Furthermore, this was accompanied by a stronger renal vasoconstrictor response to ang II in men. However, to substantiate relevance for chronic renal damage, it is crucial to demonstrate differences in the response to chronic angiotensin II administration as well. Concordant with our acute human data and the available animal data on chronic ang II infusion so far, we found a more rapid increase in blood pressure during a three-week ang II infusion in male rats compared with females. Moreover, male rats developed more proteinuria and intrarenal inflammation after ang II infusion. However, the differences in ang II induced proteinuria and macrophage infiltration were not associated with differences in the (mild) pro-fibrotic changes in the kidney. Therefore, our data, albeit consistent with a role for larger ang II responsiveness in the susceptibility of males to cardiorenal damage, do not provide conclusive proof, and would need to be complemented by infusion-studies of longer duration to ascertain whether the differences in ang II-associated proteinuria and inflammation could result in differences in renal damage on long term.

**Gender differences in expression and function of the angiotensin II receptors**

Differences in responsiveness to ang II between males and females could be due to difference in expression and function of the ang II receptors (AT1 receptor and AT2 receptor). Next to the classical ACE/ang II/AT1 axis, a new depressor arm has been identified within the RAAS, including angiotensin converting enzyme 2 (ACE2), ang (1-7) and its receptors (Mas receptor and AT2 receptor). This new pathway counter-regulates the classical ACE/ang II/AT1-receptor pathway and exerts protective effects against an overstimulation of the AT1 receptor. In our study, we found a higher expression of the AT2 receptor in the kidney in females compared with males, which is in line with the assumption that the AT2 receptor plays a role in the decreased responsiveness to ang II of females.14,17,18 The results of our *ex vivo* aorta experiments confirmed this assumption; we found that the relaxation response to ang II via the AT2 receptor was higher in females compared with males. These differences in RAAS regulation, including the presence and function of the AT2 receptor, could potentially be involved in the gender differences in development of renal disease as well as response to therapy. Our data warrant further research into the gender differences in RAAS regulation, to allow better insights in the differences in renal risk profile and allow to appropriately include gender factors in treatment recommendations for men and women.

**From preeclampsia to renal disease: the role of the renin-angiotensin aldosterone system and angiogenic factors**

Differences in regulation of the RAAS between both sexes can also be inferred from the marked changes in the RAAS in women during pregnancy, including a sharp rise in circulatory ang II levels associated with a sharp decrease in vascular sensitivity to ang II.19,20 In contrast, in preeclampsia this protective decrease in vascular ang II sensitivity is incomplete or absent. The exact explanation for this enhanced sensitivity to ang II...
during preeclampsia is not understood, but a decrease in ang 1-7 levels, increased vascular and placental AT1 receptor expression, due to altered hemopexin cleavage of the AT1 receptor and/or elevated circulating AT1 receptor autoantibodies (AT1-AA) levels might be involved. Regarding the latter, it has been shown that after injecting AT1-AA into pregnant mice and rats, hypertension, proteinuria, glomerular endothelial damage, and elevated levels of anti-angiogenic factors can be seen. Although the exact pathogenesis of preeclampsia is still incomplete, these findings suggest that the RAAS might contribute to the pathogenesis of preeclampsia.

In addition to the disturbances in the RAAS, imbalance of proangiogenic and anti-angiogenic factors has been implicated in the pathogenesis of preeclampsia. Recent observations showed that the placenta-derived anti-angiogenic proteins soluble Fms-like tyrosine kinase-1 (sFlt1) and soluble endoglin (sEng) are elevated in the maternal circulation a few weeks before the onset of preeclampsia. Elevated sEng (a TGF-β co-receptor) and sFlt1 (a soluble form of vascular endothelial growth factor (VEGF) receptor 1) might lead to endothelial dysfunction and therefore decreased endothelium dependent vasodilation and proteinuria. Furthermore, the fact that increasing the circulating sFlt1 levels in gravid mice and rats produced a syndrome resembling human preeclampsia, including hypertension, proteinuria and the typical glomerular endotheliosis, suggests that sFlt1 plays a role in the pathogenesis of preeclampsia. The exact mechanism by which (anti)-angiogenic factors are involved in the development of the typical renal phenotype during preeclampsia is not known. However, evidence shows that VEGF has a clear role in the development and function of the glomerulus, in particular the podocyte and slit diaphragm.

Hence, a consistent line of evidence has identified disturbances in the RAAS and an imbalance of proangiogenic and anti-angiogenic proteins as a key factor in the development of preeclampsia. Furthermore, animal studies suggest that impairment in the RAAS may influence the sFlt1 production, which reinforces an interaction between these two systems. Also the increased level of AT1-AA might lead to increased production of sFlt1 leading to changes in the vascular endothelium. Interestingly, patients with CKD and decreased GFR without a history of preeclampsia present with increased levels of sFlt1 too, which correlates positively with proteinuria (ref review). Thus, since the imbalance of the RAAS and imbalance between angiogenic and anti-angiogenic factors are also common in CKD, this might also explain why a history of preeclampsia predisposes women to develop CKD (chapter three). To substantiate this assumption, it would be important to see whether the altered RAAS-activity or sensitivity of preeclampsia persists after pregnancy, and hence could be involved in the increased cardiovascular and renal risk in these women.

The renin-angiotensin aldosterone system after preeclampsia

Although the elevated circulating ang II levels during preeclampsia normalize within three months after delivery, there is evidence to suggest that ang II sensitivity is still enhanced after preeclampsia. Three human studies in women with a prior hypertensive pregnancy/preeclampsia report on ang II sensitivity, and generally report increased ang II sensitivity. However, in those studies many subjects had comorbidity (i.e hypertension/obesity). Moreover, study conditions were not standardized for phase
of the menstrual cycle and for sodium status, factors that exert considerable effects on RAAS-activity and –responsiveness. Hence, the available studies do not allow to conclude that preeclampsia as such is a causal factor in altered ang II sensitivity in formerly preeclamptic women. Therefore, in chapter four, we investigated ang II sensitivity in otherwise healthy formerly early-onset preeclamptic women in comparison to healthy controls during rigorously standardized condition. While baseline blood pressure was similar between both groups, we found a trend towards a larger increase in blood pressure in response to ang II in the formerly early-onset preeclamptic women. Although the differences are subtle, our findings suggest that otherwise healthy women still have disturbances in their RAAS after preeclampsia, that cannot be attributed to co-morbid conditions, and that might be involved in the increased risk for cardiovascular diseases in formerly preeclamptic women.

The question whether the enhanced ang II sensitivity in formerly preeclamptic women and the associated increased renal and cardiovascular risk is explained by preeclampsia itself, or by underlying common risk factors and comorbidity is an important one. So far, it has been mostly hypothesized that common pre-existing vascular/metabolic risk factors (such as hypertension, obesity, insulin resistance, and endothelial dysfunction) cause both preeclampsia and later cardiovascular and renal disease. Therefore, as it has been described by Sattar et al., pregnancy might be a stress test that can reveal subclinical cardiovascular and renal disease. However, epidemiological studies revealed that preeclampsia itself could also induce deleterious effects in the kidney (ref’s Vikse (familial study) and Chamber). Since in our study (chapter four), we carefully selected healthy normotensive Caucasian formerly preeclamptic women, without co-morbidity, with a body mass index (BMI) < 30 kg/m² and excluded hypertensive formerly preeclamptic women, our results suggest that preeclampsia itself might induce persistent increased ang II sensitivity.

Furthermore, to investigate cause and effect relationships between preeclampsia and post-partum ang II sensitivity in a clean model, we studied blood pressure and kidney response to chronic ang II infusion after experimental preeclampsia. The responses of blood pressure and proteinuria were increased in the formerly preeclamptic rats compared with healthy pregnant rats and non-pregnant rats exposed to LPS. Thus, in line with our human data, our experimental study suggests that preeclampsia per se leads to subtle long-term increased blood pressure and proteinuria in response to acute and chronic ang II infusion. Therefore, our results favor the hypothesis that it is also preeclampsia itself and not only pre-pregnancy common risk factors that play an important role in the increased risk for cardiovascular and renal diseases later in life in formerly preeclamptic women.

Balance between AT1-receptor and AT2-receptor after preeclampsia

As described above, the mechanism of increased ang II sensitivity during and after preeclampsia is not completely understood. AT1-AA and sFlt-1 might be involved, since increased levels of AT1-AA and sFlt-1 after preeclampsia are described. The study of Hladunewich et al. suggested that the balance between the AT1 receptor and AT2 receptor could be involved. Indeed, our data suggest differential regulation of the AT1 receptor and AT2 receptor in and after preeclampsia (chapter four). In the thoracic
aorta of the formerly preeclamptic rats, a decreased ex vivo responsiveness of the AT2 receptor to ang II was shown, which might contribute to the increased blood pressure response upon ang II. In contrast to the situation during experimental preeclampsia, we did not find an increased ex vivo responsiveness of the AT1 receptor to ang II. Thus, although we may have observed changes in ang II sensitivity during and after preeclampsia in the rat, during preeclampsia they appeared to be induced by the AT1 receptor, while after preeclampsia they appeared to be induced by the AT2 receptor. As described above it has been suggested that the AT2 receptor plays a role in the decreased responsiveness to ang II in females. It seems that after preeclampsia the protective effects of the depressor arm of the RAAS (ACE2/ang (1-7)/AT2 receptor/Mas receptor) is less pronounced. The consequences of this dysbalance for preventive measures for premature cardiovascular and renal disease after preeclampsia warrants further investigation.

The potential of renal hemodynamics in the pathogenesis of renal damage
One of the main functions of the RAAS is the regulation of renal hemodynamics, by regulation of post-glomerular efferent arteriolar tone. The unique characteristics of the glomerulus and renal circulation, with a resistance vessel not only before, but also after the glomerular capillaries ensures tight regulation of glomerular filtration pressure. This ensures a constant glomerular filtration rate as well as protection of the glomerular capillary bed from the harmful impact of elevated arterial blood pressure. Glomerular hemodynamics also affect the hydrostatic pressure in the downstream vascular bed, namely the peritubular capillaries, thus modulating the Starling forces involved in regulation of tubular reabsorption, and medullary perfusion. Thus, regulation of renal hemodynamics also affects sodium and volume status. Derangements in renal hemodynamics therefore, can affect renal perfusion and glomerular filtration rate by short-term functional changes, but can also lead to structural renal damage on long term by loss of protection of the glomerular capillaries, and moreover, affect volume status and hence blood pressure. As elevated blood pressure is a main factor in kidney damage, a vicious circle can ensue, resulting in ongoing renal function loss. These insights have been derived from animal experiments in the ‘80s, mainly in remnant kidney models, providing convincing evidence for the pathogenic role of elevated glomerular pressure in progressive renal damage. Moreover, these studies showed that ang II was the main mediator of inappropriately high efferent vascular tone, and accordingly, RAAS-blockade turned out to be particularly effective to break this vicious circle, reduce systemic and glomerular arterial pressure and protect the kidney from long term renal damage. Human data, however, have been lagging behind considerably for a long time, to the extent that it was questioned “whether there is a human model for the 5/6 the nephrectomy rat”.

In chapter five, we review the current state of the art on the implications of renal hemodynamic alterations for long-term renal risk, with emphasis on its role in human conditions of renal damage, in particular overweight. Overweight is assumed to become the main cardiovascular and renal risk factor in the 21st century, not only in the developed world, but also in emerging countries. It is closely associated with hypertension, and one of the main co-morbidity in preeclampsia. Weight excess and
central body fat distribution is associated with an altered renal hemodynamic profile – i.e. an increased glomerular filtration rate (GFR) relative to effective renal plasma flow (ERPF), resulting in an increased filtration fraction (FF). This renal hemodynamic profile is considered to reflect glomerular hyperfiltration and glomerular hypertension, resulting from a dysbalance between afferent and efferent arterial vasomotor balance, as documented by direct measurements by micropuncture in the animal models mentioned above. Considering the long term course of renal damage in human, that typically extends over decades, it is perhaps no surprise that the first data linking an elevated FF to adverse long term renal outcome was only recently obtained, in a study in renal transplant recipients.\(^{39}\)

Also in overweight subjects it can be seen that sodium homeostasis is closely interlinked with renal hemodynamics. In young normotensive subjects, overweight is associated with a rise in FF in response to high salt intake, whereas in lean subjects GFR increases without a rise in FF. Moreover, in overweight subjects, high salt intake is associated with a larger increase in the extracellular volume (ECV) than in lean subjects, supporting the impact of subtle changes in renal hemodynamics on volume homeostasis.\(^{40}\) The long-term consequences of this unfavourable renal hemodynamic profile, elicited by the combination of overweight and excess sodium intake, have not been documented, but it may well contribute to development of salt-sensitive hypertension and renal damage later in life. Data from our group, published in abstract form, indicate that higher ECV is associated with a higher long term risk for cardiovascular events, even independent of blood pressure, in renal transplant recipients.

**Gender differences in renal hemodynamics and volume status: role of the RAAS**

Many studies describe differences in renal function, blood pressure, and RAAS-activity between men and women. It would be logical to assume that such differences could be involved in the differences in the long-term risk for cardiorenal damage between men and women. Yet, on closer scrutiny the available studies are difficult to interpret, as studies did not standardize sodium status, or phase of the menstrual cycle, which could considerably affect the results. We therefore made a systematic comparison of men and women, during standardized sodium intake and during a standardized phase of the menstrual cycle (chapter six). Two different levels of standardized sodium intake were studied – both within the range that is generally encountered in the general population in The Netherlands. By this systematic approach, we identified interesting differences between men and women.

First, we found consistent differences in the circulating components of the RAAS. For a given sodium intake, active plasma renin concentration was lower, and aldosterone level higher, in men. The changes induced by altered sodium status ran in parallel in men and women. As a consequence, for either sodium intake, the ratio of APRC to aldosterone was higher in men. The differences could not be attributed to differences in potassium intake, and, by inference, might be explained by estrogen effects on the female adrenal. Corresponding data have been obtained in hypertensive populations, and in unselected, non-standardized samples from the general population, rendering credibility to our findings.\(^{41}\) No data were available so far on the (patho-) physiological consequences of the gender differences in aldosterone level. Our study demonstrates...
a consistently and substantially higher extracellular volume in men, at both sodium intakes. Moreover, this is associated with a higher blood pressure. The higher ECV could also explain the lower APRC in men, as volume expansion suppresses renin release. Taken together, the interaction between RAAS-activity and volume status in men can be characterized as a state of mild, subclinical hyperaldosteronism, as compared to women. It is tempting to speculate that this different RAAS-volume profile is involved in the gender differences in long-term cardiorenal risk, but it must be mentioned that the generalizability of our data is not straightforward, as we studied one phase of the menstrual cycle only.

Glomerular filtration rate was not different between men and women, on either sodium intake, after correction for body surface area. However, effective renal plasma flow was substantially lower in women, on either sodium intake. This may well be due to the lower extracellular volume in women, as differences in volume status generally elicit a distinct change in renal plasma flow, with constant glomerular filtration rate. As a consequence filtration fraction is higher in women. This would be difficult to reconcile with the higher cardiorenal risk in men by straightforward extrapolation. It is important to realize however that cardiorenal risk is multifactorial, and that single factors should be interpreted in the context of their interaction with other relevant factors. It is conceivable that a rise in filtration fraction due to lower effective renal plasma flow in the context of lower extracellular volume is merely an adaptive response without pathological consequences, whereas a rise in filtration fraction due to inappropriately high ang II levels or -sensitivity, or to loss of integrity of the renal microvascular bed and consequently decreased renal plasma flow, could be harmful on long term. For aldosterone, for instance, it has been shown that elevated levels are harmful during sodium overload, but appropriate (and not related to pathology) during euvolemia and volume depletion. A corresponding frame of reference is unfortunately not available for renal hemodynamics, but our current data can contribute to the body of evidence needed to create such a frame of reference.

Renal hemodynamics during pregnancy and preeclampsia
Renal hemodynamics undergoes physiological adaptations in pregnancy. Healthy pregnant women show marked glomerular hyperfiltration by 40 to 60% in the second half of pregnancy. Furthermore, an increased rate of ERPF is found during pregnancy. In contrast, during preeclampsia these functional changes in renal hemodynamics are different. The GFR in women with preeclampsia is significantly lower when compared with healthy gravid control subjects. Of interest, no differences were found in ERPF between women with preeclampsia and healthy controls. The mechanism of hypofiltration during preeclampsia is not elucidated; both (renal) hemodynamic mechanisms, either primarily or due to relative hypovolemia, and secondary effects of structural renal changes are proposed. The depression in GFR during preeclampsia accompanies with typical histopathological changes in the kidney, called glomerular endotheliosis, which is characterized by fibrin deposition, endothelial swelling and loss of capillary space. 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.
Renal hemodynamics after preeclampsia

As mentioned above, there are data, albeit sparse, showing that formerly preeclamptic women have persistent abnormalities in renal hemodynamics early and late after pregnancy, which could be a possible mediator in the pathway to development of renal disease. However, this was mainly found in hypertensive women and thus might relate to the hypertension per se, rather than to the former preeclampsia specifically. Moreover, it is important to note that the renal hemodynamic profile is closely interlinked with sodium homeostasis and the RAAS. Therefore, in chapter seven, we investigated the renal hemodynamic profile in women with a history of early-onset preeclampsia compared with healthy controls during both low and high sodium intake. Despite the fact that all formerly preeclamptic women were carefully selected for absence of co-morbidity, we detected subtle abnormalities in renal hemodynamics, consistent with elevated glomerular pressure. Hence, our results support an independent effect of preeclampsia on renal hemodynamics.

These results may provide some clues to the mechanisms underlying the risk for long-term renal damage in subjects with prior preeclampsia. As described in chapter five, increased filtration fraction (FF) can be assumed to be a proxy for elevated glomerular capillary pressure, which contributes to progressive renal damage in animal models. The concept that renal hyperfiltration can attribute independently to progressive renal damage in CKD has been shown in our group in a cohort of transplant recipients. The mechanism underlying the higher FF in formerly preeclamptic women cannot be established with certainty, as this would require micropuncture. Hemodynamic as well as structural differences of the glomerular microvasculature should be considered. The nominally lower ERPF in the formerly preeclamptic women is compatible with a shift in glomerular vasotonus towards more efferent vasoconstriction relative to afferent vasotonus. Several neurohumoral factors could elicit such a pattern, alone or in combination, including increased activity of the RAAS and the sympathetic nervous system, vasopressin, natriuretic peptides and/or other factors. We found no differences, however, in circulating parameters of the RAAS or in ang II responsiveness. Whereas differences in tissue RAAS-activity could be involved, the possibility is not supported by similarity in renal ang II response. A difference in filtration equilibrium could also be involved, but the similar values for serum protein and albumin render this possibility less likely. Finally, structural differences in the glomerular microvascular bed could be involved. However, so far, it is thought that glomerular changes (glomerular endotheliosis, accompanied by decreased GFR) during preeclampsia resolve completely after preeclampsia.

Renal hemodynamic response to a change in sodium after preeclampsia

High sodium intake induced an increase in FF in both formerly preeclamptic women and healthy controls. This effect of high sodium intake on renal hemodynamics, associated with a sodium-sensitive blood pressure in these normotensive women, is in line with studies in sodium-sensitive hypertensives, and overweight subjects, where hyperfiltration was elicited by high sodium intake. We did not find interaction between the effect of sodium intake on FF and prior preeclampsia. However, considering the effect of high sodium on renal hemodynamics and the
alleged role of increased FF in the risk for long-term renal damage, our data suggest that sodium restriction could exert a beneficial effect on long-term renal risk. Obviously long-term studies would be required to substantiate such an assumption. The possible beneficial effect of sodium restriction is supported by Martilotti et al. showing sodium-sensitivity of blood pressure in formerly preeclamptic women.  

FUTURE PERSPECTIVES

Differences in cardiovascular and renal risk profile and gender-specific treatment recommendations

Epidemiological data clearly established that the risk for cardiorenal disease is different for men and women. Whereas gender differences are included in overall risk assessment, treatment recommendations so far lack gender-specificity. Our data demonstrate consistent differences in the RAAS, and regulation of the extracellular volume and renal hemodynamics between men and women. RAAS-blockade has been developed as an example of rational pharmacotherapy in hypertension, renal and cardiovascular disease: it would be of great importance to analyse the consequences of the gender differences in RAAS-activity and –sensitivity for gender-specific treatment recommendations.

Follow-up and prevention in formerly preeclamptic women

Preeclampsia is accompanied with an increased risk for developing ESRD and CVD. So far, no systematic renal or cardiovascular follow-up is executed in formerly preeclamptic women. The reported life-time risks for hypertension, cardiovascular and renal disease are relatively high, justifying at least follow-up in research settings and exploring the real risks and possibilities for prevention and therapeutic intervention. Currently, in the Netherlands, a guideline is developed for the prevention of CVD after complicated pregnancies. In the AHA guideline for prevention of CVD in women a blood pressure of > 140/90 in combination with a pregnancy complicated by preeclampsia is already an indication for pharmacotherapy based on the high risk scores. However, the latter is done without evidence for the best choice of drug and real benefit on endpoints.

We showed that formerly early-onset preeclamptic women without any co-morbidity have subtle abnormalities in renal hemodynamic profile, suggesting that preeclampsia per se induces an unfavorable effect to the kidney. In real life, more often than not, preeclampsia is not an isolated phenomenon, but occurs in the context of co-morbidity, with the common risk factors overweight and hypertension. The eventual cardiovascular and renal risk will accordingly be multifactorially determined, and recommendations for preventive measures and treatment will have to account for the full individual risk profile. Preventive measures could include both lifestyle recommendations, and pharmacotherapy. Whereas pathophysiology suggests that RAAS-blockade would be a logical choice for formerly preeclamptic women, at least those with hypertension, so far no data are available on comparative efficacy of
different classes of antihypertensives in formerly preeclamptic women, neither with respect to blood pressure, nor with respect to prevention of target organ damage. As to lifestyle recommendations, correction of weight excess and avoidance of excessive sodium intake would be logical steps. The average salt intake of a woman in the Netherlands is 7.5 g NaCl/day, while the current guidelines recommend 5-6 g NaCl for the general population and 3-5 g NaCl/day for high risk groups. Therefore, combining our results with recent evidence for increased sodium-sensitivity of blood pressure in formerly PE, a moderate dietary sodium restriction could have beneficial effects on cardiovascular and renal endpoints. However, long-term data on the impact of sodium intake in formerly preeclamptic women are needed to substantiate this assumption.

Taken together, our data on differences in physiology between men and women, and on the pathophysiological consequences of preeclampsia support the relevance of gender considerations in the assessment and management of cardiovascular and renal risk. Long term follow-up of women after preeclampsia, and targeted intervention studies are needed to turn these insights into clinical benefit, and a better long-term prognosis in this high-risk population.
REFERENCES


