

# Type 5 Cardiorenal Syndrome: An Underdiagnosed and Underrecognized Disease Process of the American Mother

Justin Ilagan<sup>a, c</sup>, Harshini Sahani<sup>b</sup>, Arif Bin Saleh<sup>a</sup>, Kameron Tavakolian<sup>a</sup>, Anton Mararenko<sup>a</sup>, Ndausung Udongwo<sup>a</sup>, Steven Douedi<sup>a</sup>, Vandan Upadhyaya<sup>c</sup>, Swapnil Patel<sup>a</sup>, Arman Mushtaq<sup>a</sup>, Brett Sealove<sup>c</sup>, David Gonzalez<sup>d</sup>, Arif Asif<sup>a</sup>

## Abstract

Cardiorenal syndrome (CRS) continues to be an area of concern due to the changing understanding of identification, pathophysiology and optimal management. Originally thought that diuretics were always the answer, recent literature has shed lights on the five major CRS subphenotypes, and while conceptual in their classifications, different strategies may be utilized to manage each type. The effect of CRS in pregnant women is largely under discussed and underappreciated as its own entity. Trials involving possible management, specifically utilizing serelaxin, a recombinant form of relaxin, have shown promising results but more data are needed to begin implementing it on a large scale.

**Keywords:** Cardiorenal syndrome; Type 5; Pregnant women; Serelaxin

## Introduction

Preeclampsia is a hypertensive disorder of pregnancy affecting approximately 2-8% of pregnant women worldwide. It is characterized by the core issue of hypertension and proteinuria [1]. According to the American Journal of Managed Care (AJMC), the United States has the “highest maternal mortality

rate” of the studied developed countries, and the most common cause of maternal mortality is cardiovascular compromise [2, 3]. Cardiorenal syndrome (CRS) types 1 through 4 are a spectrum of conceptual disease processes involving the kidneys and heart in which a chronic or acute disruption in one primary organ activates a chronic or acute disruption of its secondary organ counterpart [4]. Type 5 CRS is defined as a secondary disease process, in this case uncontrolled hypertension, that has deleterious effects on both the heart and kidneys [5]. The goal of this review paper is to further explore CRS in the setting of pregnancy with respect to pathogenesis, epidemiology, identification, and management to better identify patients earlier on and improve downstream outcomes.

## Hemodynamics of Pregnancy

A variety of hemodynamic adaptations occur during an uncompromised pregnancy, including total body and extracellular volume expansion, increases in cardiac output (CO), heightened arterial compliance and diminished blood pressure and total peripheral resistance [6]. Moreover, it has been elucidated that maternal heart rate will increase throughout pregnancy, and peak in the third trimester as elevated heart rate acts to maintain adequate CO [7]. The purposes of these physiological changes are multifactorial, and are, in part, due to the 15% increase in metabolic rate and 20% increase in oxygen consumption during pregnancy to maintain adequate fetal perfusion [8]. Although the mechanism(s) are not all fully understood by which these processes occur, some theorized mechanisms currently exist. First, the levels of nitric oxide (NO) are elevated during a normal pregnancy [9]. NO synthesis is influenced by hormones present during a normal pregnancy, such as relaxin, produced by the corpus luteum [10]. NO as one of the reasons for these hemodynamic changes observed during pregnancy is supported by animal models of pregnancy where NO production is stunted leading to an increase of total peripheral resistance (TPR) and a decrease in CO [10].

In pregnant animal models where antibodies neutralized the relaxin hormone, there was a markedly impaired arterial compliance and CO, and mirrored the relatively lower CO and higher TPR in that of nonpregnant animal models [11]. Vasodilatory prostacyclins found in increased levels during preg-

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<sup>a</sup>Department of Internal Medicine, Jersey Shore University Medical Center, Neptune City, NJ 07753, USA

<sup>b</sup>Department of Obstetrics and Gynecology, Monmouth Medical Center, Long Branch, NJ 07740, USA

<sup>c</sup>Department of Cardiovascular Disease, Jersey Shore University Medical Center, Neptune City, NJ 07753, USA

<sup>d</sup>Department of Maternal and Fetal Medicine, Monmouth Medical Center, Long Branch, NJ 07740, USA

<sup>e</sup>Corresponding Author: Justin A. Ilagan, Department of Internal Medicine, Jersey Shore University Medical Center, Neptune City, NJ 07753, USA. Email: Ilaganjustin0608@gmail.com

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nancy in the uterine artery also play a key role in vasodilatation and overall hemodynamics [12]. This is further supported by a relationship between hypertensive pregnancy (i.e., preeclampsia) and abnormally low levels of prostacyclins, specifically PGI<sub>2</sub>, while in normotensive pregnancies, there is an increased level of PGI<sub>2</sub> [13].

Overall, these changes serve as a measure to improve effective circulating volume, or the volume found intravascularly that is actively perfusing tissue. Many of these changes cascade into one of the earliest signs in pregnancy, a decrease in blood pressure by roughly 10 mm Hg by the second trimester [14]. As a result of poor effective circulating volume, sensed by the renal system as relative hypotension, the renin-angiotensin-aldosterone-system (RAAS) is activated resulting in electrolyte and water retention, and thus higher effective circulating volume and therefore cardiac output which is essential for the metabolic demand of pregnancy [15]. These changes are all essential for the plasma volume expansion and hemodynamic changes required in a healthy pregnancy despite a reduced vascular tone.

## Hormonal Influence on Hemodynamics of Pregnancy

Hormones are well understood to influence many different physiological aspects of pregnancy. Progesterone, for example, is a steroid hormone that rises during pregnancy. Here, we will focus on its responsibility related to hemodynamics and NO synthesis in renal arterial endothelial cells [16], and to induce vascular refractoriness to angiotensin II and norepinephrine [17] which ultimately enables the profound vasodilatation and decreased blood pressure in a normal pregnancy. Angiotensinogen, the protein precursor for angiotensin also rises by way of maternal placental production and fetal hepatic production, and acts as a means to increase electrolyte and volume retention downstream in its cascade, further expanding total body volume [18]. Finally, relaxin, produced by the corpus luteum and placenta is suspected to exert vasodilatory effects via its G protein-coupled receptor (GPCR), relaxin family peptide receptor 1 (RXFP1). Downstream, it reduces fibrosis and stimulates NO action through all three NOS subtypes: endothelial NOS (eNOS), inducible NOS (iNOS) and neuronal NOS (nNOS), although the mechanism is poorly understood and tissue-dependent [19]. Interestingly, relaxin has also been shown to also reduce the reactivity of alpha-1 adrenergic agonist receptors to phenylephrine in hypertensive rats, which further supports relaxin-induced improvement of forward perfusion and vasodilatation, while also reducing mean systolic blood pressures, specifically in trimesters 2 and 3 of said animal models [20, 21].

## Preeclampsia: Conceptually a Type 5 CRS

Preeclampsia is defined by the American College of Obstetrics and Gynecology (ACOG) as the presence of hypertension (systolic blood pressure > 140 mm Hg or diastolic blood pressure > 90 mm Hg) and proteinuria (> 300 mg/24 h urine

protein collection or protein/creatinine > 0.3) occurring after 20 weeks gestation in a previously normotensive patient [22]. The disease process of preeclampsia overlaps the cardiovascular and renovascular circuits resulting in multisystem dysfunction. Cardiovascular impairment is a result of increased systemic vascular resistance and afterload that can compromise the ejection phase of the cardiac cycle, thus indirectly leading to an imbalance in end organ oxygen supply and demand systemically [23]. One example of a disease process that may transition into a type 5 CRS is acute fatty liver of pregnancy (AFLP). AFLP, typically in trimester 3, is described as progressive lipid accumulation in hepatocytes leading to coagulopathy and hypoglycemia due to hepatic failure [24]. Consequently, arrhythmias including widened QTc and bradycardia lead to poor renal perfusion and injury in the acute setting. Although acute kidney injury can occur at any time throughout pregnancy, it generally occurs in trimester 2, and is thought to be most commonly due to a hypertensive disease process (i.e., preeclampsia) [25]. The pathophysiology is complex but can be summarized by two fundamental pathways. First, hypertension results in tunica media hypertrophy that results in uteroplacental ischemia. This in turn leads to multiorgan involvement as a means to shunt blood away from the mother and towards the fetus followed by an excess of antiangiogenic factors late in the second or third trimester [26]. Second, abnormal cytotrophoblastic cells not transitioning from a proliferative epithelial subtype to an invasive epithelial subtype prevent normal migration of spiral arteries which would otherwise create the maternal-fetal interface for exchange of nutrients [27]. One way to evaluate perfusion to the fetus is through color flow Doppler studies. In an uncomplicated pregnancy, color flow Doppler studies demonstrate robust and patent flow compared to an abnormal perfusion gradient resulting in a characteristic bilateral uterine notching in patients with preeclampsia [28]. Uterine notching is an independent risk factor for developing preeclampsia [28]. Many risk factors and mechanisms by which preeclampsia, a type 5 CRS, occurs have been identified. A systematic review conducted from 1966 to 2002 revealed that women with a prior history of preeclampsia were at increased risk (risk ratio (RR) 7.19, 95% confidence interval (CI) 5.85 - 8.83). Additional risk factors included a history of diabetes mellitus (RR 3.56, CI 2.54 - 4.99), maternal age > 40 (RR 1.96, CI 1.34 - 2.87), for multiparous women and in those with antiphospholipid antibodies (RR 9.72, CI 4.34 - 21.75) [29]. A matched case-control study by Stamilio et al revealed that women with autoimmune disease were also more likely to develop preeclampsia (RR 6.9, CI 1.1 - 42.3) [29]. This sheds light on the idea that degenerative autoimmune disease and inflammation in general may play a critical role in the development of preeclampsia. Moreover, this creates a niche for novel biomarkers and possible antibodies to be identified to better risk stratify these mothers earlier on in pregnancy. This continues to be an area of active investigation.

## Management of CRS in Pregnancy

The management of this conceptual disease process, a type 5 CRS, is dynamic requiring a multidisciplinary approach fo-

cused on treating the underlying cause. In the setting of a septic abortion, another potential type 5 CRS, for example, due to its severe peripheral vasodilatation leading to high output heart failure and pre-renal acute kidney injury, treatment is removal of infected tissue, antimicrobial therapy, and volume expansion with adequate resuscitation [30, 31]. In the setting of uncontrolled blood pressure, such as that in preeclampsia, appropriate agents such as nifedipine, labetalol, and methyldopa should be employed per national guidelines [28]. Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) should be avoided given their teratogenic effects [32, 33]. In the setting in which preeclampsia progresses to its convulsive subtype, the risk of maternal demise is more than halved when administering magnesium sulfate [34]. In addition to magnesium, aspirin may play a promising role as well. The World Health Organization (WHO), ACOG and the United States Prevention and Screening Task Force (USPSTF) all recommend the use of low-dose aspirin in the appropriate patient population [35-37]. Aspirin, despite being a non-steroidal anti-inflammatory drug, has a favorable safety profile towards the fetus. The benefit has been well studied and summarized in a report by Rolnik et al, who published a multicenter randomized placebo-controlled double-blinded trial of high-risk women assessing aspirin use (150 mg) versus placebo in the prevention of women at risk for preterm preeclampsia. Aspirin, when compared to placebo, was found to have a 62% RR reduction [38].

## Conclusion and Future Directions of CRS in Pregnancy

Cardiovascular disorders such as cardiomyopathy, heart failure leading to CRS, and hypertensive disorders such as preeclampsia, a type 5 CRS, remain the leading cause of morbidity and mortality in pregnancy [39]. Recent data have shown a naturally occurring peptide in pregnancy known as relaxin-2 that is responsible for NO regulated renovascular dilation and therefore aids in cardiovascular and renal alterations [40, 41]. A recombinant form of relaxin-2, known as serelaxin, has been studied in the RELAX-AHF trial and has been found to have promising outcomes. The study demonstrated that patients admitted for acute heart failure that were treated with serelaxin resulted in lesser rises of end organ damage biomarkers (i.e., troponin T for cardiac damage, and creatinine and cystatin-C for renal damage) [42]. Although this study demonstrated the possibility of using relaxin-2 and analogs in CRS, further studies are needed to validate the data as well as examine the utility in pregnant patients who already have measurable levels of relaxin-2. Additional pharmacotherapy that may have utility is the use of low-dose aspirin. Preeclampsia is known to be a significant risk factor for the development of coronary artery disease post-pregnancy and chronic kidney disease [43, 44]. The use of low-dose aspirin has been found to decrease the incidence of preeclampsia in patients at risk [45]. However, aspirin use and cardiovascular risk reduction in patients with diagnosed preeclampsia have not been defined in literature and require further investigational studies given this disease burden.

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## Conflict of Interest

None to declare.

## Author Contributions

Dr. Justin Ilgan: primary manuscript writer; Dr. Harshini Sahani: primary manuscript writer; Dr. Arif Bin Saleh: secondary editing; Dr. Kameron Tavakolian: primary manuscript writer; Dr. Anton Mararenko: primary manuscript writer; Dr. Ndausung Udongwo: primary manuscript writer; Dr. Steven Douedi: primary manuscript writer; Dr. Vandan Upadhyaya: primary manuscript writer; Dr. Swapnil Patel: primary editing and funding; Dr. Arman Mushtaq: secondary editor; Dr. Brett Sealove: primary editor; Dr. David Gonzalez: primary editor; Dr. Arif Asif: primary editor.

## Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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