PREECLAMPSIA: A GESTATIONAL CARDIORENAL SYNDROME

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ABSTRACT

It is generally accepted today that there are two different types of preeclampsia: an early-onset or placental type and a late-onset or maternal type. in the latent phase, the first one presents with a low output/high resistance circulation eventually leading in the late second or early third trimester to an intense and acutely aggravating systemic disorder with important impact on maternal and neonatal mortality and morbidity; the other type presents initially as a high volume/low resistance circulation, gradually evolving to a state of circulatory decompensation usually in the later stages of pregnancy, with less severe impact on maternal and neonatal outcome. For both processes, numerous dysfunctions of the heart, kidneys, arteries, veins and interconnecting systems are reported, most of them presenting earlier and more severe in early- than in late- onset preeclampsia, however some very specific dysfunctions exist for either type. Experimental, clinical and epidemiologic observations before, during and after pregnancy are consistent with early- onset preeclampsia as a gestation induced worsening of subclinical pre-existing chronic cardiovascular dysfunction, as such sharing the pathophysiology of cardiorenal syndrome Type II, and with acute volume overload decompensation of the maternal circulation in late onset preeclampsia, sharing the pathophysiology of cardiorenal syndrome Type 1. Cardiorenal syndrome type V is consistent with the process of preeclampsia superimposed upon clinical cardiovascular and/or renal disease, alone or as part of a systemic disorder. This review focusses on the specific differences of hemodynamic dysfunctions between the two types of preeclampsia, with special emphasis on the interorgan interactions between heart and kidneys, introducing the theoretical concept that the pathophysiologic processes of preeclampsia can be regarded as the gestational manifestations of cardiorenal syndromes.

INTRODUCTION

Preeclampsia is a gestational hypertensive disorder with an overall incidence of around 3-3.5% of pregnancies (Thornton *et al.* 2013; Shih *et al.* 2016). It is one of the most important complications during pregnancy, with major impact on maternal and neonatal outcome. The burden to health care economics is estimated at 40-100 times the costs of term pregnancy depending on gestational age at delivery (Shih *et al*. 2016). Preeclampsia is defined as gestational hypertension associated with signs of systemic dysfunction with signs of impaired liver, renal, cardiovascular and haematological function - either as a primary disorder or superimposed on pre-existing maternal disease (Thornton *et al*. 2013).

The precise aetiology of preeclampsia remains to be determined, and because of countless hypotheses postulated over time, preeclampsia has been labelled "the disease of theories" (Jeffcoate 1966; Schlembach 2003). Distinct origins of preeclampsia have been discussed (Ness *et al.* 1996), however the epidemiological and genetic associations as well as the inflammatory, vasoactive, endocrine and metabolic perturbations all support the key involvement of placenta and cardiovascular system in the pathophysiology of preeclampsia (Thilaganathan and Kalafat 2019; Perry H *et al.* 2018). Currently, a vivid debate is ongoing as to whether the initiating process of placental dysfunction in preeclampsia is the cause or the consequence of maternal cardiovascular dysfunction (Redman 2014; Kalafat *et al.* 2017; Thilaganathan *et al.* 2019). The placental origins hypothesis is supported by the evidence for role of placentally-mediated vasoactive factors in the pathophysiology of preeclampsia (Redman 2014), whereas the hemodynamic model is supported by evidence for subclinical maternal cardiovascular dysfunction both preconceptually and post-partum in women who developed preeclampsia (Foo *et al.*2018; Melchiorre *et al.* 2011).

Irrespective of the outcome of the ongoing debate on the aetiology of preeclampsia, it is generally accepted today that the eventual clinical syndrome of preeclampsia is triggered by placental dysfunction – predominantly associated with abnormal placentation in early preeclampsia and with

uteroplacental malperfusion in later disease (Redman 2104 ; Thilaganathan *et al*. 2019; Perry H *et al*. 2018). Despite the lack of experimentally measurable reduced oxygen concentrations in placentas of hypertensive pregnancies (Huppertz B et al. 2014), it has been theorised that placental hypoxemia is induced with the subsequent release into the maternal circulation of pro-inflammatory, and anti-angiogenic factors that lead to generalised endothelial dysfunction and the cluster of signs currently recognised as preeclampsia (Hlanudewich *et al*. 2007). Generalised maternal endothelial dysfunction at all sites of the vascular tree results in dysfunction of the heart, kidneys and other organs (Palei *et al*. 2013). The clinical presentation of preeclampsia varies depending on the dominance of placental or maternal organ systems involved in the active stage of the disease. The clinical syndrome is conventionally divided as early and late based on gestational age at presentation, but only a decade ago used to be classified on the basis of severity of signs and symptoms (Redman *et al.* 2005; Steegers *et al.* 2010; Von Dadelszen *et al.* 2003). Regardless of a temporal or severity-based classification for preeclampsia, it is evident that the cardiovascular and renal systems play a major role in disease pathophysiology and presentation. This manuscript presents an overview of the cardiorenal interactions with the placenta, introducing the theoretical concept that cardiorenal syndrome is an intrinsic part of the pathophysiology of preeclampsia.

CARDIOVASCULAR AND RENAL CHARACTERISTICS OF PREECLAMPSIA

Pregnancy-related changes in circulatory volume load
Hemodynamic changes in early pregnancy start with a primary vasodilation, triggering volume retaining mechanisms leading to an increase in intravascular volume and cardiac output (Duvekot *et al.* 1993). This process is already active post-conception, long before placentation is complete, and presents with reduced mean arterial pressure and systemic vascular resistance in association with increased cardiac output and glomerular filtration rate - all preceding significant plasma volume expansion (Chapman *et al.* 1998). As such, very early pregnancy can be considered as a state of arterial underfilling with relative restriction of arterial blood volume, which is known to activate RAAS, the sympathetic nervous system and non-osmotic release of vasopressin (Chapman et al. 1998). Contrary to other states of arterial underfilling, where systemic vasodilatation presents with renal vasoconstriction, pregnancy is a unique condition that combines systemic and renal vasodilatation, in association with an escape from sodium-retaining effects of aldosterone (Chapman et al. 1998; Bekheirnia *et al.* 2006). All these mechanisms lead to an increase of total body water by 5–8L over the course of pregnancy (Widen *et al.* 2014), with 1L of this being confined to plasma volume (de Haas *et al.* 2017). The latter volume expansion in pregnancy is reflected by a measurable increase of intrathoracic fluid from as early as 7 weeks' gestation (Smeets *et al.* 2016; Lanssens *et al.* 2018). Increased circulating volume is a cardiovascular stressor, and signs of chronic volume overload are present in a significant proportion of previously healthy women with apparently normal pregnancies at term (Melchiorre *et al*. 2016). This volume overload related gestational cardiovascular dysfunction, may predispose to uteroplacental hypoperfusion and placental stress leading to fetal growth restriction and/or preeclampsia depending on the gestation of onset and maternal endothelial response (Figure 1; Thilaganathan 2018A; Thilaganathan 2018B).

Cardiovascular function in preeclampsia
Electrocardiography studies in latent and clinical phase of preeclampsia showed evidence of P-wave dispersion and delayed left atrial electromechanical coupling (Inci *et al.* 2015), together with prolonged QT-interval indicative for abnormal ventricular repolarisation (Raffaelli *et al.* 2014). These ECG abnormalities also precede the onset of clinical symptoms of PE (Angeli *et al.* 2011; Angeli et al. 2015; Kirbas *et al.* 2016; Baumert *et al.* 2010). Invasive assessment of cardiovascular function in pregnancy is both impractical and inadvisable other than in exceptional clinical circumstances and scenarios. There are many non-invasive methods of assessment of cardiac function, but most are inaccurate compared to the benchmark of echocardiography (Vinagayam *et al*. 2017), and therefore

require the application of population-and device-specific reference ranges applied under stringent standardised conditions (Meah *et al.* 2018). A recent systematic review, summarizing 19 echocardiographic studies in pregnancy demonstrated that increased left ventricular mass and total vascular resistance were the most consistent findings in preeclampsia (Castleman *et al.* 2016). The finding of diastolic dysfunction and left ventricular remodelling were seen before clinical manifestation of preeclampsia, more marked in severe and early-onset disease, and also associated with adverse pregnancy outcome. There was disagreement between studies with regard to changes in cardiac output, which was attributed by the authors to heterogeneity in timing of echocardiography. Others have interpreted differences in maternal cardiac output as representing two phenotypes – a low output/high resistance circulation in early preeclampsia and high output/low resistance circulation in late preeclampsia (Tay *et al*. 2018; Ferrazzi *et al*. 2018). These apparent cardiovascular phenotypes provide some insight and a potential explanation for the differing clinical and pathological differences between early and late preeclampsia – one that is lacking when taking the conventional view of preeclampsia as a primary placental disorder.

Cardiovascular phenotypes of early and late preeclampsia
Early and late preeclampsia present with similar clinical characteristics in nearly all organ systems involved, although mostly to a lesser degree in late than in early preeclampsia. From this, it is tempting to conclude that early- and late preeclampsia are two phenotypes of one common pathophysiologic background process, mainly differing in severity of clinical presentation. Consistent with the clinical presentation, echocardiographic findings in preeclampsia are typical of chronic volume overload and characterized by left ventricular concentric remodelling and increased relative wall thickness (Melchiorre *et al.* 2016; Borges *et al.* 2017; Valensise *et al.* 2008), reduced myocardial contractility and with diastolic dysfunction (Melchiorre *et al.* 2016). These findings occur earlier and are more severe in early preeclampsia, where systolic dysfunction is also apparent in a proportion of cases.

Paradoxical differences in cardiac output between early and late preeclampsia have led researchers to hypothesise the existence of two types of maternal circulation during preeclampsia: a low output/high resistance state in early and high output/low resistance state in late preeclampsia. A major inconsistency with this hypothesis is that regardless of gestation, preeclampsia is consistently associated with reduced stroke volume and higher/normal total vascular resistance (Castleman *et al.* 2016). The latter is in keeping with the findings of hypertension and myocardial dysfunction in both early and late preeclampsia (Castleman *et al*. 2016; Melchiorre *et al.* 2014). This hypothesis is further undermined by interpretation of cardiac output indices independent of maternal morphological characteristics. Interpretation of maternal cardiac output in the majority of studies has been undertaken without taking into consideration maternal haemodynamic demands which vary with height, weight, age and gestation (Vinagayam *et al.* 2018; Perry *et al.* 2018B; Bijl *et al.* 2019). To correctly interpret whether measured cardiac output is 'high' or 'low', one needs to consider what the appropriate or 'normal' cardiac output would be for maternal characteristics and gestational age – a process called indexing. *Normal, resting cardiac output differs among people of different size - the resting cardiac output of someone who weighs 100Kg would be greater than the cardiac output found in a person that weighs 60Kg. In the non-pregnant state where body weight and surface area does not change dramatically over a short time frame, it is appropriate to use non-indexed measurements as they will accurately reflect the change in cardiac function between serial assessments. However, in pregnancy as in pediatric medicine, where body weight can change significantly over a short time period, measured (non-indexed) values for cardiac output do not distinguish change due to increased body mass versus those representing pathology. Therefore, cardiac output is indexed against body surface area so as to appreciate whether cardiac function is adequate for the*

anticipated demands of increased body mass. The indexing of cardiac output is limited by the fact that body surface area may not accurately reflect the metabolic demands of increased bod massy, but presently, no other method of indexing is available and such indexing remains the best way of understanding whether cardiac output is appropriate for maternal body size in pregnancy. Indexing cardiac output may be an approximating process but provides a better understanding of the underlying pathophysiology which demonstrates that early preeclampsia is characterised by lower maternal cardiac output, whilst late preeclampsia is associated with normal or lowered cardiac output compared to normal controls (Buddeberg *et al.* 2018A; Buddeberg *et al.* 2018A; Gyselaers *et al.* 2019).

The severity and temporal nature of cardiovascular dysfunction in early and late preeclampsia provides important insights into the pathophysiology of the disorder. In recurrent early preeclampsia, myocardial dysfunction is evident in the first trimester (Sep *et al.* 2011) in combination with low plasma volume and increased left atrial dimensions (Andrietti *et al.* 2008). In the second trimester, echocardiographic abnormalities are already present (Valensise *et al.* 2008), but diastolic dysfunction is observed in early, but not late preeclampsia (Melchiorre *et al.* 2016) – suggesting that diastolic dysfunction of late preeclampsia develops during the second half of pregnancy as a consequence of chronic volume overload (Valensise *et al.* 2008; Melchiorre *et al.* 2016). Importantly, in both early and late onset preeclampsia, cardiac morphologic changes such as adverse ventricular remodelling and increase in left ventricular mass precede the onset of chamber dysfunction (Cong *et al.* 2015), and are not only restricted to the left side but also present in the right ventricle (Caglar *et al.* 2016; Buddeberg *et al.* 2018A).

The observed longitudinal changes in maternal cardiovascular function in preeclampsia suggest that early preeclampsia is associated with poor pre- and/or peri-conceptional cardiovascular reserve, low vascular volume and early pregnancy chamber dysfunction. In contrast, late preeclampsia occurs secondary to cardiovascular dysfunction as a consequence of chronic volume overload (Figure 2). Epidemiological evidence for the existence of two cardiovascular phenotypes of preeclampsia was reported by Verlohren et al, supported by different early pregnancy Doppler measurements of uterine artery pulsatility index in both groups and a bimodal skewing of birth weight distribution (Verlohren *et al.* 2014). The implications of the cardiovascular phenotypes on elucidating disease aetiology are discussed in more detail later in this review.

Renal function
Glomerular endotheliosis is considered the histologic landmark of preeclampsia, and is characterized by endothelial swelling, loss of endothelial fenestrae with disruption of the glomerular filtration barrier and "empty" occluded capillary lumens (Stillman *et al.* 2007). These lesions are thought to result from glomerular endothelial dysfunction, probably mediated via placental sFlt-1 inactivation of podocyte-VGEF and via sEng-inhibition of TGFβ. Both factors are needed for a normal function of the glomerular endothelium (Henao *et al.* 2010). Disrupted endothelial function triggers further impairment of renal function via induction of podocyte dysfunction with subsequent podocyturia (Craici *et al.* 2014) and increased nephrin concentrations in serum and urine (Jung *et al.* 2017), but also via thrombotic micro-angiopathy (Johnson *et al.* 2016). The latter results from increased arterial and venous resistance by inhibition of endothelial NO-mediated gestational vasodilatation, sympathetic sensitivity (Van Dongelen *et al.* 2014) and relaxin (Conrad *et al.* 2014).

Preeclampsia-related acute kidney injury results from ADAMTS-12/13 associated microangiopathy and from activation of the alternative and/or classical complement pathway (Fakhouri *et al.* 2012; Prakash *et al.* 2017). Compared to normal pregnancy, glomerular filtration rate in preeclampsia is reduced despite maintenance of effective renal plasma flow (EFPR) and oncotic pressure (Lafayette *et al.* 1998), which suggests that structural glomerular damage is the main cause of preeclampsia-

related proteinuria (Robson 1976). Preeclampsia is also characterized with reduced proximal tubular reabsorption of intraluminal non-albumin proteins (Jeyabalan *et al.* 2007). As such, the urinary content of around 50 different specific proteins is different in preeclampsia than in normal pregnancy – the focus of current research using urinary proteomics (Guo *et al.* 2014) to discriminate between types of gestational hypertensive disorders.

Uric acid is an important mediator of endothelium function via inhibition of NO-release, stimulation of endothelin-1 production, enhancement of Angiotensin II and smooth muscle contraction, with subsequent endovascular inflammation and CRP-release (Borghi *et al.* 2014). Renal handling of uric acid is altered in preeclampsia, with impaired intratubular secretion at the S2 segment of the proximal tubule resulting in increased UA serum concentrations (Hayashi *et al.* 2002).

CARDIORENAL SYNDROMES

Cardiorenal syndrome describes a group of disorders where cardiac dysfunction is responsible for the deterioration of renal function or vice versa. Five pathological types of cardiorenal interactions are thought to be possible (Ronco *et al.* 2008). *Types I and II* comprise acute/chronic dysfunction of the kidneys arising as a result from acute/chronic cardiac failure. *Types III and IV* are acute/chronic cardiac dysfunction as a result of acute/chronic renal disease. *Type V* describes the situation of combined cardiac and renal dysfunction, usually the end-stage of one of the former types, resulting from gradual and progressive worsening of organ function.

Several mechanisms have been reported to contribute to heart-kidney interactions including neuro-endocrine (RAAS, ADH and natriuretic peptides), endothelium-derived vasoactive substances (endothelin or products of oxidative stress), activation of the autonomic nervous system, inflammatory/immune dysregulation, as well as various molecular and epigenetic pathways (Shamseddin *et al.* 2009*;* Garcia-Donaire *et al.* 2011; Colombo *et al.* 2012; Bongartz *et al.* 2005; Virzi *et al.* 2016; Napoli *et al.* 2011; Muhlberger *et al.* 2012). Type I and II CRS most represent the pregnancy and preeclampsia phenotypes (Shamseddin *et al.* 2009).

Cardiac systolic dysfunction can be responsible in anterograde direction for renal hypoperfusion, whereas diastolic dysfunction in retrograde direction leads to hampered drainage of intrarenal venous blood and reduced venous return with subsequent venous congestion. Increased arterial stiffness and vascular resistance are important contributors to cardiorenal interactions into anterograde direction (Fu *et al.* 2014), however it is well documented that renal arterial hypoperfusion is rarely the single cause of worsening of renal function (Nohria *et al.* 2008). Retrograde interactions via the central veins are considered much more important than the anterograde mechanisms, interacting via increase of central venous pressure (Damman *et al.* 2009; Ohuchi *et al.* 2013), venous congestion (Mullens *et al.* 2009; Testani *et al.* 2010) with our without increased intra-abdominal pressure (Mullens *et al.* 2008) and volume load (Ronco *et al.* 2010).

Direct cardiorenal interactions

There are several potential mechanisms that could contribute to cardiorenal interactions. Support for these interactions come from molecular, tissue, biomarker and epidemiological studies. Differences in findings between early and late preeclampsia have previously been interpreted according to these temporal disease phenotypes but may be more appropriately viewed as a continuum representing either pre-existing cardiorenal dysfunction in early preeclampsia or pregnancy-mediated cardiorenal dysfunction in late preeclampsia (Figure 1). The cardiovascular and renal systems are interdependent and have a number of direct interactions, which are likely to be stronger than indirect interactions.

Arteries

Peripheral and central blood pressure measurements in the first trimester are higher in pregnancies destined to develop preeclampsia as compared to uncomplicated pregnancies - with the difference being more pronounced for early than late PE (Macdonald-Wallis *et al.* 2012; Vonck *et al.* 2017; Namugowa *et al.* 2017; Khalil *et al.* 2014A). Similarly, arterial pulse wave augmentation index was observed to increase from the second trimester onward in early onset (Franz *et al.* 2013, Khalil *et al.* 2014B) but not in Late onset PE (Khalil 2014B). Consistent with recent echocardiographic studies (Foo *et al.* 2019), this data suggests that pre-existing cardiac dysfunction predisposes to chronic (Type II) cardiorenal dysfunction and early preeclampsia.

Veins

The observation of secondary hypertension in pregnant ewes after ligation of the uterine vein is very interesting because of the important implication that arterial hypertension can occur as a consequence of abnormal venous hemodynamic function (Lotgering *et al.* 1986). In humans, preeclampsia related microcirculatory dysfunction has been linked to precapillary flow reduction or cessation (Anim Nyame *et al.* 2003; Anim Nyame *et al.* 2004). Changes of venous Doppler characteristics during uncomplicated pregnancy were reported at the level of maternal liver (Roobottom *et al.* 1995) and kidneys (Karabulut *et al.* 2003), and noted to be different from the patterns observed during preeclampsia (Bateman *et al.* 2004). More recently, ECG-guided Doppler assessment of maternal venous haemodynamics in preeclampsia demonstrated that renal interlobar venous impedance index is increased several weeks before the onset of early preeclampsia, is raised much higher, has an parallel left-right undulating pattern and is associated with a shorter venous pulse transit time compared to late preeclampsia (Gyselaers *et al*. 2010*;* Gyselaers et al. 2011; Gyselaers et al. 2014; Mesens *et al.* 2015). These findings are again consistent with chronic (Type II) cardiorenal dysfunction and early preeclampsia. Late preeclampsia presented with a more acute (Type I) cardiorenal picture with maternal venous Doppler measurements being related to maternal cardiac output and proteinuria (Mesens *et al.* 2014).

Intravascular volume

During pregnancy, total body water increases due to expansion of all maternal body fluid compartments (Davison 1997). Bio-impedance measurements have shown that overall total body water increase is more pronounced in preeclampsia than in normal pregnancy and that this effect is more pronounced in the third trimester with late compared to early onset PE (Yasuda *et al.* 2003; Levario-Carillo *et al.* 2006; Gyselaers *et al.* 2018). In contrast, plasma volume (PV) expansion is known to be less pronounced in preeclampsia than in uncomplicated pregnancy (De Haas *et al.* 2017), but increased PV volume has also been reported in late preeclampsia (Friedberg *et al.* 1963; Schrier *et al.* 1991) with or without persistence of high cardiac output (Easterling *et al.* 1990; Bosio *et al.* 1999). Another way to estimate an individual's intravascular filling state non-invasively is ultrasound derived Inferior Vena Cava collapsibility index (IVCI) (Finnerty *et al.* 2017). In intensive care patients, IVCI correlates well with invasively measured central venous pressure and pulmonary artery pressure (Stawicki *et al.* 2016, Ilyas *et al.* 2017). In comparison to uncomplicated pregnancies, reduced IVCI was observed in late onset but not in early onset PE, suggesting a higher intravascular filling state in LPE than in EPE (Stergiotou *et al.* 2013). Similarly, hormones regulating volume and electrolyte homeostasis such as antidiuretic hormone and natriuretic peptides are more elevated in early but not late preeclampsia (Tuten *et al.* 2015; Sandgren *et al.* 2015; Borges *et al.* 2018; Álvarez-Fernández *et al.* 2016). Decreased PV expansion in early preeclampsia may result from constitutionally low plasma volume before conception, poor expansion due to dysfunctional mechanisms of neurohormonal volume retention or extravascular leakage of intravascular fluids (Salas *et al.* 2006; De Haas *et al.* 2017), and is consistent with pre-existing cardiovascular dysfunction leading to chronic (Type II) cardiorenal syndrome.

Indirect cardiorenal interactions

A number of extra-cardiac and extra-renal biological mechanisms are modulated in pregnancy and under stressed conditions may have indirect effects on both cardiovascular and renal function.

Endothelium and vascular inflammation
The endothelium can be considered as a distinct organ within the cardiovascular system with widespread, but very specific functions (Galley *et al.* 2004). Endothelial dysfunction triggers a chronic endovascular inflammatory response via activation of the complement system (Liszewski *et al.* 2011), with increased serum concentration of highly sensitive C-reactive protein being a characteristic feature of preeclampsia (Kwiatkowski *et al.* 2017). Furthermore, in severe end-stage preeclampsia regardless of gestation, actived intravascular inflammation stimulates the coagulation cascade with formation of intravascular microthrombi and eventually micro-angiopathy (Liszewski *et al.* 2011). The latter is associated with acute kidney injury and consistent with acute (Type I) cardiorenal dysfunction. Endothelium dysfunction has been reported as a direct consequence of pre-existing cardiac and/or renal dysfunction, clinically illustrated by the generalized endothelial dysfunction in congestive heart failure *(*Bauersach*s et al.* 2004) and in individuals with a congenital reduction in the number of nephrons *(*Zoccali *et al.* 2007; Keller *et al.* 2003). The normal or abnormal function of the maternal endothelium is known to be strongly linked with the process of embryo implantation, where numerous hormones, cytokines, immunomodulatory and vaso-active mechanisms are involved in the adaptation process of the maternal vasculature (Boeldt et al. 2017; Nejabati et al. 2017; Burnett et al. 2016; Burton 2009; Lima et al. 2014; Chen et al. 2017; Robertson et al. 2018).

Endocrine and metabolic
The Renin-Angiotensin-Aldosterone System (RAAS) changes dramatically during pregnancy (Lumbers *et al.* 2014). Early pregnancy cardiovascular changes induce increased release of Renin, resulting in conversion/metabolism of angiotensinogen to AngII (Irani *et al.* 2011). AngII is responsible for vasoconstriction, increased sensitivity to sympathetic stimulation and release of Aldosterone via the AT type 1 (AT1) receptor - and to a lesser extent vasodilatation, apoptosis and reduced cell growth via the AT type 2 receptor. Normotensive pregnant women are refractory to the vasoconstrictive effects of AngII due to AT1 inactivation by progesterone, prostacyclin and ROS. In preeclampsia, AngII sensitivity increases (Abdalla *et al.* 2001), despite of decreased circulating RAAS components (Anton *et al.* 2008). Women with preeclampsia also demonstrate increased activity of an auto-antibody against the AT1 receptor, resulting in increased hypoxia induced SFlt-1 and Plasminogen Activator Inhibitor 1 (PAI-1) (Irani *et al.* 2008, Xia *et al.* 2007). Increase of AT1 autoantibodies is more pronounced in late than in early preeclampsia (Herse *et al.* 2009) and conversely, homozygous ACE genotypes are more frequent in early compared to late preeclampsia (Uma *et al.* 2010).

Genetics
Studies of placental gene expression in preeclampsia have shown dysregulated genes involved in cell proliferation/differentiation, lipid metabolism, immunity, inflammation and endothelin-related NO pathway, were affected principally in early compared to late preeclampsia (Sitras *et al.* 2009). Although all of these biological systems have anticipated effects on the cardiovascular and renal systems, what is not entirely certain is whether such gene dysregulation is cause or effect. Most previous studies of maternal genetic polymorphisms have shown that preeclampsia and cardiovascular diseases share genetic predispositions. A recent candidate gene association study in a Finnish cohort demonstrated that a variant of the sFlt1 gene is protective against preeclampsia - the same alleles were also associated with lower risk of heart failure (Lokki *et al*. 2017). Moreover, the largest and most comprehensive genome wide association study also implicated a locus near fetal/placental FLT1 region for the development of preeclampsia supporting the hypothesis that a placental isoform of sFlt1 is involved in the pathophysiology of the disease (McGinnis R *et al*. 2017).

Lipid metabolism

Dyslipidemia of preeclampsia is characterized with increase in cholesterol, LHDL, VLDL, free fatty acids and triglycerides, with reduction in APO-1 and HDL (Spracklen *et al.* 2014; Austdal *et al.* 2014; Jin *et al.* 2016; Timur *et al.* 2016; Leon-Reyes *et al.* 2017; Baumfield *et al.* 2015, Spracklen *et al.* 2015). High cholesterol and triglyceride plasma levels have been demonstrated to be independent risk factors for progression of renal disease in humans. Although not clearly delineated, the underlying pathophysiologic mechanisms is thought to involve oxidative stress and insulin resistance may mediate the lipid-induced renal and cardiovascular damage (Trevisan *et al*. 2006). Oxidised LDL, free fatty acids and triglycerides are higher in early preeclampsia, in support of a chronic (Type II) cardiorenal syndrome in early preeclampsia (Tuten *et al.* 2014, Yan *et al.* 2015).

COMMON CLINICAL CHARACTERISTICS OF CARDIORENAL SYNDROMES AND PREECLAMPSIA

Cardiorenal syndromes and preeclampsia have similar clinical presentations and in many aspects share predisposing risk factors, pathophysiologic background mechanisms, biomarkers and long term outcomes.

Predisposing risk factors for preeclampsia, renal and cardiac dysfunction
Clinical risk factors predisposing to the development of cardiorenal syndromes and preeclampsia are shared: pre-existing renal (Vellanki 2013; Piccoli et al. 2018) or cardiac disease (van Hagen *et al.* 2017), diabetes and chronic hypertension (Bartsch *et al.* 2016), hypertriglyceridemia (Gallos *et al.* 2013), obesity and metabolic syndrome (Whaley-Connell *et al.* 2014), connective tissue disorders (Spinillo *et al.* 2017) or systemic diseases such as lupus erythematodes and antiphospholipid syndrome (Fischer-Betz *et al.* 2017), sarcoidosis (Hadid *et al.* 2015), amyloidosis (Mordel *et al.* 1993*),* thrombotic thrombocytopenic purpura (Vesely *et al.* 2015), and sickle cell anaemia (Bartsch et al. 2016).

Pathophysiology of renal and cardiac dysfunction
Crosstalk between the cardiovascular system and kidneys occurs via organ-specific mechanisms or via dysfunction of the interconnective systems as outlined above in cardiorenal interaction. The consequences of cardiac dysfunction are reduced systemic arterial blood supply and organ ischemia as well as impaired venous return resulting in venous congestion. Renal dysfunction results in water retention and volume overload (Figure 1).

Hypoperfusion / ischemia
Impaired cardiac systolic function is responsible for a reduced effective circulatory volume, which in turn leads to renal hypoperfusion with reduced glomerular filtration rate and effective renal plasma flow (Stevenson *et al.* 1989). In acute situations, these changes are reversible after restoring cardiac functionality (Hanada *et al.* 2012). In chronic situations however, renal ischemia may occur with renal tubular cell damage and apoptosis (Havasi *et al.* 2011; Bonventre 2003). Cyanotic nephropathy is a clinical example of ischemic renal damage eventually leading to chronic kidney disease in patients with cyanogenic congenital heart disease (Perloff 1993).

Volume overload
Volume overload induces cardiac remodelling with left ventricular hypertrophy and dilation, predisposing to diastolic and systolic dysfunction (Harnett *et al.* 1995). Generally, volume overload is associated with rising serum concentrations of B-type Natriuretic Peptide (BNP) and N-terminal proBNP (Maisel *et al.* 2011). Oliguria is an important feature of renal dysfunction, leading to an imbalance of water and electrolyte homeostasis (De Deyn *et al.* 2003; Scheuer *et al.* 1973). Sodium and water retention result in further volume expansion and overload and raised serum concentrations of urea can depress myocyte activity (Kingma *et al.* 2006).

Venous congestion
Diastolic dysfunction is predominant in preeclampsia irrespective of gestation at onset and predisposes to reduced venous return and venous congestion. Reflex venoconstriction occurs to support venous return, resulting in systemic venous hypertension and increased central venous pressure (Paulus *et al.* 2008). Localised renal vein congestion leads to reduced kidney perfusion with subsequent renal dysfunction - the severity of which depends on the level of preserved arterial blood flow (Mullens *et al.* 2009). Increase of renal venous pressure activates RAAS (Kishimoto *et al.* 1973) with associated rise of Angiotensin II and aldosterone resulting in increased oncotic pressure in the peritubular capillaries and further rise of blood pressure and volume load.

Intra-abdominal hypertension
Increasing intra-abdominal pressure is associated with gradually deteriorating function and eventually failure of abdominal organs. In intensive care units, the extreme clinical presentation of this phenomenon is known as the intra-abdominal compartment syndrome (Maluso *et al.* 2016) – as a consequence of reduced venous return, congestion and microcirculatory dysfunction (Funk *et al.* 2013). The growing pregnant uterus is responsible for a gradual increase of intra-abdominal pressure worsening near term, leading researchers to propose preeclampsia as a renal compartment syndrome (Chun *et al.* 2012; Sawchuck *et al.* 2014; Sugerman 2011; Reuter *et al.* 2016). Patient-specific conditions such as obesity and multiple pregnancy which result in higher intra-abdominal pressure predispose to this evolution.

Chronic inflammation and reactive oxygen species
Cardiac and renal failure are associated with a cascade of inflammatory pathway activation (Machnik *et al.* 2009) and increased serum concentrations of pro-inflammatory cytokines such as TNFα and interleukins (Elmore 2007; Virzi *et al.* 2015; Bryant *et al.* 1998; Blake *et al.* 1996; Prabhu 2004). At the level of the kidney, these inflammatory processes are responsible for renal tubular cell apoptosis (Akcay *et al.* 2009), further deteriorating renal function. Similarly, the heart is subject to further myocardial damage (Rauchhaus *et al.* 2000), myocyte apoptosis (Kelly 2003) and infarction (Bryant *et al.* 1998).

Biomarkers of renal and cardiac dysfunction
The majority of biomarkers are cardiovascular in origin and shared between cardiorenal syndrome and preeclampsia. Biomarkers include clinical patient's characteristics, biochemical (Lau *et al.* 2017) and biophysical markers of cardiovascular (Monteith *et al.* 2017; Oben *et al.* 2014) and renal function (Jim *et al.* 2014; Le Jemtel *et al.* 2015) and of their interconnecting systems.

Long-term outcome of renal and cardiac dysfunction
The cardiorenal syndrome is reported as an independent predictor of all-cause mortality in heart failure patients with preserved ejection fraction (Lu *et al.* 2013; Kajimoto *et al*. 2014*)*. Similarly, preeclampsia is considered a strong risk factor for long term cardiovascular and/or renal disease (Figure 2). A 4-fold increased risk for heart failure and a 2-fold increased risk for coronary heart disease, stroke and cardiovascular death have been reported at 2-3 decades following birth (Wu *et al.* 2017). More recent data has demonstrated that cardiovascular function is more prevalent in the immediate postpartum period with a high incidence of new-onset chronic hypertension occurring within a few years of birth (Behrens *et al.* 2017). Postmenopausal focal segmental glomerulosclerosis was also only present in those women with a past history of preeclampsia (Suzuki *et al.* 2008). In spite of the debate as to whether cardiovascular and renal dysfunctions predated the pregnancy (Mahendru *et al.* 2013*;* Foo *et al.* 2018*)* or developed during the course of the pregnancy complicated by preeclampsia, it is evident that the postpartum maternal risks are clinically significant and more immediate than previously presumed (Matsubara 2018).

Pharmacotherapeutic targets

Cardiorenal interactions in pregnant and non-pregnant individuals share many important pathophysiologic background mechanisms. However, pharmacologic treatment of these patient groups may be very different: drugs such as diuretics and NO-donors are commonly used in internal medicine and intensive care but very rarely in pregnancy despite reported potential benefits. Similarly, magnesium sulphate is a drug well known to obstetricians and maternal fetal specialists, but not commonly used by physicians and intensivists.

Nitroglycerin and other nitrates are well known endothelium dependent vasodilating agents targeting (Silber et al. 1990), successfully applied in the management of preeclampsia, with or without pulmonary oedema (Cetin et al. 2004; Cotton et al. 1986). Improvements of abnormal Doppler flow measurements in uterine and umbilical arteries during nitroglycerin administration have been reported (Grunewald et al. 1995; Cacciatore et al. 1998). More recently, NO-donors have come into attention of obstetric researchers again, mainly because of the combination of beneficial cardiovascular effects with maternal and fetal safety (Johal et al. 2014). No-donors associated with plasma volume expansion have shown to improve diastolic blood flow velocity in the umbilical artery in parallel with a reduction of maternal peripheral arterial resistance (Valensise et al. 2008, Vasapollo et al. 2012). Despite the use of diuretics as antihypertensive agents outside pregnancy (Veena et al. 2017), abstinence from application during pregnancy has long been advocated because of the observed increase of peripheral resistance in a group of pregnant women with chronic hypertension (Carr et al. 2007). The lack of terotogenic or clinical neonatal side effects in pregnancies with maintenance of chronic diuretic treatment or with acute cardiac or nephrologic problems (al-Abas et al. 2009; von Dadelszen et al. 2007), has stimulated the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy to formulate the statement that the concern for the use of diuretics in pregnancy should be considered primarily theoretical (NHBPEPWGHBPP 2000; Brown et al. 2014). These arguments, together with the recognition that late-onset preeclampsia is predominantly related to a volume overloaded state, has initiated research into the value of diuretics in the management of late-onset preeclampsia, with preliminary promising effects (Tamas et al. 2017). Magnesium sulphate is widely used for the prevention and treatment of maternal eclamptic seizures and for neonatal neuroprotection during preterm birth (Pryde et al. 2009). A role for magnesium has been reported in the physiologic control of blood pressure and the pathophysiology of hypertension (Touyz 2003). Beneficial effects of magnesium sulphate as an adjunct to conventional pharmacotherapy has been reported for arrhythmia in congestive heart failure (Gottlieb et al. 1993) or ischemic cardiomyopathy (Ince et al. 2001) and for improved myocardial performance after coronary angioplasty (Nakashima et al. 2004). Reversal of vasospasms offers potential to magnesium supplementation as a pharmacologic treatment for cerebral or coronary vasoconstriction (Keyrouz et al. 2007; Teragawa et al. 2000). Before the introduction of these drugs in other settings or indications than generally used today, more experimental, clinical and epidemiological research is required.

CARDIORENAL INTERACTIONS IN THE PATHOPHYSIOLOGY OF PREECLAMPSIA

From the evidence outlined above and summarized in Figure 1, there are three main pathways of cardiorenal interactions in preeclampsia: (1) pre-existing subclinical cardiovascular dysfunction associated with early-onset preeclampsia, impaired placental development with fetal growth restriction and Type II (chronic) cardiorenal syndrome, (2) a healthy woman whose gestational volume expansion leads to cardiovascular dysfunction and Type I (acute) cardiorenal syndrome and (3) preeclampsia superimposed upon pre-existing clinical syndromes of cardiovascular and/or renal disease and Type V cardiorenal syndrome (Figure 2).

Preconceptional subclinical cardiovascular dysfunction predisposing to Type II cardiorenal syndrome and early-onset preeclampsia

Abnormal trophoblast invasion in myometrial spiral arteries has been reported in placental biopsies of pregnancies complicated with preeclampsia, and for decades this mechanism has been considered the main etiologic event triggering a cascade of maternal cardiovascular events eventually leading to severe complications as preeclampsia and/or fetal growth restriction (De Wolf et al. 1982; Brosens et al. 2002). More recent data has shown that abnormal placentation is neither specific nor sensitive for the occurrence of preeclampsia, even though placental lesions are seen more frequently in early preeclampsia (Falco *et al*. 2017). Today, evidence is growing that pre-existing or early pregnancy suboptimal cardiac dysfunction may predispose to subsequent placental maldevelopment (Foo *et al*. 2018; Thilaganathan *et al.* 2019; Mahendru *et al. 2013*) and worsening maternal cardiovascular function with the increased volume load of pregnancy (Melchiorre *et al.* 2016; Buddeberg BS *et al.* 2018A; Buddeberg BS et al. 2018B). It is still to be elucidated whether maternal endothelium dysfunction prior to conception is a prerequisite for development of preeclampsia, or whether sometimes this complication results from an imbalanced maternal – conceptus communication during implantation, a process involving numerous cellular, molecular and biochemical mechanisms such as angiogenetic factors (Boeldt *et al.* 2017; Nejabati *et al.* 2017*),* cellular exosomes (Burnett *et al.* 2016), oxygen tension (Burton 2009), leucocytes (Lima *et al.* 2014), Natural Killer (Chen *et al.* 2017) and regulatory T cells (Robertson *et al.* 2018). Longitudinal studies from preconception to postpartum, such as reported by Foo et al. (Foo *et al.* 2018), are needed to find out whether all women with early onset preeclampsia had pregestational cardiovascular dysfunction or whether women with normal cardiovascular function can also develop this complication.

Normal early pregnancy placentation is associated with a decrease in maternal uterine artery resistance indices as measured using Doppler ultrasound (Lin *et al*. 1995, Prefumo *et al*. 2004). This phenomenon has always been interpreted as implying that the physiological decrease in uterine artery resistance is a consequence of placental invasion into the myometrium (Figure 2). However, more recent evidence has demonstrated that uterine artery Doppler waveforms better reflect maternal systemic vascular resistance rather than local uterine artery resistance (Kalafat *et al*. 2018, Perry H *et al* 2018C). The latter data would indicate that maternal uterine perfusion dictates the degree of placental invasion rather than the other way round – a hypothesis which is consistent with cellular and mechanistic studies of trophobalsat function (Charolidi *et al.* 2019; James-Allan *et al*. 2018; Leslie *et al*. 2015; Wallace *et al*. 2015).

Epidemiological evidence supports this hypothesis, as both preeclampsia and cardiovascular disease share the same predisposing factors such as age, obesity, diabetes, ethnicity and co-morbidities like essential hypertension or chronic renal disease. Furthermore, irrespective of whether dealing with early or late preeclampsia, mothers present with cardiovascular signs (hypertension and oedema) and chamber dysfunction. Finally, preeclampsia has a significant cardiovascular legacy with up to 30% of women developing essential hypertension within the first 10 years following birth (Behrens *et al.* 2017). Cardiorenal interactions in early preeclampsia act via different pathways - increased cardiac afterload and reduced cardiac output are responsible for reduced renal arterial blood flow and oxygenation. Additionally, impaired diastolic dysfunction predisposes to venous congestion and venous hypertension. Associated endothelial dysfunction and inflammatory response further disturb the normal cardiorenal crosstalk.

Pregnancy-induced cardiovascular dysfunction predisposing to Type I cardiorenal syndrome and late-onset preeclampsia
Volume expansion and increasing volume load is a feature of late pregnancy and is exaggerated by fetal macrosomia, prolonged or multiple pregnancy. The latter is associated with subclinical chamber diastolic dysfunction in approximately 15% of healthy pregnant women at term. Thus, it is evident that even in uncomplicated pregnancies, the maternal cardiovascular system is pushed to its maximum functional limits at the edge of decompensation. This is evident when assessing cardiovascular condition in obese women, advanced maternal age or multiple gestation, where the

prevalence and severity of maternal cardiovascular dysfunction at term is significantly increased (Budderberg *et a*l 2018B, Ghi *et al.* 2015). As maternal cardiovascular dysfunction occurs acutely and at the end of pregnancy, late preeclampsia is only infrequently associated with fetal growth restriction – placental dysfunction is short lived and rarely results in fetal growth restriction (Verlohren *et al.* 2014). Similarly, the acute nature of the cardiovascular insult resulting in hypoperfusion of the placenta is short-lived and unlikely to result in histologically evident placental damage (Falco *et a*l. 2017). The links between cardiac and renal dysfunction in this process are comparable to those involved in early onset preeclampsia, however venous congestion dominates over arterial hypoperfusion and reflex hypertonia, due to which the clinical presentation of this type of preeclampsia is less fulminant and usually in a later stage of pregnancy.

Preeclampsia superimposed upon pre-existing cardiorenal disease predisposing to type V cardiorenal syndrome.

It is well known that chronic hypertension and renal disease are risk factors for development of preeclampsia, and also that pregnancy often induces faster progress of pre-existing cardiac and renal disease. Pregnant women with systemic or autoimmune disorders, who are particularly at risk for combined cardiorenal dysfunctions, are considered a high risk group requiring highly specialised prenatal follow up and management. As such, this group fulfils all criteria of the cardiorenal syndrome type V with simultaneous presentation and worsening of cardiac and renal dysfunction (Di Lullo *et al.* 2017).

PATHOPHYSIOLOGICAL AND CLINCIALIMPLICATIONS OF CARDIORENAL DYSFUNCTION

The concept of cardiorenal crosstalk in young pregnant women suffering preeclampsia provides several pathophysiological insights and clinical implications.

Pathophysiological insights
- Preeclampsia shares similar risk factors with cardiovascular and renal disease
- Pre-existing cardiovascular or renal disease predisposes to chronic volume overload, cardiovascular dysfunction and type II cardiorenal syndrome – recognised as early preeclampsia
- A significant proportion of healthy women develop subclinical diastolic dysfunction at term as a consequence of the volume load of pregnancy. In some, it leads to type I cardiorenal syndrome and the disease we recognise as late preeclampsia.

Clinical implications
- Maternal hemodynamic assessment is likely to become a cornerstone of management of preeclampsia
- Specific biochemical markers for cardiorenal syndrome may be of value in the routine workup of preeclampsia
- Management of hypertension may be optimally tailored by assessing haemodynamic effects (cardiac output, total vascular resistance) of therapy in addition to monitoring control of blood pressure.
- Regardless of the phenotype of preeclampsia, there is a significant postpartum maternal legacy with a high incidence of essential hypertension which is a public health priority

Captions to Figures

Abstract Figure

Summary of abnormal characteristics at the level of heart, kidneys, arteries, veins and interconnecting systems as reported for early- (EPE) and late-onset preeclampsia (LPE). Arrows ↑ and ↓ represent enhanced or hampered functioning relative to uncomplicated pregnancy respectively. The features show similarities for early onset preeclampsia and chronic cardiorenal syndrome (Type II) as well as late onset preeclampsia and acute cardiorenal syndrome (Type I). PI: pulsatility index ; RI: resistance index ; Abnl: abnormal

Figure 1

Schematic presentation of the pathophysiologic mechanisms contributing to deterioration of renal function from excessive volume load (fetal macrosomia, twin pregnancy, prolonged pregnancy, excessive weight gain and placental hydrops) as well as limiting cardiovascular reserve (age, obesity, ethnicity, diabetes, chronic hypertension and renal disease). Subsequent changes to circulating volume and cardiac contractility will influence maternal cardiac output and peripheral vascular resistance thereby impairing placental perfusion – a prerequisite for the development of preeclampsia.

Figure 2

Abnormal cardiorenal interactions during pregnancy predispose to early placental dysfunction predominantly from poor cardiovascular reserve and late placental dysfunction from volume overload. Placental dysfunction may manifest as preeclampsia and/or fetal growth restriction. Women whose pregnancies were complicated by either preeclampsia or fetal growth restriction are at increased post-partum risk for cardiovascular, cerebrovascular and renal disease long-term.

References

AbdAlla S, Lother H, el Massiery A, Quitterer U (2001). Increased AT(1) receptor heterodimers in preeclampsia mediate enhanced angiotensin II responsiveness. *Nat Med*. **7**:1003-9.

Akcay A, Nguyen Q, Edelstein CL (2009). Mediators of inflammation in acute kidney injury. *Mediators Inflamm.* **2009**:137072. doi: 10.1155/2009/137072. Epub 2010 Feb 21.

Álvarez-Fernández I, Prieto B, Rodríguez V, Ruano Y, Escudero AI, Álvarez FV (2016). N-terminal pro B-type natriuretic peptide and angiogenic biomarkers in the prognosis of adverse outcomes in women with suspected preeclampsia. Clin Chim Acta 463:150-157.

Andrietti S, Kruse AJ, Bekkers SC, Sep S, Spaanderman M, Peeters LL (2008). Cardiac adaptation to pregnancy in women with a history of preeclampsia and a subnormal plasma volume. *Reprod Sci* **15**:1059-65.

Angeli E, Verdecchia P, Narducci P, Angeli F (2011). Additive value of standard ECG for the risk prediction of hypertensive disorders during pregnancy. *Hypertens Res* **34**:707-13.

Angeli F, Angeli E, Verdecchia P (2015). Novel Electrocardiographic Patterns for the Prediction of Hypertensive Disorders of Pregnancy--From Pathophysiology to Practical Implications. *Int J Mol Sci*. **16**:18454-73.

Anim-Nyame N, Gamble J, Sooranna SR, Johnson MR, Sullivan MH, Steer PJ (2003). Evidence of impaired microvascular function in pre-eclampsia: a non-invasive study. *Clin Sci (Lond).* **104**:405-12.

Anim-Nyame N, Sooranna SR, Johnson MR, Sullivan MH, Gamble J, Steer PJ (2004). Impaired retrograde transmission of vasodilatory signals via the endothelium in pre-eclampsia: a cause of reduced tissue blood flow? *Clin Sci (Lond)* **106**:19-25.

Anton L, Brosnihan KB (2008). Systemic and uteroplacental renin--angiotensin system in normal and pre-eclamptic pregnancies. Ther Adv Cardiovasc Dis 2:349-62.

Austdal M, Skråstad RB, Gundersen AS, Austgulen R, Iversen AC, Bathen TF (2014). Metabolomic biomarkers in serum and urine in women with preeclampsia. *PLoS One* **9**(3):e91923. doi: 10.1371/journal.pone.0091923. eCollection 2014.

Bartsch E, Medcalf KE, Park AL, Ray JG; High Risk of Pre-eclampsia Identification Group (2016). Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. *BMJ.* **Apr 19;353**:i1753. doi: 10.1136/bmj.i1753.

Bateman GA, Giles W, England SL (2004). Renal venous Doppler sonography in preeclampsia. *J Ultrasound Med.* **23**:1607-11.

Bauersachs J, Schäfer A (2004). Endothelial dysfunction in heart failure: mechanisms and therapeutic approaches. *Curr Vasc Pharmacol* **2**:115-24.

Baumert M, Seeck A, Faber R, Nalivaiko E, Voss A (2010). Longitudinal changes in QT interval variability and rate adaptation in pregnancies with normal and abnormal uterine perfusion. *Hypertens Res* **33**:555-60.

Baumfeld Y, Novack L, Wiznitzer A, Sheiner E, Henkin Y, Sherf M, Novack V (2015). Pre-Conception Dyslipidemia Is Associated with Development of Preeclampsia and Gestational Diabetes Mellitus. *PLoS One* Oct 9;10(10):e0139164. doi: 10.1371/journal.pone.0139164. eCollection 2015. Erratum in: PLoS One. 2015;10(11):e0142462.

Behrens I, Basit S, Melbye M, Lykke JA, Wohlfahrt J, Bundgaard H, Thilaganathan B, Boyd HA (2017). Risk of post-pregnancy hypertension in women with a history of hypertensive disorders of pregnancy: nationwide cohort study. BMJ. 2017 Jul 12;358:j3078. doi: 10.1136/bmj.j3078.

Bekheirnia MR1, Schrier RW (2006). Pathophysiology of water and sodium retention: edematous states with normal kidney function. *Curr Opin Pharmacol* **6**:202-7.

Bijl RC, Valensise H, Novelli GP, Vasapollo B, Wilkinson I, Thilaganathan B, Stöhr EJ, Lees C, van der Marel CD, Cornette JMJ; International Working Group on Maternal Hemodynamics (2019). Methods and considerations concerning cardiac output measurement in pregnant women: recommendations of the International Working Group on Maternal Hemodynamics. *Ultrasound Obstet Gynecol* Feb 8. doi: 10.1002/uog.20231. [Epub ahead of print]

Blake P, Hasegawa Y, Khosla MC, Fouad-Tarazi F, Sakura N, Paganini EP (1996). Isolation of "myocardial depressant factor(s)" from the ultrafiltrate of heart failure patients with acute renal failure. *ASAIO J*. **42**:M911-5.

Boeldt DS, Bird IM (2017). Vascular adaptation in pregnancy and endothelial dysfunction in preeclampsia. *J Endocrinol* **232**:R27-R44.

Bongartz LG, Cramer MJ, Doevendans PA, Joles JA, Braam B (2005). The severe cardiorenal syndrome: 'Guyton revisited'. *Eur Heart J* **26**:11-7. Epub 2004 Nov 30.

Bonventre JV (2003). Dedifferentiation and proliferation of surviving epithelial cells in acute renal failure. *J Am Soc Nephrol*. **14 Suppl 1**:S55-61.

Borges VTM, Zanati SG, Peraçoli MTS, Poiati JR, Romão-Veiga M, Peraçoli JC, Thilaganathan B (2018). Maternal left ventricular hypertrophy and diastolic dysfunction and brain natriuretic peptide concentration in early- and late-onset pre-eclampsia. *Ultrasound Obstet Gynecol* **51**:519-523.

Borghi C, Verardi FM, Pareo I, Bentivenga C, Cicero AF (2014). Hyperuricemia and cardiovascular disease risk. *Expert Rev Cardiovasc Ther* **12**:1219-25.

Brosens JJ, Pijnenborg R, Brosens IA (2002). The myometrial junctional zone spiral arteries in normal and abnormal pregnancies: a review of the literature. *Am J Obstet Gynecol*. **187**:1416-23.

Bryant D, Becker L, Richardson J, Shelton J, Franco F, Peshock R, Thompson M, Giroir B (1998). Cardiac failure in transgenic mice with myocardial expression of tumor necrosis factor-alpha. *Circulation.* **97**:1375-81.

Buddeberg BS, Sharma R, O'Driscoll JM, Kaelin Agten A, Khalil A, Thilaganathan B (2018A). Cardiac maladaptation in term pregnancies with preeclampsia. *Pregnancy Hypertens* **13**:198-203.

Buddeberg BS, Sharma R, O'Driscoll JM, Kaelin Agten A, Khalil A, Thilaganathan B (2018B). Cardiac maladaptation in obese pregnancy at term. *Ultrasound Obstet Gynecol*. Oct 31. doi: 10.1002/uog.20170. [Epub ahead of print]

Burnett LA, Nowak RA (2016). Exosomes mediate embryo and maternal interactions at implantation and during pregnancy. *Front Biosci (Schol Ed)* **8**:79-96.

Burton GJ (2009). Oxygen, the Janus gas; its effects on human placental development and function. J Anat. **215**:27-35.

Çağlar FN, Ozde C, Bostancı E, Çağlar İM, Çiftçi S, Unğan İ, Demir B, Karakaya O (2016). Assessment of right heart function in preeclampsia by echocardiography. *Pregnancy Hypertens* **6**:89-94.

Castleman JS, Ganapathy R, Taki F1, Lip GY, Steeds RP, Kotecha D (2016). Echocardiographic Structure and Function in Hypertensive Disorders of Pregnancy: A Systematic Review. *Circ Cardiovasc Imaging* **9**. pii: e004888. doi: 10.1161/CIRCIMAGING.116.004888.

Chapman AB, Abraham WT, Zamudio S, Coffin C, Merouani A, Young D, Johnson A, Osorio F, Goldberg C, Moore LG, Dahms T, Schrier RW (1998). Temporal relationships between hormonal and hemodynamic changes in early human pregnancy. *Kidney Int* **54**:2056-63.

Charolidi N, Host AJ, Ashton S, Tryfonos Z, Leslie K, Thilaganathan B, Cartwright JE, Whitley GS (2019). First trimester placental endothelial cells from pregnancies with abnormal uterine artery Doppler are more sensitive to apoptotic stimuli. *Lab Invest*. **99**:411-420.

Chen X, Man GCW, Liu Y, Wu F, Huang J, Li TC1, Wang CC (2017). Physiological and pathological angiogenesis in endometrium at the time of embryo implantation. *Am J Reprod Immunol*Aug;78(2). doi: 10.1111/aji.12693. Epub 2017 May 3.

Chun R, Kirkpatrick AW (2012). Intra-abdominal pressure, intra-abdominal hypertension, and pregnancy: a review. *Ann Intensive Care*. **2 Suppl 1**:S5.

Colombo PC, Ganda A, Lin J, Onat D, Harxhi A, Iyasere JE, Uriel N, Cotter G 2012). Inflammatory activation: cardiac, renal, and cardio-renal interactions in patients with the cardiorenal syndrome. *Heart Fail Rev.* **17**:177-90.

Cong J, Fan T, Yang X, Shen J, Cheng G, Zhang Z (2015). Maternal cardiac remodeling and dysfunction in preeclampsia: a three-dimensional speckle-tracking echocardiography study. *Int J Cardiovasc Imaging* **31**:1361-8.

Conrad KP, Davison JM (2014). The renal circulation in normal pregnancy and preeclampsia: is there a place for relaxin? *Am J Physiol Renal Physiol* **306**:F1121-35.

Craici IM, Wagner SJ, Weissgerber TL, Grande JP, Garovic VD (2014). Advances in the pathophysiology of pre-eclampsia and related podocyte injury. *Kidney Int*. **86**:275-85.

Damman K, van Deursen VM, Navis G, Voors AA, van Veldhuisen DJ, Hillege HL (2009). Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease. *J Am Coll Cardiol* **53**:582-588.

Davison JM (1997). Edema in pregnancy. *Kidney Int Suppl* **59**:S90-6.

de Haas S, Ghossein-Doha C, van Kuijk SM, van Drongelen J, Spaanderman ME (2017). Physiological adaptation of maternal plasma volume during pregnancy: a systematic review and meta-analysis. *Ultrasound Obstet Gynecol*. **49**:177-187.

De Deyn PP, Vanholder R, D'Hooge R (2003). Nitric oxide in uremia: effects of several potentially toxic guanidino compounds. *Kidney Int Suppl*. **84**:S25-8.

De Wolf F, Brosens I, Robertson WB (1982). Ultrastructure of uteroplacental arteries. *Contrib Gynecol Obstet.* **9**:86-99.

Di Lullo L, Bellasi A, Barbera V, Russo D, Russo L, Di Iorio B, Cozzolino M, Ronco C (2017). Pathophysiology of the cardio-renal syndromes types 1-5: An uptodate. *Indian Heart J.* **69**:255-265.

Duvekot JJ, Cheriex EC, Pieters FA, Menheere PP, Peeters LH (1993). Early pregnancy changes in hemodynamics and volume homeostasis are consecutive adjustments triggered by a primary fall in systemic vascular tone. *Am J Obstet Gynecol* **169**:1382-92.

Easterling TR, Benedetti TJ, Schmucker BC, Millard SP (1990). Maternal hemodynamics in normal and preeclamptic pregnancies: a longitudinal study. *Obstet Gynecol* **76**:1061-9

Elmore S (2007). Apoptosis: a review of programmed cell death. *Toxicol Pathol*. **35**:495-516.

Fakhouri F, Vercel C, Frémeaux-Bacchi V (2012). Obstetric nephrology: AKI and thrombotic microangiopathies in pregnancy. *Clin J Am Soc Nephrol* **7**:2100-6.

Falco ML, Sivanathan J, Laoreti A, Thilaganathan B, Khalil A (2017). Placental histopathology associated with pre-eclampsia: systematic review and meta-analysis. *Ultrasound Obstet Gynecol*. **50**:295-301.

Ferrazzi E, Stampalija T, Monasta L, Di Martino D, Vonck S, Gyselaers W (2018). Maternal hemodynamics: a method to classify hypertensive disorders of pregnancy. *Am J Obstet Gynecol* **218**:124.e1-124.e11.

Finnerty NM, Panchal AR, Boulger C, Vira A, Bischof JJ, Amick C, Way DP1, Bahner DP. Inferior Vena Cava Measurement with Ultrasound: What Is the Best View and Best Mode? *West J Emerg Med*. 2017 **18**:496-501.

Fischer-Betz R, Specker C (2017). Pregnancy in systemic lupus erythematosus and antiphospholipid syndrome. *Best Pract Res Clin Rheumatol* **31**:397-414.

Foo FL, Mahendru AA, Masini G, Fraser A, Cacciatore S, MacIntyre DA, McEniery CM, Wilkinson IB, Bennett PR, Lees CC (2018). Association Between Prepregnancy Cardiovascular Function and Subsequent Preeclampsia or Fetal Growth Restriction. *Hypertension* **72**:442-450.

Franz MB, Burgmann M, Neubauer A, Zeisler H, Sanani R, Gottsauner-Wolf M, Schiessl B, Andreas M (2013). Augmentation index and pulse wave velocity in normotensive and pre-eclamptic pregnancies. *Acta Obstet Gynecol Scand* **92**:960-6.

Friedberg V, Lutz J (1963). Studies on capillary permeability in pregnancy. (A contribution to the cause of proteinuria in toxemias. *Arch Gynakol* **199**:96-106.

Fu Q, Cao L, Li H, Wang B, Li Z (2014). Cardiorenal syndrome: pathophysiological mechanism, preclinical models, novel contributors and potential therapies. *Chin Med J (Engl)* **127**:3011-8.

Funk DJ, Jacobsohn E, Kumar A (2013). The role of venous return in critical illness and shock-part I: physiology. Crit Care Med. 41:255-62.

García-Donaire JA, Ruilope LM (2011). Cardiovascular and Renal Links along the Cardiorenal Continuum. *Int J Nephrol*. **2011**:975782. doi: 10.4061/2011/975782. Epub 2011 Mar 31

Galley HF, Webster NR (2004). Physiology of the endothelium. *Br J Anaesth* **93**:105-13.

Gallos ID, Sivakumar K, Kilby MD, Coomarasamy A, Thangaratinam S, Vatish M (2013). Pre-eclampsia is associated with, and preceded by, hypertriglyceridaemia: a meta-analysis. *BJOG* **120**:1321-32.

Ghi T, degli Esposti D, Montaguti E, Rosticci M, Tancredi S, Youssef A, di Giovanni MV, Pilu G, Borghi C, Rizzo N (2015). Maternal cardiac evaluation during uncomplicated twin pregnancy with emphasis on the diastolic function. Am J Obstet Gynecol. 2015 Sep;213(3):376.e1-8. doi: 10.1016/j.ajog.2015.05.003. Epub 2015 May 5.

Guo HX, Zhu YB, Wu CP, Zhong M, Hu SW (2019). Potential urine biomarkers for gestational hypertension and preeclampsia. *Mol Med Rep*. Jan 30. doi: 10.3892/mmr.2019.9911. [Epub ahead of print]

Gyselaers W, Mesens T, Tomsin K, Molenberghs G, Peeters L (2010). Maternal renal interlobar vein impedance index is higher in early- than in late-onset pre-eclampsia. *Ultrasound Obstet Gynecol*. **36**:69-75.

Gyselaers W, Mullens W, Tomsin K, Mesens T, Peeters L (2011). Role of dysfunctional maternal venous hemodynamics in the pathophysiology of pre-eclampsia: a review. *Ultrasound Obstet Gynecol.* **38**:123-9.

Gyselaers W, Tomsin K, Staelens A, Mesens T, Oben J, Molenberghs G (2014). Maternal venous hemodynamics in gestational hypertension and preeclampsia. *BMC Pregnancy Childbirth*. Jun 23;14:212. doi: 10.1186/1471-2393-14-212.

Gyselaers W, Vonck S, Staelens AS, Lanssens D, Tomsin K, Oben J, Dreesen P, Bruckers L. Body fluid volume homeostasis is abnormal in pregnancies complicated with hypertension and/or poor fetal growth. PLoS One **13**:e0206257. doi: 10.1371/journal.pone.0206257. eCollection 2018

Gyselaers WJ, Vonck S, Staelens ASE, Lanssens D, Tomsin K, Oben J, Dreesen P, Bruckers L (2019). Gestational hypertensive disorders show unique patterns of circulatory deterioration with ongoing pregnancy. *Am J Physiol Regul Integr Comp Physiol* Jan 23. doi: 10.1152/ajpregu.00075.2018. [Epub ahead of print]

Hadid V, Patenaude V, Oddy L, Abenhaim HA (2015). Sarcoidosis and pregnancy: obstetrical and neonatal outcomes in a population-based cohort of 7 million births. *J Perinat Med*. **43**:201-7.

Hanada S, Takewa Y, Mizuno T, Tsukiya T, Taenaka Y, Tatsumi E (2012). Effect of the technique for assisting renal blood circulation on ischemic kidney in acute cardiorenal syndrome. *J Artif Organs*. **15**:140-5.

Harnett JD, Foley RN, Kent GM, Barre PE, Murray D, Parfrey PS (1995). Congestive heart failure in dialysis patients: prevalence, incidence, prognosis and risk factors. *Kidney Int.* **47**:884-90.

Havasi A, Borkan SC (2011). Apoptosis and acute kidney injury. *Kidney Int.* **80**:29-40.

Hayashi M, Ueda Y, Hoshimoto K, Ota Y, Fukasawa I, Sumori K, Kaneko I, Abe S, Uno M, Ohkura T, Inaba N (2002). Changes in urinary excretion of six biochemical parameters in normotensive pregnancy and preeclampsia. *Am J Kidney Dis*. **39**:392-400.

Henao DE, Saleem MA, Cadavid AP (2010). Glomerular disturbances in preeclampsia: disruption between glomerular endothelium and podocyte symbiosis. *Hypertens Pregnancy* **29**:10-20.

Herse F, Verlohren S, Wenzel K, Pape J, Muller DN, Modrow S, Wallukat G, Luft FC, Redman CW, Dechend R (2009). Prevalence of agonistic autoantibodies against the angiotensin II type 1 receptor and soluble fms-like tyrosine kinase 1 in a gestational age-matched case study. *Hypertension* **53**:393-8.

Hladunewich M, Karumanchi SA, Lafayette R (2007). Pathophysiology of the clinical manifestations of preeclampsia. *Clin J Am Soc Nephrol* **2**:543-9.

Huppertz B, Weiss G, Moser G (2014). Trophoblast invasion and oxygenation of the placenta: measurements versus presumptions. *J Reprod Immunol*. **101-102**:74-79.

Inci S, Nar G, Aksan G, Sipahioğlu H, Soylu K, Dogan A (2015). P-Wave Dispersion and Atrial Electromechanical Delay in Patients with Preeclampsia. *Med Princ Pract* **24**:515-21.

Ilyas A, Ishtiaq W, Assad S, Ghazanfar H, Mansoor S, Haris M, Qadeer A, Akhtar A (2017). Correlation of IVC Diameter and Collapsibility Index With Central Venous Pressure in the Assessment of Intravascular Volume in Critically Ill Patients. *Cureus* **9**(2):e1025. doi: 10.7759/cureus.1025.

Irani RA, Xia Y (2008). The functional role of the renin-angiotensin system in pregnancy and preeclampsia. *Placenta* **29**:763-71.

Irani RA, Xia Y (2011). Renin angiotensin signaling in normal pregnancy and preeclampsia. *Semin Nephrol* **31**:47-58.

James-Allan LB, Whitley GS, Leslie K, Wallace AE, Cartwright JE (2018). Decidual cell regulation of trophoblast is altered in pregnancies at risk of pre-eclampsia. *J Mol Endocrinol*. **60**:239-246.

Jeffcoate TN (1966). Pre-eclampsia and eclampsia: the disease of theories. *Proc R Soc Med*. **59**:397-404.

Jeyabalan A, Conrad KP (2007). Renal function during normal pregnancy and preeclampsia. *Front Biosci* **12**:2425-37.

Jim B, Mehta S, Qipo A, Kim K, Cohen HW, Moore RM, He JC, Sharma S (2014). A comparison of podocyturia, albuminuria and nephrinuria in predicting the development of preeclampsia: a prospective study. *PLoS One* **9**(7):e101445. doi: 10.1371/journal.pone.0101445. eCollection 2014.

Jin WY, Lin SL, Hou RL, Chen XY, Han T, Jin Y, Tang L, Zhu ZW, Zhao ZY (2016). Associations between maternal lipid profile and pregnancy complications and perinatal outcomes: a population-based study from China. *BMC Pregnancy Childbirth* **16**:60. doi: 10.1186/s12884-016-0852-9.

Johnson RJ, Nangaku M (2016). Endothelial Dysfunction: The Secret Agent Driving Kidney Disease. J *Am Soc Nephrol*. **27**:3-5.

Jung YJ, Cho HY, Cho S, Kim YH, Jeon JD, Kim YJ, Lee S, Park J, Kim HY, Park YW, Kwon JY (2017). The Level of Serum and Urinary Nephrin in Normal Pregnancy and Pregnancy with Subsequent Preeclampsia. *Yonsei Med J* **58**:401-406.

Kajimoto K, Sato N, Keida T, Sakata Y, Takano T; Acute Decompensated Heart Failure Syndromes (ATTEND) Investigators (2014). Associations of anemia and renal dysfunction with outcomes among patients hospitalized for acute decompensated heart failure with preserved or reduced ejection fraction. *Clin J Am Soc Nephrol*. **9**:1912-21.

Kalafat E, Thilaganathan B (2017). Cardiovascular origins of preeclampsia. *Curr Opin Obstet Gynecol* **29**:383-389.

Kalafat E, Laoreti A, Khalil A, Da Silva Costa F, Thilaganathan B (2018). Ophthalmic artery Doppler for prediction of pre-eclampsia: systematic review and meta-analysis. *Ultrasound Obstet Gynecol* **51**:731-737.

Karabulut N, Baki Yağci A, Karabulut A (2003). Renal vein Doppler ultrasound of maternal kidneys in normal second and third trimester pregnancy. *Br J Radiol* **76**:444-7.

Keller G, Zimmer G, Mall G, Ritz E, Amann K(2003). Nephron number in patients with primary hypertension. *N Engl J Med* **348**:101-8.

Kelly KJ (2003). Distant effects of experimental renal ischemia/reperfusion injury. *J Am Soc Nephrol.* **14**:1549-58.

Khalil A, Garcia-Mandujano R, Maiz N, Elkhouli M, Nicolaides KH (2014A). Longitudinal changes in uterine artery Doppler and blood pressure and risk of pre-eclampsia. *Ultrasound Obstet Gynecol*. **43**:541-7. Erratum in: Ultrasound Obstet Gynecol. 2014 Aug;44(2):244.

Khalil A, Garcia-Mandujano R, Maiz N, Elkhouli M, Nicolaides KH (2014B). Longitudinal changes in maternal hemodynamics in a population at risk for pre-eclampsia. *Ultrasound Obstet Gynecol*. **44**:197-204.

Kingma JG Jr, Vincent C, Rouleau JR, Kingma I (2006). Influence of acute renal failure on coronary vasoregulation in dogs. *J Am Soc Nephrol*. **17**:1316-24.

Kirbas A, Kirbas O, Daglar K, Inal HA, Kurmus O, Kara O, Timur H, Gencosmanoglu G, Danisman N (2016). Novel indexes of arrhythmogenesis in preeclampsia: QT dispersion, Tp-e interval, and Tp-e/QT ratio. *Pregnancy Hypertens* **6**:38-41.

Kishimoto T, Maekawa M, Abe Y, Yamamoto K (1973). Intrarenal distribution of blood flow and renin release during renal venous pressure elevation. *Kidney Int*. **4**:259-66.

Kwiatkowski S, Dołegowska B, Kwiatkowska E, Rzepka R, Marczuk N, Loj B, Torbè A (2017). Maternal endothelial damage as a disorder shared by early preeclampsia, late preeclampsia and intrauterine growth restriction. *J Perinat Med* **45**:793-802.

Lafayette RA, Druzin M, Sibley R, Derby G, Malik T, Huie P, Polhemus C, Deen WM, Myers BD (1998). Nature of glomerular dysfunction in pre-eclampsia. *Kidney Int* **54**:1240-9.

Lanssens D, Smeets CJP, Vandervoort P, Grieten L, Gyselaers W (2018). Intrathoracic fluid changes from preconception to postpartum as measured by bio-impedance monitoring. *J Matern Fetal Neonatal Med* **30**:1-3.

Lau ES, Sarma A (2017). The Role of Cardiac Biomarkers in Pregnancy. *Curr Treat Options Cardiovasc Med.* **19**:49.

Le Jemtel TH, Rajapreyar I, Selby MG, Payne B, Barnidge DR, Milic N, Garovic VD (2015). Direct evidence of podocyte damage in cardiorenal syndrome type 2: preliminary evidence. *Cardiorenal Med.* **5**:125-34.

León-Reyes G, Maida-Claros RF, Urrutia-Medina AX, Jorge-Galarza E, Guzmán-Grenfell AM, Fuentes-García S, Medina-Navarro R, Moreno-Eutimio MA, Muñoz-Sánchez JL, Hicks JJ, Torres-Ramos YD (2017). Oxidative profiles of LDL and HDL isolated from women with preeclampsia. *Lipids Health Dis* **16**:90. doi: 10.1186/s12944-017-0480-z.

Leslie K, Whitley GS, Herse F, Dechend R, Ashton SV, Laing K, Thilaganathan B, Cartwright JE (2015). Increased apoptosis, altered oxygen signaling, and antioxidant defenses in first-trimester pregnancies with high-resistance uterine artery blood flow. *Am J Pathol*. **185**:2731-41.

Levario-Carrillo M, Avitia M, Tufiño-Olivares E, Trevizo E, Corral-Terrazas M, Reza-López S (2006). Body composition of patients with hypertensive complications during pregnancy. *Hypertens Pregnancy* **25**:259-69.

Lima PD, Zhang J, Dunk C, Lye SJ, Croy BA (2014). Leukocyte driven-decidual angiogenesis in early pregnancy. *Cell Mol Immunol* **11**:522-37.

Lin S, Shimizu I, Suehara N, Nakayama M, Aono T (1995). Uterine artery Doppler velocimetry in relation to trophoblast migration into the myometrium of the placental bed. *Obstet Gynecol*. **85**:760-5.

Liszewski MK, Atkinson JP (2011). Too much of a good thing at the site of tissue injury: the instructive example of the complement system predisposing to thrombotic microangiopathy. *Hematology Am Soc Hematol Educ Program* **2011**:9-14. doi: 10.1182/asheducation-2011.1.9.

Lokki AI, Daly E, Triebwasser M, Kurki MI, Roberson EDO, Häppölä P, Auro K, Perola M, Heinonen S, Kajantie E, Kere J, Kivinen K, Pouta A, Salmon JE, Meri S, Daly M, Atkinson JP, Laivuori H (2017). Protective Low-Frequency Variants for Preeclampsia in the Fms Related Tyrosine Kinase 1 Gene in the Finnish Population. *Hypertension* **70**:365-371.

Lotgering FK, Wallenburg HC (1986). Hemodynamic effects of caval and uterine venous occlusion in pregnant sheep. *Am J Obstet Gynecol* **155**:1164-70.

Lu KJ, Kearney LG, Hare DL, Ord M, Toia D, Jones E, Burrell LM, Srivastava PM (2013). Cardiorenal anemia syndrome as a prognosticator for death in heart failure. *Am J Cardiol*. **111**:1187-91.

Lumbers ER, Pringle KG (2014). Roles of the circulating renin-angiotensin-aldosterone system in human pregnancy. *Am J Physiol Regul Integr Comp Physiol* **306**:R91-101. doi: 10.1152/ajpregu.00034.2013. Epub 2013 Oct 2.

Macdonald-Wallis C, Lawlor DA, Fraser A, May M, Nelson SM, Tilling K (2012). Blood pressure change in normotensive, gestational hypertensive, preeclamptic, and essential hypertensive pregnancies. *Hypertension* **59**:1241-8.

Machnik A, Neuhofer W, Jantsch J, Dahlmann A, Tammela T, Machura K, Park JK, Beck FX, Müller DN, Derer W, Goss J, Ziomber A, Dietsch P, Wagner H, van Rooijen N, Kurtz A, Hilgers KF, Alitalo K, Eckardt KU, Luft FC, Kerjaschki D, Titze J (2009). Macrophages regulate salt-dependent volume and blood pressure by a vascular endothelial growth factor-C-dependent buffering mechanism. *Nat Med*. **15**:545-52.

Mahendru AA, Everett TR, McEniery CM, Wilkinson IB, Lees CC (2013). The feasibility of prospectively studying maternal cardiovascular changes from before conception. *Hypertens Res*. **36**:698-704.

Maisel AS, Katz N, Hillege HL, Shaw A, Zanco P, Bellomo R, Anand I, Anker SD, Aspromonte N, Bagshaw SM, Berl T, Bobek I, Cruz DN, Daliento L, Davenport A, Haapio M, House AA, Mankad S, McCullough P, Mebazaa A, Palazzuoli A, Ponikowski P, Ronco F, Sheinfeld G, Soni S, Vescovo G, Zamperetti N, Ronco C; Acute Dialysis Quality Initiative consensus group (2011). Biomarkers in kidney and heart disease. *Nephrol Dial Transplant* **26**:62-74.

Maluso P, Olson J, Sarani B (2016). Abdominal Compartment Hypertension and Abdominal Compartment Syndrome. *Crit Care Clin*. **32**:213-22.

Matsubara S (2018). Pre-pregnancy cardiovascular indices and birth outcomes of subsequent pregnancies: a 'sequential stress test' revealing hidden cardiovascular weakness? BJOG **125**:1135.

McGinnis R, Steinthorsdottir V, Williams NO, Thorleifsson G, Shooter S, Hjartardottir S, Bumpstead S, Stefansdottir L, Hildyard L, Sigurdsson JK, Kemp JP, Silva GB, Thomsen LCV, Jääskeläinen T, Kajantie E, Chappell S, Kalsheker N, Moffett A, Hiby S, Lee WK, Padmanabhan S, Simpson NAB, Dolby VA, Staines-Urias E1, Engel SM, Haugan A, Trogstad L, Svyatova G, Zakhidova N, Najmutdinova D; FINNPEC Consortium; GOPEC Consortium, Dominiczak AF, Gjessing HK, Casas JP, Dudbridge F, Walker JJ, Pipkin FB, Thorsteinsdottir U, Geirsson RT, Lawlor DA, Iversen AC, Magnus P, Laivuori H, Stefansson K, Morgan L (2017). Variants in the fetal genome near FLT1 are associated with risk of preeclampsia. *Nat Genet* **49**:1255-1260.

Meah VL, Backx K, Davenport MH; International Working Group on Maternal Hemodynamics (2018). Functional hemodynamic testing in pregnancy: recommendations of the International Working Group on Maternal Hemodynamics. *Ultrasound Obstet Gynecol* **51**:331-340.

Melchiorre K, Sutherland GR, Liberati M, Thilaganathan B (2011). Preeclampsia is associated with persistent postpartum cardiovascular impairment. *Hypertension* **58**:709-15.

Melchiorre K, Sharma R, Thilaganathan B (2014). Cardiovascular implications in preeclampsia: an overview. *Circulation* **130**:703-14.

Melchiorre K, Sharma R, Khalil A, Thilaganathan B (2016). Maternal Cardiovascular Function in Normal Pregnancy: Evidence of Maladaptation to Chronic Volume Overload. *Hypertension* **67**:754-62.

Mesens T, Tomsin K, Staelens AS, Oben J, Molenberghs G, Gyselaers W (2014). Is there a correlation between maternal venous hemodynamic dysfunction and proteinuria of preeclampsia? Eur J Obstet Gynecol Reprod Biol. 181:246-50.

Mesens T, Tomsin K, Oben J, Staelens A, Gyselaers W (2015). Maternal venous hemodynamics assessment for prediction of preeclampsia should be longitudinal. *J Matern Fetal Neonatal Med*. **28**:311-5.

Monteith C, McSweeney L, Breatnach CR, Doherty A, Shirren L, Tully EC, Dicker P, Malone FD, El-Khuffash A, Kent E (2017). Non-invasive cardiac output monitoring (NICOM®) can predict the evolution of uteroplacental disease-Results of the prospective HANDLE study. *Eur J Obstet Gynecol Reprod Biol.* **216**:116-124.

Mordel N, Birkenfeld A, Rubinger D, Schenker JG, Sadovsky E (1993). Successful full-term pregnancy in familial Mediterranean fever complicated with amyloidosis: case report and review of the literature. *Fetal Diagn Ther*. **8**:129-34.

Mühlberger I, Mönks K, Fechete R, Mayer G, Oberbauer R, Mayer B, Perco P (2012). Molecular pathways and crosstalk characterizing the cardiorenal syndrome. *OMICS* **16**:105-12.

Mullens W, Abrahams Z, Skouri HN, Francis GS, Taylor DO, Starling RC, Paganini E, Tang WH (2008). Elevated intra-abdominal pressure in acute decompensated heart failure: a potential contributor to worsening renal function? *J Am Coll Cardiol* **51**:300-6.

Mullens W, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, Young JB, Tang WHW (2009). Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. *J Am Coll Cardiol* **53**:589-596.

Namugowa A, Iputo J, Wandabwa J, Meeme A, Buga GAB (2017). Comparison of arterial stiffness in preeclamptic and normotensive pregnant women from a semi-rural region of South Africa. *Clin Exp Hypertens* **39**:277-283.

Napoli C, Casamassimi A, Crudele V, Infante T, Abbondanza C (2011). Kidney and heart interactions during cardiorenal syndrome: a molecular and clinical pathogenic framework. *Future Cardiol* **7**:485-97.

Nejabati HR, Latifi Z, Ghasemnejad T, Fattahi A, Nouri M (2017). Placental growth factor (PlGF) as an angiogenic/inflammatory switcher: lesson from early pregnancy losses. *Gynecol Endocrinol* **33**:668-674.

Ness RB, Roberts JM (1996). Heterogeneous causes constituting the single syndrome of preeclampsia: a hypothesis and its implications. *Am J Obstet Gynecol* **175**:1365-70.

Nohria A, Hasselblad V, Stebbins A, Pauly DF, Fonarow GC, Shah M, Yancy CW, Califf RM, Stevenson LW, Hill JA (2008). Cardiorenal interactions: insights from the ESCAPE trial. *J Am Coll Cardiol*. **51**:1268-74.

Oben J, Tomsin K, Mesens T, Staelens A, Molenberghs G, Gyselaers W (2014). Maternal cardiovascular profiling in the first trimester of pregnancies complicated with gestation-induced hypertension or fetal growth retardation: a pilot study. *J Matern Fetal Neonatal Med*. **27**:1646-51.

Ohuchi H, Ikado H, Noritake K, Miyazaki A, Yasuda K, Yamada O (2013). Impact of central venous pressure on cardiorenal interactions in adult patients with congenital heart disease after biventricular repair. *Congenit Heart Dis* **8**:103-10.

Palei AC, Spradley FT, Warrington JP, George EM, Granger JP (2013). Pathophysiology of hypertension in pre-eclampsia: a lesson in integrative physiology. *Acta Physiol (Oxf)* **208**:224-33.

Paulus BM, Ali S, Zia AA, Munir A, Davis RC Jr, Mansbach CM, Smith WC, Weber KT (2008). Causes and consequences of systemic venous hypertension. *Am J Med Sci*. **336**:489-97.

Perloff JK (1993). Systemic complications of cyanosis in adults with congenital heart disease. Hematologic derangements, renal function, and urate metabolism. *Cardiol Clin*. **11**:689-99.

Perry H, Khalil A, Thilaganathan B (2018A). Preeclampsia and the cardiovascular system: An update. *Trends Cardiovasc Med* **28**:505-513.

Perry H, Stirrup O, Gutierrez J, Vinayagam D, Thilaganathan B, Khalil A (2018B). Influence of maternal characteristics and gestational age on haemodynamic indices: NICOM device-specific reference ranges. *Ultrasound Obstet Gynecol* Nov 22. doi: 10.1002/uog.20179. [Epub ahead of print]

Perry H, Lehmann H, Mantovani E, Thilaganathan B, Khalil A (2018C). Correlation between central and uterine haemodynamics in hypertensive disorders of pregnancy. *Ultrasound Obstet Gynecol*. **Aug 6.** doi: 10.1002/uog.19197. [Epub ahead of print]

Piccoli GB, Zakharova E, Attini R, Ibarra Hernandez M, Orozco Guillien A, Alrukhaimi M, Liu ZH, Ashuntantang G, Covella B, Cabiddu G, Li PKT, Garcia-Garcia G, Levin A (2018). Pregnancy in Chronic Kidney Disease: Need for Higher Awareness. A Pragmatic Review Focused on What Could Be Improved in the Different CKD Stages and Phases. *J Clin Med* **7(11)**. pii: E415. doi: 10.3390/jcm7110415

Prabhu SD (2004). Cytokine-induced modulation of cardiac function. *Circ Res*. **95**:1140-53.

Prakash J, Ganiger VC (2017). Acute Kidney Injury in Pregnancy-specific Disorders. *Indian J Nephrol*. **27**:258-270.

Prefumo F, Sebire NJ, Thilaganathan B (2004). Decreased endovascular trophoblast invasion in first trimester pregnancies with high-resistance uterine artery Doppler indices. *Hum Reprod*. **19**:206-9

Raffaelli R, Prioli MA, Parissone F, Prati D, Carli M, Bergamini C, Cacici G, Balestreri D, Vassanelli C, Franchi M (2014). Pre-eclampsia: evidence of altered ventricular repolarization by standard ECG parameters and QT dispersion. *Hypertens Res* **37**:984-8.

Rauchhaus M, Doehner W, Francis DP, Davos C, Kemp M, Liebenthal C, Niebauer J, Hooper J, Volk HD, Coats AJ, Anker SD (2000). Plasma cytokine parameters and mortality in patients with chronic heart failure. *Circulation.* **102**:3060-7.

Redman C (2014). Pre-eclampsia: A complex and variable disease. *Pregnancy Hypertens* **4**:241-2.

Redman CW, Sargent IL (2005). Latest advances in understanding preeclampsia. *Science* **308**(5728):1592-4.

Reuter DG, Law Y, Levy WC, Seslar SP, Zierler RE, Ferguson M, Chattra J, McQuinn T, Liu LL, Terry M, Coffey PS, Dimer JA, Hanevold C, Flynn JT, Stapleton FB (2016). Can preeclampsia be considered a renal compartment syndrome? A hypothesis and analysis of the literature. *J Am Soc Hypertens*. **10**:891-899.

Robertson SA, Care AS, Moldenhauer LM (2018). Regulatory T cells in embryo implantation and the immune response to pregnancy. *J Clin Invest* **128**:4224-4235.

Robson JS (1976). Proteinuria and the renal lesion in preeclampsia and abruptio placentae. *Perspect Nephrol Hypertens* **5**:61-73.

Ronco C, House AA, Haapio M (2008). Cardiorenal syndrome: refining the definition of a complex symbiosis gone wrong. *Intensive Care Med* **34**:957-62.

Ronco C, Maisel A (2010). Volume overload and cardiorenal syndromes. *Congest Heart Fail*. **16 Suppl 1**:Si-iv; quiz Svi.

Roobottom CA, Hunter JD, Weston MJ, Dubbins PA (1995). Hepatic venous Doppler waveforms: changes in pregnancy. *J Clin Ultrasound* 23:477-82.

Salas SP, Marshall G, Gutiérrez BL, Rosso P (2006). Time course of maternal plasma volume and hormonal changes in women with preeclampsia or fetal growth restriction. *Hypertension* **47**:203-8.

Sandgren JA, Scroggins SM, Santillan DA, Devor EJ, Gibson-Corley KN, Pierce GL, Sigmund CD, Santillan MK, Grobe JL (2015). Vasopressin: the missing link for preeclampsia? *Am J Physiol Regul Integr Comp Physiol* **309**:R1062-4. doi: 10.1152/ajpregu.00073.2015. Epub 2015 Mar 25.

Sawchuck DJ, Wittmann BK (2014). Pre-eclampsia renamed and reframed: Intra-abdominal hypertension in pregnancy. *Med Hypotheses*. **83**:619-32.

Scheuer J, Stezoski W (1973). The effects of uremic compounds on cardiac function and metabolism. *J Mol Cell Cardiol*. **5**:287-300.

Schlembach D (2003). Pre-eclampsia--still a disease of theories. *Fukushima J Med Sci.* **49**:69-115.

Schrier RW, Briner VA (1991). Peripheral arterial vasodilation hypothesis of sodium and water retention in pregnancy: implications for pathogenesis of preeclampsia-eclampsia. *Obstet Gynecol*. **77**:632-9.

Sep SJ, Schreurs MP, Bekkers SC, Kruse AJ, Smits LJ, Peeters LL (2011). Early-pregnancy changes in cardiac diastolic function in women with recurrent pre-eclampsia and in previously pre-eclamptic women without recurrent disease. *BJOG* **118**:1112-9.

Shamseddin MK, Parfrey PS (2009). Mechanisms of the cardiorenal syndromes. Nat Rev Nephrol 5:641-9.

Shih T, Peneva D, Xu X, Sutton A, Triche E, Ehrenkranz RA, Paidas M, Stevens W (2016). The Rising Burden of Preeclampsia in the United States Impacts Both Maternal and Child Health. *Am J Perinatol* **33**:329-38.

Sitras V, Paulssen RH, Grønaas H, Leirvik J, Hanssen TA, Vårtun A, Acharya G (2009). Differential placental gene expression in severe preeclampsia. *Placenta* **30**:424-33.

Smeets CJ, Lanssens D, Gyselaers W, Bertrand PB, Grieten L, Vandervoort P (2016). Detection of subclinical transient fluid accumulation during pregnancy in a patient with an implantable cardioverter defibrillator and OptiVol® fluid monitoring algorithm. *Int J Cardiol* **214**:163-5.

Spinillo A, Beneventi F, Caporali R, Ramoni V, Montecucco C (2017). Undifferentiated connective tissue diseases and adverse pregnancy outcomes. An undervalued association? *Am J Reprod Immunol.* **78**. doi: 10.1111/aji.12762. Epub 2017 Sep 16.

Spracklen CN, Smith CJ, Saftlas AF, Robinson JG, Ryckman KK (2014). Maternal hyperlipidemia and the risk of preeclampsia: a meta-analysis. *Am J Epidemiol* **180**:346-58

Spracklen CN, Saftlas AF, Triche EW, Bjonnes A, Keating B, Saxena R, Breheny PJ, Dewan AT, Robinson JG, Hoh J, Ryckman KK (2015). Genetic Predisposition to Dyslipidemia and Risk of Preeclampsia. *Am J Hypertens* **28**:915-23.

Stawicki SP, Papadimos TJ, Bahner DP, Evans DC4, Jones C (2016). Correlations between pulmonary artery pressures and inferior vena cava collapsibility in critically ill surgical patients: An exploratory study. *Int J Crit Illn Inj Sci* **6**:194-199.

Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R (2010). Pre-eclampsia. *Lancet* **376**(9741):631-44.

Stergiotou I, Crispi F, Valenzuela-Alcaraz B, Bijnens B, Gratacos E (2013). Patterns of maternal vascular remodeling and responsiveness in early- versus late-onset preeclampsia. *Am J Obstet Gynecol* **209**:558.e1-558.e14. doi: 10.1016/j.ajog.2013.07.030. Epub 2013 Jul 31.

Stevenson LW, Perloff JK (1989). The limited reliability of physical signs for estimating hemodynamics in chronic heart failure. *JAMA* **261**:884-8.

Stillman IE, Karumanchi SA (2007). The glomerular injury of preeclampsia. *J Am Soc Nephrol* **18**:2281-4.

Sugerman HJ (2011). Hypothesis: preeclampsia is a venous disease secondary to an increased intra-abdominal pressure. *Med Hypotheses*. **77**:841-9.

Suzuki H, Watanabe Y, Arima H, Kobayashi K, Ohno Y, Kanno Y (2008). Short- and long-term prognosis of blood pressure and kidney disease in women with a past history of preeclampsia. *Clin Exp Nephrol*. **12**:102-109.

Tay J, Foo L, Masini G, Bennett PR, McEniery CM, Wilkinson IB, Lees CC (2018). Early and late preeclampsia are characterized by high cardiac output, but in the presence of fetal growth restriction, cardiac output is low: insights from a prospective study. *Am J Obstet Gynecol* **218**:517.e1-517.e12.

Testani JM, Khera AV, St John Sutton MG, Keane MG, Wiegers SE, Shannon RP, Kirkpatrick JN. Effect of right ventricular function and venous congestion on cardiorenal interactions during the treatment of decompensated heart failure. *Am J Cardiol* **105**:511-6.

Thilaganathan B (2018A). Pre-eclampsia and the cardiovascular-placental axis. *Ultrasound Obstet Gynecol* **51**:714-717.

Thilaganathan B (2018B) .Ultrasound fetal weight estimation at term may do more harm than good. *Ultrasound Obstet Gynecol* **52**:5-8.

Thilaganathan B, Kalafat E (2019). Cardiovascular System in Preeclampsia and Beyond. *Hypertension* **73**:522-531

Thornton C, Dahlen H, Korda A, Hennessy A (2013). The incidence of preeclampsia and eclampsia and associated maternal mortality in Australia from population-linked datasets: 2000-2008. *Am J Obstet Gynecol* **208**:476.e1-5.

Timur H, Daglar HK, Kara O, Kirbas A, Inal HA, Turkmen GG, Yilmaz Z, Elmas B, Uygur D (2016). A study of serum Apo A-1 and Apo B-100 levels in women with preeclampsia. *Pregnancy Hypertens*. **6**:121-5.

Trevisan R, Dodesini AR, Lepore G. Lipids and renal disease. *J Am Soc Nephrol* **17(4 Suppl 2)**:S145-7.

Tuten A, Erman H, Korkmaz GG, Oncul M, Gelisgen R, Sozer V, Acıkgoz S, Simsek G, Uzun H. Comparison of maternal and umbilical cord blood soluble lectin-like oxidized low-density lipoprotein receptor 1 levels in early- and late-onset preeclampsia. *Arch Gynecol Obstet* **290**:1007-13.

Tuten A, Oncul M, Kucur M, Imamoglu M, Ekmekci OB, Acıkgoz AS, Cebe FS, Yesilbas C, Madazlı R (2015). Maternal serum copeptin concentrations in early- and late-onset pre-eclampsia. *Taiwan J Obstet Gynecol* **54**:350-4.

Uma R, Forsyth SJ, Struthers AD, Fraser CG, Godfrey V, Murphy DJ (2010). Polymorphisms of the angiotensin converting enzyme gene in early-onset and late-onset pre-eclampsia. *J Matern Fetal Neonatal Med* **23**:874-9.

Valensise H, Vasapollo B, Gagliardi G, Novelli GP (2008). Early and late preeclampsia: two different maternal hemodynamic states in the latent phase of the disease. *Hypertension* **52**:873-80.

van Drongelen J, de Vries R, Lotgering FK, Smits P, Spaanderman ME (2014). Functional vascular changes of the kidney during pregnancy in animals: a systematic review and meta-analysis. *PLoS One* **9**:e112084. doi: 10.1371/journal.pone.0112084. eCollection 2014.

van Hagen IM, Roos-Hesselink JW, Donvito V, Liptai C, Morissens M, Murphy DJ, Galian L, Bazargani NM, Cornette J, Hall R, Johnson MR (2017). Incidence and predictors of obstetric and fetal complications in women with structural heart disease. *Heart*. **103**:1610-1618.

Vellanki K. Pregnancy in chronic kidney disease (2013). *Adv Chronic Kidney Dis*. **20**:223-8.

Verlohren S, Melchiorre K, Khalil A, Thilaganathan B (2014). Uterine artery Doppler, birth weight and timing of onset of pre-eclampsia: providing insights into the dual etiology of late-onset pre-eclampsia. *Ultrasound Obstet Gyneco*. **44**:293-8.

Vesely SK (2015). Life after acquired thrombotic thrombocytopenic purpura: morbidity, mortality, and risks during pregnancy. *J Thromb Haemost*. **13 Suppl 1**:S216-22.

Vinayagam D, Patey O, Thilaganathan B, Khalil A (2017). Cardiac output assessment in pregnancy: comparison of two automated monitors with echocardiography. *Ultrasound Obstet Gynecol* **49**:32-38.

Vinayagam D, Thilaganathan B, Stirrup O, Mantovani E, Khalil A (2018). Maternal hemodynamics in normal pregnancy: reference ranges and role of maternal characteristics. *Ultrasound Obstet Gynecol* **51**:665-671.

Virzì GM, Clementi A, de Cal M, Brocca A, Day S, Pastori S, Bolin C, Vescovo G, Ronco C (2015). Oxidative stress: dual pathway induction in cardiorenal syndrome type 1 pathogenesis. *Oxid Med Cell Longev.* 2015:391790. doi: 10.1155/2015/391790. Epub 2015 Mar 4.

Virzì GM, Clementi A, Brocca A, de Cal M, Ronco C (2016). Molecular and Genetic Mechanisms Involved in the Pathogenesis of Cardiorenal Cross Talk. *Pathobiology* **83**:201-10.

Vonck S, Oben J, Staelens AS, Lanssens D, Molenberghs G, Gyselaers W (2017). Optimization of Simple Sphygmomanometric Blood Pressure Measurement in Routine Prenatal Care. *Health Care Current Reviews* **5**: 185. doi: 10.4172/2375-4273.1000185.

von Dadelszen P, Magee LA, Roberts JM (2003). Subclassification of preeclampsia. *Hypertens Pregnancy* **22**:143-8.

Wallace AE, Whitley GS, Thilaganathan B, Cartwright JE (2015). Decidual natural killer cell receptor expression is altered in pregnancies with impaired vascular remodeling and a higher risk of pre-eclampsia. *J Leukoc Biol*. **97**:79-86.

Whaley-Connell A, Sowers JR (2014). Basic science: Pathophysiology: the cardiorenal metabolic syndrome. *J Am Soc Hypertens* **8**:604-6.

Widen EM, Gallagher D (2014). Body composition changes in pregnancy: measurement, predictors and outcomes. *Eur J Clin Nutr* **68**:643-52.

Wu P, Haththotuwa R, Kwok CS, Babu A, Kotronias RA, Rushton C, Zaman A, Fryer AA, Kadam U, Chew-Graham CA, Mamas MA (2017). Preeclampsia and Future Cardiovascular Health: A Systematic Review and Meta-Analysis. Circ Cardiovasc Qual Outcomes. 2017 Feb;10(2). pii: e003497. doi: 10.1161/CIRCOUTCOMES.116.003497. Epub 2017 Feb 22.

Xia Y, Zhou CC, Ramin SM, Kellems RE (2007). Angiotensin receptors, autoimmunity, and preeclampsia. *J Immunol* **179**:3391-5.

Yan JY, Jiang LL (2015). Expression of advanced glycation end products in placenta and concentration in maternal and umbilical serum in pre-eclampsia. *J Obstet Gynaecol Res* **41**:843-9

Yasuda R1, Takeuchi K, Funakoshi T, Maruo T (2003). Bioelectrical impedance analysis in the clinical management of preeclamptic women with edema. *J Perinat Med* **31**:275-80.

Zoccali C (2007). The endothelium as a target in renal diseases. *J Nephrol* **20 Suppl 12**:S39-44.

New References from paragraph on Pharmacotherapeutic targets.

Silber S (1999). Nitrates: why and how should they be used today? Current status of the clinical usefulness of nitroglycerin, isosorbide dinitrate and isosorbide-5-mononitrate. Eur J Clin Pharmacol 38 Suppl 1:S35-51.

Cetin A, Yurtcu N, Guvenal T, Imir AG, Duran B, Cetin M (2004). The effect of glyceryl trinitrate on hypertension in women with severe preeclampsia, HELLP syndrome, and eclampsia. Hypertens Pregnancy 23:37-46.

Cotton DB, Jones MM, Longmire S, Dorman KF, Tessem J, Joyce TH 3rd (1986). Role of intravenous nitroglycerin in the treatment of severe pregnancy-induced hypertension complicated by pulmonary edema. Am J Obstet Gynecol 154:91-3.

Grunewald C1, Kublickas M, Carlström K, Lunell NO, Nisell H (1995). Effects of nitroglycerin on the uterine and umbilical circulation in severe preeclampsia. Obstet Gynecol 86:600-4.

Cacciatore B1, Halmesmäki E, Kaaja R, Teramo K, Ylikorkala O (1998). Effects of transdermal nitroglycerin on impedance to flow in the uterine, umbilical, and fetal middle cerebral arteries in pregnancies complicated by preeclampsia and intrauterine growth retardation. Am J Obstet Gynecol. 179:140-5.

Johal T, Lees CC, Everett TR, Wilkinson IB (2014). The nitric oxide pathway and possible therapeutic options in pre-eclampsia. Br J Clin Pharmacol. 78:244-57.

Valensise H, Vasapollo B, Novelli GP, Giorgi G, Verallo P, Galante A, Arduini D (2008). Maternal and fetal hemodynamic effects induced by nitric oxide donors and plasma volume expansion in pregnancies with gestational hypertension complicated by intrauterine growth restriction with absent end-diastolic flow in the umbilical artery. Ultrasound Obstet Gynecol 31:55-64.

Vasapollo B, Novelli GP, Gagliardi G, Tiralongo GM, Pisani I, Manfellotto D, Giannini L, Valensise H (2012). Medical treatment of early-onset mild gestational hypertension reduces total peripheral vascular resistance and influences maternal and fetal complications. Ultrasound Obstet Gynecol 40:325-31.

Veena P, Perivela L1, Raghavan SS (2017). Furosemide in postpartum management of severe preeclampsia: A randomized controlled trial. Hypertens Pregnancy 36:84-89.

Carr DB, Gavrila D, Brateng D, Easterling TR (2007). Maternal hemodynamic changes associated with furosemide treatment. Hypertens Pregnancy 26:173–8.

Al-Balas M, Bozzo P, Einarson A (2009). Use of diuretics during pregnancy. Can Fam Physician 55:44-5.

von Dadelszen P, Menzies J, Gilgoff S, Xie F, Douglas MJ, Sawchuck D, Magee LA (2007). Evidence-based management for preeclampsia. Front Biosci 12:2876-89.

Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy (2000). Am J Obstet Gynecol 183:S1-S22.

Brown CM, Garovic VD (2014). Drug treatment of hypertension in pregnancy. Drugs 74:283-96.

Tamás P, Hantosi E, Farkas B, Ifi Z, Betlehem J, Bódis J (2017). Preliminary study of the effects of furosemide on blood pressure during late-onset pre-eclampsia in patients with high cardiac output. Int J Gynaecol Obstet 136:87-90.

Pryde PG, Mittendorf R (2009). Contemporary usage of obstetric magnesium sulfate: indication, contraindication, and relevance of dose. Obstet Gynecol 114:669-73.

Euser AG, Cipolla MJ (2009). Magnesium sulfate for the treatment of eclampsia: a brief review. Stroke 40:1169-75.

Touyz RM (2003). Role of magnesium in the pathogenesis of hypertension. Mol Aspects Med 24:107-36.

Gottlieb SS, Fisher ML, Pressel MD, Patten RD, Weinberg M, Greenberg N (1993). Effects of intravenous magnesium sulfate on arrhythmias in patients with congestive heart failure. Am Heart J 125:1645-50.

Ince C, Schulman SP, Quigley JF, Berger RD, Kolasa M, Ferguson R, Silver B, Haigney MC (2001). Usefulness of magnesium sulfate in stabilizing cardiac repolarization in heart failure secondary to ischemic cardiomyopathy. Am J Cardiol 88:224-9.

Nakashima H, Katayama T, Honda Y, Suzuki S, Yano K (2004). Cardioprotective effects of magnesium sulfate in patients undergoing primary coronary angioplasty for acute myocardial infarction. Circ J 68:23-8.

Keyrouz SG, Diringer MN (2007). Clinical review: Prevention and therapy of vasospasm in subarachnoid hemorrhage. Crit Care 11:220.

Teragawa H, Kato M, Yamagata T, Matsuura H, Kajiyama G (2000). The preventive effect of magnesium on coronary spasm in patients with vasospastic angina. Chest 118:1690-5.

Yang ZW, Gebrewold A, Nowakowski M, Altura BT, Altura BM (2000). Mg(2+)-induced endothelium-dependent relaxation of blood vessels and blood pressure lowering: role of NO. Am J Physiol Regul Integr Comp Physiol.278:R628-39.

Upton RN, Ludbrook GL (2005). Pharmacokinetic-pharmacodynamic modelling of the cardiovascular effects of drugs - method development and application to magnesium in sheep. BMC Pharmacol 5:5.

Additional information section

Photograph

Abstract Figure

Heart

	EPE	LPE
Heart Rate	↓	↓
Stroke Volume	↓	=
Cardiac Output	↓	=
Left ventricle Mass (index)	↑	↑
Diameter	↑	↑
Wall thickness	↑	↑

Arteries

	EPE	LPE
Blood pressure	↑	↑
Total peripheral resistance	↑	↑
Doppler Index PI, RI	↑	↑
Arterial stiffness	↑	↑
Pulse wave velocity	↑	↑
Carotid Intima Thickness	↑	↑

Interconnecting systems

	EPE	LPE
Endothelial dysfunction	↑	↑
Orthosympathetic dominance	↑	=
Angiogenetic imbalance	↑	↑
Chronic inflammation	↑	↑
Oxidative stress activation	↑	↑

Veins & volume

	EPE	LPE
Abnl hepatic vein Doppler	↑	↑
Abnl renal interlobar vein Doppler	↑	↑
Venous pulse transit time	↓	↓
Total body water volume	↑	↑
Extracellular water volume	↑	↑
Plasma volume	↓	↑

Kidneys

	EPE	LPE
Glomerular filtration rate	↓	↓
Effective renal plasma flow	↓	↓
Podocyturia	↑	↑
Serum creatinin	↑	↑
Serum Uric Acid	↑	↑
Urinary proteomics	↑	↑

Figure 1

Figure 2