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Two Preeclampsia Phenotypes with Opposing Maternal Cardiovascular Profiles: Fetal Growth Restriction as a Key Discriminator

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Two preeclampsia phenotypes with opposing maternal cardiovascular profiles: fetal growth restriction as a key discriminator

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RESUMO

A pré-eclâmpsia afeta aproximadamente 2-8% das gravidezes, contudo, a sua fisiopatologia permanece em grande parte por elucidar. Embora a invasão trofoblástica inadequada e os sistemas placentários de alta resistência estejam bem documentados, o papel da função cardiovascular materna tem vindo a ganhar proeminência. Os perfis hemodinâmicos em mulheres com pré-eclâmpsia apresentam uma heterogeneidade significativa, o que inicialmente levou à divisão em fenótipos de início precoce e tardio.

No entanto, evidências emergentes sugerem que esta classificação pode ser inconsistente, indicando que a hemodinâmica materna difere de forma mais significativa conforme a presença ou ausência de restrição de crescimento fetal. Deste modo, esta revisão sistemática visa comparar os perfis cardiovasculares de mulheres com pré-eclâmpsia isolada e de mulheres com pré-eclâmpsia associada à restrição de crescimento fetal. A distinção destes fenótipos poderá conduzir à melhor compreensão da patologia e, em última análise, otimizar as estratégias terapêuticas e a abordagem terapêutica.

Palavras-Chave: Pré-eclâmpsia; Restrição de Crescimento Fetal; Débito Cardíaco; Resistência Vascular; Hemodinâmica; Gravidez.

ABSTRACT

Preeclampsia affects about 2-8% of pregnancies, yet its pathophysiology remains largely elusive. While inadequate trophoblastic invasion and high-resistance placental systems are well-documented, the role of maternal cardiovascular function has gained prominence. Hemodynamic profiles in preeclamptic women exhibit significant heterogeneity, initially supporting the division into early- and late-onset phenotypes.

However, emerging evidence suggests that this classification may be inconsistent, indicating that maternal hemodynamics differ more significantly depending on the presence or absence of fetal growth restriction. Therefore, this systematic review aims to compare the cardiovascular profiles of women with isolated preeclampsia and those with preeclampsia associated with fetal growth restriction. Distinguishing these phenotypes could lead to a better understanding of the disease and may ultimately improve therapeutic strategies and clinical management.

Keywords: Preeclampsia; Fetal growth restriction; Cardiac output; Vascular resistance; Hemodynamics; Pregnancy;

ABBREVIATION LIST | LISTA DE ABREVIAÇÕES

A – Atrial Contraction
ACOG – American College of Obstetricians and Gynecologists
AIx – Augmentation Index
ANP – Atrial Natriuretic Peptide
BP – Blood Pressure
CCBs – Calcium Channel Blockers
cfPWV – Carotid-Femoral Pulse Wave Velocity
CHD – Congenital Heart Disease
CI – Cardiac Index
CO – Cardiac Output
CV – Cardiovascular
DBP – Diastolic Blood Pressure
E – Early Diastolic Filling
ECG – Electrocardiogram
EF – Ejection Fraction
EVT – Extravillous Trophoblasts
FGR – Fetal Growth Restriction
FS – Fractional Shortening
HDP – Hypertensive Disorders of Pregnancy
HR – Heart Rate
LV – Left Ventricle
LVEDD – Left Ventricular End-Diastolic Diameter
LVEDV – Left Ventricular End-Diastolic Volume
MAP – Mean Arterial Pressure
PE – Preeclampsia
PE/FGR – Preeclampsia and Fetal Growth Restriction
PlGF – Placental Growth Factor
PV – Plasma Volume
RI – Resistance Index
SBP – Systolic Blood Pressure
SGA – Small-For-Gestational-Age
SV – Stroke Volume
sVEGFR-1 – Soluble Vascular Endothelial Growth Factor Receptor-1
SVR – Systemic Vascular Resistance
uNK – Uterine Natural Killer Cells
UBF – Uterine Blood Flow;
UtA – Uterine Artery.
VEGF – Vascular endothelial growth factor
VEGFR-1 – Vascular Endothelial Growth Factor Receptor-1

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INTRODUCTION | INTRODUÇÃO

Hypertensive disorders of pregnancy (HDP) are among the leading causes of complications, hospitalizations, and consumption of maternal and child health resources [1]. Preeclampsia (PE) stands out as a HDP that affects about 2 to 8% of pregnant women, characterized by the diagnosis of new-onset hypertension after 20 weeks of gestation associated with proteinuria and/or signs of target organ damage [2, 3]. According to the American College of Obstetricians and Gynecologists (ACOG), PE is defined by the presence of systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg in 2 measurements with at least an interval of 4 hours in a woman previously normotensive, combined with proteinuria or end-organ damage [3].

Throughout pregnancy, several physiological changes occur, especially in the cardiovascular setting, described as early as 6 gestational weeks [4, 5]. One of the most significant changes is the increase in cardiac output, initially due to an increase in systolic volume, a consequence of reduced peripheral vascular resistance and elevated circulating blood volume [5-7]. Changes in vascular resistance are also reflected in blood pressure values. In an uncomplicated pregnancy, diastolic blood pressure starts decreasing around the 6-7th gestational week, reaching a decline of approximately 5-10 mmHg around the second trimester, and then returns to preconception values near term [5, 6]. Concurrently, proper remodeling of spiral arteries during adequate implantation allows an increase in placental blood flow [2]. The sum of these adaptive changes helps improve uteroplacental circulation and minimize maternal cardiac strain [6].

The mechanisms behind the development of PE have been vastly studied. For several years, the placenta was considered the primary site of origin of pregnancies complicated by PE, being the focus of numerous studies [8, 9]. Phenomena of abnormal placentation have been reported on histological examination of uterine spiral arteries, showing impaired vascular remodeling of maternal spiral arteries in preeclamptic pregnancies, with an absence of physiological adaptations in the myometrial segments, potentially leading to decreased uteroplacental flow and inducing placental ischemia [2, 8, 10]. A correlation was established between uteroplacental vascular pathology and abnormal uterine artery Doppler flow in various studies, however Aardema et al. verified that these abnormalities in the placental bed could also be present in uncomplicated pregnancies and normal Doppler flow could coexist with abnormalities in spiral arteries, validating other studies that reported various false negatives [11, 12]. The theory behind these results promoted the idea that there are other factors contributing to the development of PE [11, 13, 14]. Although not completely understood, PE is now recognized as a multisystemic pregnancy disorder [10, 14].

Cardiovascular function and hemodynamics are central to normal physiological adaptation in pregnancy and have therefore become a major focus of recent research into the

pathophysiological mechanisms underlying PE [13, 15, 16]. Women with a history of PE have shown different cardiovascular characteristics and an increased risk of developing cardiovascular disease in the future compared with women with uncomplicated pregnancies [15, 17]. However, numerous studies have identified distinct cardiovascular profiles and pathophysiological patterns in PE, revealing a broad clinical spectrum of the disorder. Consequently, the classifications of early- and late-onset PE were established [18, 19].

Early-onset PE is used to describe PE that develops before 34 + 0 weeks, strongly associated with placental insufficiency, increased total vascular resistance, and fetal complications, such as fetal growth restriction. Conversely, in late-onset PE, diagnosed at 34 weeks or after, a higher maternal body mass index, higher maternal cardiac output and appropriate or large-for-gestational-age neonates were typically seen [19-21].

Fetal growth restriction (FGR) is a condition present in 5-10% of pregnancies and involves fetuses whose estimated fetal weight or abdominal circumference, according to gestational age, are at or below the 10th percentile, potentially linked to pathological mechanisms and preventing the fetus from reaching its potential intrauterine development [22, 23]. As is known, the placenta is responsible for gas exchange and the transfer of nutrients into the fetal circulation and is therefore fundamental to proper fetal development. In this way, processes that affect adequate placentation, such as the absence of normal remodeling of spiral arteries, which creates high-resistance systems, reduces placental blood flow, and leads to uteroplacental insufficiency, cause impaired fetal exchanges, which is one of the most common abnormalities related to FGR [23]. In this way, pathological changes in normal placentation, such as those frequently observed in early-onset PE, are more prone to FGR [23].

More recently, several studies have reported inconsistencies in the dichotomy between early- and late-onset PE, suggesting that differences in cardiovascular hemodynamics are not solely determined by the timing of disease onset but are more closely associated with the risk of FGR, a variable rarely examined in earlier research. Consequently, it has become essential to further investigate and redefine PE into two phenotypes, based on the presence or absence of FGR [24, 25].

The significance of this topic lies not only in understanding the pathophysiology and clinical manifestations of the different forms of PE, but also in its potential to indicate disease severity, predict progression to FGR or future cardiovascular disease, and guide the development of tailored therapeutic approaches based on maternal cardiovascular profiles [26].

This review aims to compare the cardiovascular profiles of women with isolated PE and those with PE associated with FGR, thereby supporting a novel classification of the disorder.

METHODS | MÉTODOS

This systematic review was conducted in accordance with the PRISMA 2020 guidelines. The literature search was performed using the PubMed and Scopus databases, between January 1st and April 20th, 2026.

The search strategy was based on keywords and MeSH terms, including “pre-eclampsia”, “fetal growth restriction”, “fetal growth retardation”, “placental bed”, “hemodynamics”, “physiology”, “cardiovascular”, “cardiac output”, “vascular resistance”, “stroke volume”, “heart rate”, “phenotypes”, “treatment”, “therapeutic”, “preconception”, “postpartum”, “healthy”, “normal”, “normotensive”, “uncomplicated”, “pregnancy” and “gestation”. These terms were systematically combined in various configurations using Boolean operators to ensure a comprehensive search.

Regarding eligibility criteria, only primary research studies were included. Automatic filters were used to help exclude secondary literature, non-English publications, animal models and ongoing studies or protocols without available results. No restrictions were applied for the publication year.

Initially, automated tools were used to eliminate duplicate citations and studies that did not satisfy the inclusion criteria. Afterwards, articles were screened by title and abstract. Lastly, after a thorough full-text review of the remaining studies, 119 articles were selected. The study selection process is detailed in Figure 1.

INTERPLAY BETWEEN THE PLACENTAL BED, PREECLAMPSIA, AND FETAL GROWTH RESTRICTION

Over the years, the uteroplacental interface has been the focus of studies regarding the etiology behind different pregnancy disorders, such as PE and FGR.

During pregnancy, several changes take place to enhance normal placentation and ensure nutritional support from the earliest stages [27-29]. The basal decidua, myometrium, and spiral arteries form the placental bed, the maternal component responsible for nutrient and gas exchanges [27-29]. The transformation of the spiral arteries is a crucial step in turning these previously high-resistance structures into high-capacity vessels [27-29]. This process can only occur with the invasion of trophoblast cells, the extravillous trophoblasts (EVT), into the placental bed [27-29].

The physiological changes in the spiral arteries refer to the transformations essentially observed in the placental bed in uncomplicated pregnancies. These are described by the presence of trophoblasts in both decidual and myometrial segments, as well as intramural trophoblasts, and the replacement of the muscular and elastic components of the arterial wall, as the tunica media and internal elastic lamina, by fibrinoid material, with the consequent enlargement of the arterial lumen [27-31].

The absence of physiological changes in spiral arteries results in a high-resistance system, leading to poor perfusion of the placental intervillous space, explaining the interplay between PE and FGR [11, 32]. Brosen et al. were among the first to report the interaction between the placental bed and these conditions, finding no physiological changes in myometrial segments of pregnant women diagnosed with PE, regardless of fetal weight, and in approximately half of those who presented with a birth weight at or below the 10th percentile [27]. More authors have since supported this finding, reporting a higher rate of completely preserved tunica media at the decidual and myometrial levels than in uncomplicated pregnancies [27-30, 33, 34]. Recently, Brouwers et al. showed that impaired remodeling was seen in approximately 42% of women with PE, increasing to 66,7% if isolated FGR and reaching 71,6% if both were present, a significant difference compared to the 9,5% observed in the control group [30].

Other vascular pathological changes were also perceived. The incidence of acute atherosis and thrombosis is significantly higher in placental bed biopsies when PE or FGR is detected, which helps establish a strong correlation between the impaired spiral artery remodeling and inadequate vascular adaptation of the placental bed [29, 30, 34-37].

The depth of trophoblast invasion was an additional parameter of analysis. The absence of intramural trophoblasts in pathological spiral arteries raised the question of whether this was a phenomenon caused by the failure in invasion of trophoblasts in the uterine wall. Although some studies have suggested a decrease in interstitial EVT, current evidence shows no variations in the depth of penetration of trophoblast between uncomplicated pregnancies and those complicated by PE or FGR [28, 30, 31, 38]. The absence of differences in interstitial and endovascular EVT, in contrast to differences in intramural EVT, supports the hypothesis that lack of physiological remodeling does not correlate with the deficiency of EVT in the myometrium, highlighting the potential role of other factors in vascular adaptation [31]. In this line of thought, proteolytic pro-enzymes expressed by EVT, in particular matrix metalloproteinases, were investigated as they appear to regulate extracellular matrix degradation, thereby promoting EVT invasion. However, available evidence reports conflicting results regarding the relationship between reduced expression and the occurrence of PE and FGR [39-41]. Other cellular mediators and adhesion molecules were also evaluated, but no association was observed [42, 43].

Thus, the invasion and remodeling of spiral arteries were previously thought to be processes solely dependent on trophoblast cells. In contrast, the role of other cell types has become increasingly recognized. Within the placental bed, leukocytes constitute a substantial proportion of the cellular population, raising the question of their potential role in proper vascular adaptation [44].

Uterine natural killer cells (uNK) represent about 40% of the lymphocyte population in the basal decidua. These cells play a part in the degradation of vascular extracellular matrix, the loss of vascular muscle, the production of cytokines and are also speculated to release angiogenic factors, contributing to EVT function [44]. Conflicting data about the impact of uNK in complicated pregnancies have emerged, posing a challenge in determining their role in the mechanisms behind either PE or FGR [44, 45]. Some studies report a significant decrease in uNK in both PE and FGR, suggesting a contribution to impaired vascular remodeling [44, 45]. On the other hand, the study by Stallmach et al. does not support these results, as no differences in uNK cells were observed between PE and control groups [46]. In contrast, evidence regarding other leucocyte populations is inconsistent, with divergent findings across the literature [44-46].

Placental vasculogenesis is a critical step in a successful pregnancy, being mediated by proangiogenic factors. Vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), also expressed by EVT, as well as their receptors, are considered to contribute to spiral artery remodeling, as illustrated in Figure 2 [47, 48].

In maternal plasma, a relationship has already been established between the expression of VEGF, PlGF and the soluble VEGFR-1 (sVEGFR-1) and the risk of developing PE, and consequently FGR. sVEGFR-1, which acts as an antagonist for VEGF, is increased in maternal circulation, whereas PlGF is decreased [48]. This interaction is represented in Figure 3. As for the placental bed, no discrepancy was observed in the expression of VEGF and PlGF, but the density of VEGFR-1 was diminished in both PE and FGR, suggesting that this may be implicated in impaired remodeling [47, 48]. Other vasoactive substances, such as vasodilators like nitric oxide, are also considered to potentially interact with spiral arteries, however no definitive connection has been established [49-51].

DYNAMIC MATERNAL HEMODYNAMIC SHIFTS FROM PRECONCEPTION TO THE POSTPARTUM

Cardiovascular Remodeling from Preconception to Term

Pregnancy is marked by profound structural and functional transformations, driven by the escalating maternal and fetal metabolic demands. To meet these demands, the maternal system undergoes significant hemodynamic expansion, with plasma volume increasing by approximately 50%, accompanied by a substantial rise in red blood cells [52, 53]. The cardiovascular system exhibits significant changes, adapting to this new physiological state, characterized by a systemic reduction in total vascular resistance and an increase in cardiac output and heart rate [54-56]. Notably, these adjustments are initiated very early in pregnancy, with detectable cardiovascular shifts occurring as early as the sixth week of gestation [4].

Cardiac output (CO) increases throughout pregnancy, with studies typically indicating an increment between 30% and 50%, however, some variability is observed across the literature, depending on methodological differences and gestational stage at the time of assessment [52, 54-61]. Evidence suggests that hemodynamic changes are already present by the 6th week of gestation, for instance, Ogueh et al. reported a rise in CO from a preconception baseline of 5.28 L/min to 5.64 L/min during this period [4, 62, 63]. CO generally peaks by the late second trimester, with third-trimester adaptations still debated, with different authors describing stabilization [4, 64, 65], a modest decrease [56, 62, 66-71] or a persistent increase towards term [58, 60, 72-75].

These adjustments in CO directly correlate with heart rate (HR) and stroke volume (SV). Most authors find that HR has a linear progression throughout the gestational period [4, 54, 60, 62, 65-67, 69, 74, 76-79], while others show a plateau after the end of the second trimester [56, 73], with a slight decline at term [58, 72, 80, 81]. Regarding SV, although a general gestational increment is observed, such results often lack statistical significance [4, 52, 56, 58-60, 68, 73, 74, 82, 83]. Furthermore, a terminal decline of SV in the third trimester was documented in some studies, likely attributable to caval compression by the gravid uterus and subsequent reduction in venous return [65, 67, 69]. Thus, it seems that the increase in CO is primarily due, in the early stages, to an increase in SV and, later on, to changes in HR [73, 75, 84, 85]. Additionally, the inconsistent statistical significance of SV increments across the literature led Andreas et al. to posit that the primary driver of elevated CO is the pronounced reduction in systemic vascular resistance (SVR) [72].

Systemic vasodilation is an essential physiological adaptation in a healthy pregnancy, with sex hormones acting as key modulators of vascular tone and reactivity [59, 86]. This reduction in SVR facilitates an increase in CO, according to the mechanisms previously discussed [70, 79, 86]. In the early stages of pregnancy, resistance values drop from 1229 ± 232 dynes.s^{-1}.cm^{-5} to 1129 ± 291 dynes.s^{-1}.cm^{-5} between preconception and the 6th gestational week according to Mahendru et al., results in line with the study performed by Foo et al. [4, 63] From early gestation through the second trimester, SVR tends to show a profound decline, of approximately 40% [56], reaching its nadir between the late second and early third trimesters, following a modest rise towards term, which may explain the decrease in CO in certain studies [4, 54, 56, 58, 60, 62, 67-69, 72-75, 80, 82, 84, 87-93]. Moreover, the assessment of arterial stiffness also represents a critical clinical parameter. Carotid-femoral pulse wave velocity (cfPWV) is the gold standard for quantifying arterial stiffness in the central elastic arteries, evidencing a statistically significant decrease, achieving its nadir in the second trimester [4, 66, 86]. On the other hand, the augmentation index (AIx) indirectly reflects arterial stiffness, showing a more pronounced decline early on, reaching a nadir in the second trimester, and then increasing near-term [4, 63, 66, 79, 86, 94, 95]. This rise in arterial compliance helps accommodate the increase in

intravascular volume [70, 79, 89, 96]. It is worth noting that the role of ANP has been the subject of study and is believed to be related to the vasodilatation observed during pregnancy [91, 93, 97].

These hemodynamic changes are reflected in blood pressure (BP). The pattern of SBP, DBP and mean arterial pressure (MAP) is well described in the literature, with strong evidence demonstrating a decline that reaches its nadir between 20 and 27 gestational weeks [55, 69, 72, 74-77, 81, 83, 90, 95, 98]. This substantial reduction occurs very early in pregnancy, with a marked decline already evident within the first 6 weeks [4, 62, 95, 99]. Because many protocols begin assessment only after 10–14 weeks, only slight decreases or non-significant changes are detected until the nadir is reached [56, 66, 72, 73]. MAP is estimated to decrease by 7–10% [54, 66, 94]. Subsequently, BP increases as the term approaches [58, 65, 67, 72, 74, 75, 81, 83, 90, 100]. A study by Mahendru et al. reported MAP values of 84 ± 8 mmHg, 78 ± 6 mmHg, 76 ± 5 mmHg and 81 ± 6 mmHg in the preconception period, early pregnancy, second trimester and third trimester, respectively [4]. Overall, these changes occur similarly in both central and peripheral BP, although values increase as blood flows towards the periphery [66, 94].

The expansion of total circulating volume, driven by maternal and fetal demands also triggers significant adaptations in cardiac structure and function [52]. This intravascular volume expansion, coupled with enhanced venous return, represents a marked increase in preload [52, 88]. At the cardiac level, this is manifested by enlargement of chamber dimensions [74, 84], specifically reflected in left ventricular end-diastolic volume and diameter (LVEDV and LVEDD) [52, 55, 59, 75, 78, 82, 89], leading to a physiological eccentric hypertrophy [75, 99]. To preserve cardiac performance, ventricular dilation is compensated by a concomitant increase in ventricular mass and wall thickness of roughly 40% [88] and 20% [56] , respectively, across the gestational period. Additionally, a significant reduction in afterload is characterized by a concurrent decrease in SVR and MAP, along with diminished end-systolic wall stress [88].

Current literature regarding systolic function in pregnancy presents conflicting findings. While some authors report an enhancement in intrinsic contractility and fractional shortening (FS) [59, 60, 82, 84, 88, 98], others observe a progressive decline in ejection fraction (EF) towards term [54-56, 61, 62], potentially indicating a maladaptation in late gestation [101]. Nevertheless, the prevailing consensus suggests that global cardiac function remains largely preserved [61, 74, 89].

Regarding diastolic function, changes are usually less pronounced [55, 88]. In the near-term, studies often described a decrease in the E/A ratio, caused by a subtle decrease in early diastolic filling (E) and an increase in atrial contraction (A) [60, 74, 78, 92, 99, 102]. This could be explained by a diminished ventricular compliance due to a continuous rise in left ventricular mass, an increase in left ventricular end-diastolic pressure, or a combination of both, resulting in a subtle impairment

of diastolic filling [60, 62, 88, 101]. Furthermore, Melchiorre et al. suggest that up to 20% of pregnant women may meet criteria for diastolic dysfunction [88].

Hemodynamic Transition into Postpartum

The intrapartum period is marked by profound hemodynamic oscillations, with significant fluctuations in CO between peaks of uterine contractions and baseline intervals [103]. While CO, HR, SV and SVR tend to revert from their intrapartum peaks shortly after delivery, the subsequent 6 to 12 weeks involve a more complex cardiovascular remodeling [103].

During the early postpartum phase, a marked decline in CO, HR, and SV is typically observed, alongside an increase in SVR [4, 56, 60, 69, 72, 75, 78, 80, 90, 99]. While parameters such as SBP and DBP, as well as left ventricular structural indices (mass, wall stress, diameter and volume), generally trend towards preconception values [55, 56, 62, 78, 98, 104], the timeline for full restoration remains a subject of debate.

Although some literature suggests a return to baseline within the first 6 to 12 weeks postpartum, conflicting evidence highlights a more protracted recovery [60, 75, 100, 104]. For instance, Capeless et al. demonstrated that at 12 weeks postpartum, CO, LVEDV and SV remained elevated, while SVR remained lower than preconception levels [104]. Similarly, Savu et al. noted that SVR did not return to its baseline during this period [75].

Furthermore, BP dynamics appear to deviate from prepregnancy norms longer than previously thought [4, 98, 100]. Mahendru et al. reported a lower SBP at 16 weeks postpartum compared to preconception, a finding supported by Meah et al. and Blake et al., who observed lower BP values in postpartum women than in their non-pregnant counterparts [4, 98, 100]. Structural recovery also appears incomplete in the medium term, according to Estensen et al., who observed that although LVEDV and LVEDD might normalize within standard ranges, LV wall thickness and mass do not fully revert to specific preconception values [55]. Ultimately, it appears that while most geometric and hemodynamic indices converge towards standard reference ranges by one year postpartum [88], the return to individual preconception baselines is a gradual process that may extend well beyond the traditional puerperium [4, 78, 88, 98, 100].

PREPREGNANCY MATERNAL CARDIOVASCULAR FUNCTION AND RISK OF PREECLAMPSIA OR FETAL GROWTH RESTRICTION

Women with a history of PE face a significantly elevated risk of future cardiovascular disease compared to those with normotensive pregnancies [15, 105, 106]. The underlying mechanism of this association is still under investigation, and it remains unclear whether PE acts as a causal trigger through pregnancy-induced physiological changes or if it is simply due to pre-existing shared risk

factors [15, 105, 106]. Consequently, evaluating women's cardiovascular profile before conception has become increasingly relevant [107, 108]. However, few studies have successfully achieved this due to the logistical challenges of preconception follow-up and confounding factors, such as infertility, miscarriages, or other pregnancy-related complications [109]. Table I summarizes the cardiovascular parameters of non-pregnant women who later develop PE and/or FGR compared with those in healthy pregnancies.

Numerous studies have established a correlation between preconception BP and the risk of subsequent PE and/or FGR. Given that PE and FGR frequently co-occur, a shared pathophysiological mechanism is suggested, with PE being characterized by pathological elevations in BP [15]. Women with higher prepregnancy SBP and DBP tend to experience more pronounced BP spikes throughout the entire gestational period [110]. Consequently, the prevalence of these conditions is higher in women with pre-existing cardiovascular disease or cardiac impairment compared to those who are previously healthy [111, 112]. Furthermore, studies in women planning to conceive, even in the absence of cardiovascular or hypertensive history, demonstrate that those who present with PE, FGR or small-for-gestation-age (SGA) infants tend to exhibit significantly higher baseline SBP, DBP and MAP compared to those with uncomplicated pregnancies [15, 106, 109, 113-116].

While the evolution of CO during pregnancy has been extensively studied, data regarding the preconception period remain scarce. Generally, an increased CO is believed to be beneficial for fetal weight gain [15]. A study conducted by Foo et al. found that pregnancies complicated by PE and/or FGR had lower CO than control groups, a finding corroborated by Hale et al [15, 107]. On the other hand, research specifically focusing on preterm PE has observed a paradoxical increase in CO [109, 113].

Plasma volume (PV) also appears to follow a distinct pattern in women who later develop PE [109, 113, 117, 118]. There is a notable trend towards reduced PV and impaired expansion compared with those in healthy pregnancies [109, 113, 117, 118]. In a research involving women with a history of PE, Aardenburg et al. demonstrated that those who experienced a recurrence of the condition exhibited lower PV [117]. The authors linked this deficiency to fetal birth weight, supporting the hypothesis that hemodynamic alterations are present prior to conception [117]. As for SVR and arterial stiffness, studies have indicated a significantly higher risk of developing PE and/or FGR when these parameters are elevated [15, 113, 115].

Regarding cardiac function, a higher prevalence of echocardiographic abnormalities has been observed in women who subsequently develop PE (32% in PE vs 12% in uncomplicated pregnancy), as well as significant preconception cardiac impairment in cases of FGR [118]. However,

findings remain inconsistent. A study by Ormesher et al. found no correlation between the severity of LV impairment and either PE prevalence or birth weight, nor was a significant link established regarding LV systolic or diastolic function [112]. In contrast, Siegmund et al. reported an association between preconception right ventricular diastolic dysfunction and impaired uteroplacental circulation beginning in early pregnancy [108].

ASSOCIATION BETWEEN MATERNAL CARDIAC OUTPUT AND RISK OF ISOLATED PREECLAMPSIA OR PREECLAMPSIA WITH FETAL GROWTH RESTRICTION

The identification of distinct PE phenotypes has been extensively studied, with these phenotypes often correlating with divergent pathophysiological mechanisms [119, 120]. Traditionally, this differentiation was based on the timing of clinical onset, under the premise that early-onset PE stems primarily from a placental component, whereas late-onset PE is driven more by a maternal constitutional factor [24, 119]. Although these phenotypes are expected to manifest through different maternal cardiovascular profiles, clinical findings have not always been linear, since disease does not change at 34 + 0 weeks' gestation [15, 24, 121]. As previously established, PE is robustly associated with FGR, which appears to be significantly and independently linked to specific hemodynamic characteristics [15, 122]. Consequently, recent research has shifted towards analyzing the distinct nuances of maternal cardiovascular presentation in PE when FGR is concurrently present, and comparing it with isolated PE to better understand the interplay between these two conditions [24, 25].

Isolated PE is frequently characterized by a stronger association with maternal constitutional factors, which are predominantly reflected in women's cardiovascular profiles [16]. Research consistently identifies an increase in SVR, a hallmark already well established in the disease's pathophysiology [16, 120, 121, 123-125].

Regarding CO in isolated PE, the literature remains diverse. While some authors have observed a reduction in CO regardless of the PE phenotype [123-125], others have found no significant differences between the isolated PE and control groups [16, 120, 121]. This lack of significance supports the hypothesis that isolated PE may not originate in early maladaptation, but rather in metabolic factors, which would justify the tendency towards a later clinical presentation [120, 121]. Conversely, growing evidence suggests an opposing hyperdynamic state driven by volume overload, with an increase in CO, CI and SV [25, 126-128], correlating with enhanced left ventricular systolic function due to increased preload [126]. Furthermore, women with isolated PE often present with a higher body mass index [25, 120]. Studies by Tay et al. reported not only an increase in CO in patients with isolated PE, but also a decrease in SVR in this group of women [25, 129].

In contrast, when PE occurs in association with FGR (PE/FGR), the hemodynamic conclusions differ significantly from those in isolated cases. According to Chen et al., women with the PE/FGR phenotype often exhibit clinical signs of PE before the onset of FGR [119]. This temporal sequence suggests a shared pathophysiological mechanism rooted in maladaptation of the spiral arteries [119, 120]. In these instances, the maternal hemodynamic profile more closely mirrors the characteristics of FGR than those of isolated PE [122, 126].

In the PE/FGR group, clinical results are more consistent, characterized by a marked increase in SVR, typically more pronounced than in isolated PE, and a CO that is statistically diminished compared to both normotensive pregnancies and patients with only PE [15, 16, 25, 119-121, 124, 125, 127, 130-132]. Consequently, the elevation in MAP appears to be primarily due to increases in afterload and SVR rather than to a hyperdynamic state [126, 128].

PE/FGR is also strongly associated with elevated uterine artery PI and other Doppler abnormalities [120, 129, 131]. These markers of high uteroplacental resistance explain the intrinsic link between PE and FGR [119], as well as the predisposition towards an early-onset disease progression, given the early involvement of the placenta [121, 133]. These changes were not seen in isolated PE [129].

Accordingly, CO appears to exert a direct positive influence on birth weight [15]. Notably, no significant differences in maternal hemodynamic presentation were observed between conditions, regardless of whether the condition manifested before or after 34 weeks, in both isolated PE and PE/FGR [24, 25].

DISTINCT PREECLAMPSIA PHENOTYPES DEMAND TAILORED THERAPEUTIC APPROACHES

Although the management of arterial hypertension has evolved significantly over the years, therapeutic approaches for pregnant women have remained largely unchanged [134]. Current treatment strategies rely heavily on pharmacological agents with well-established safety profiles [134]. However, studies comparing their efficiency based on maternal hemodynamic characteristics remain scarce [134].

Nevertheless, growing evidence suggests that tailoring therapy to each woman may be superior [134, 135]. In patients presenting with PE characterized by reduced CO and elevated SVR, a profile frequently associated with FGR, the use of vasodilators, such as dihydropyridine calcium channel blockers and alpha-methyldopa, is increasingly considered the most appropriate intervention [134, 135]. Conversely, women exhibiting high CO and lower SVR, often associated with large-for-gestational-age fetuses, appear to benefit more from an initial treatment with beta-blockers, specifically labetalol [134, 135].

A study conducted by Di Pasquo et al. tested this hypothesis, defining tailored treatment as the administration of a vasodilator in women with HDP exhibiting a predominantly hypodynamic

profile, and the use of labetalol for those with a hyperdynamic profile [134]. Non-tailored treatment was thus characterized by the inverse application of these therapies [134]. The results demonstrated that the progression to severe hypertension was significantly lower in the cohort receiving adequate treatment compared to those receiving non-tailored treatment (6.0% versus 19.4%) [134]. Furthermore, an untailored approach was associated with a significantly greater need for second-line therapies [134].

These findings align with research by Stott et al., which demonstrated that pregnant women who failed to respond to first-line treatment with labetalol presented with higher BP, elevated SVR and lower CO upon admission [136]. Consequently, research showed a greater need for concomitant vasodilator therapy and a higher incidence of FGR in these cases [136, 137].

The benefits of this hemodynamically directed approach have also been observed in women at high risk of developing PE, leading to decreased rates of progression to PE and FGR, alongside an increase in term deliveries [138, 139]. Therefore, there is growing evidence that targeted therapeutic interventions yield a better overall prognosis, enabling earlier BP control and reducing the need for polypharmacy [134-136].

DISCUSSION | DISCUSSÃO

Still, little is known about the etiology of PE [24]. The association between a prior history of PE and a higher risk of future cardiovascular disease is well established, as is the greater predisposition to disease recurrence in subsequent pregnancies [15, 105, 106]. However, it remains to be clarified whether this susceptibility is due to maternal factors present before conception or due to alterations induced by the pathology itself [15, 105, 106].

An increasing number of studies have refuted the idea that PE is exclusively a disease of uteroplacental origin, pointing instead to a strong maternal component in its progression or even to a genesis completely independent from the placenta [15, 107]. In this review, we observed that the development of both PE and FGR is linked to cardiovascular dysfunction as early as the preconception period, emphasizing the potential role of the maternal hemodynamic profile in these conditions. Women with a history of PE or FGR tend to exhibit higher BP levels than those with uncomplicated pregnancies [15, 106, 109, 113-116, 140]. Regarding preconception CO, some studies show a decrease, evidencing a hypodynamic state prior to the onset of placental dysfunction or the emergence of PE-derived cardiovascular diseases [15]. This could indicate a triggering factor that directly impacts placental development [15]. Conversely, studies focusing on preterm PE have demonstrated increased CO [109, 113]. We suggest that this discrepancy in results may stem from insufficient stratification regarding the presence or absence of FGR, which could reflect distinct underlying pathophysiological mechanisms.

Throughout pregnancy, a tendency towards distinct cardiovascular profiles has been observed in women with PE.

In its isolated form, PE showed a profile characterized by higher CO and lower SVR than that of PE/FGR [25, 126-128]. Compared to control groups, these alterations were not always linear with some studies reporting a tendency towards lower CO and higher SVR, but not reaching the extreme values observed in PE/FGR [123-125]. It is hypothesized that these discrepancies arise from the combined analysis of PE with other HDP, which introduces confounding factors [131]. In contrast, other studies focusing exclusively on PE have already demonstrated a tendency towards higher CO and lower SVR relative to controls [25, 127, 129].

FGR manifests with increased SVR and reduced CO compared with an uncomplicated pregnancy [122]. The PE/FGR association presents a cardiovascular profile closer to that of FGR than to what is typically described in isolated PE [122, 126]. In these cases, a more pronounced reduction in CO is observed, coupled with a markedly increased SVR [25, 129, 132].

Characteristically, isolated PE is categorized as having a predominant maternal component in its pathophysiology [24, 120], without alterations in uteroplacental flow [129]. On the other hand, PE/FGR is described as arising from a mechanism of uteroplacental origin [24, 119, 120]. When associated, these conditions present the highest percentage of impaired spiral artery invasion compared to controls or to either disease isolated [30], translating into a higher incidence of abnormalities in uterine artery assessments [129]. The literature indicates that one PE subtype results from inadequate trophoblast invasion of the spiral arteries, while the other is potentially driven by endothelial dysfunction secondary to a pre-existing maternal pro-inflammatory state, such as cardiovascular risk factors or metabolic syndrome [24, 119].

Nevertheless, evidence of distinct hemodynamic profiles throughout gestation and of alterations as early as the preconception period leads us to question the true role of the maternal component in the disease's pathophysiology, specifically whether it might directly influence inadequate uteroplacental development.

The traditional classification of PE by time of onset has shown inconsistencies. Tay et al. reported that the clinical differences between early- and late-onset PE are essentially attributable to their association with FGR, given that early- or late-onset isolated PE do not exhibit significant hemodynamic differences [25]. Therefore, we propose a new classification of PE into two phenotypes, based on the presence or absence of FGR.

This new classification could impact how we address the treatment of PE, in the way that antihypertensive therapy should be tailored to these distinct cardiovascular characteristics [26, 134, 135].

Currently, the standard of care in several countries relies on labetalol [26]. As a combined alpha- and beta-adrenergic antagonist, labetalol promotes initial vasodilation alongside a stronger negative chronotropic effect, ultimately lowering BP [141]. Consequently, it may not be the optimal choice for pregnant women presenting with pre-existing low CO and high SVR [139].

Calcium channel blockers (CCBs) are another widely used class of antihypertensives [134]. Several studies highlight their potent vasodilatory properties, which lead to a marked decrease in peripheral vascular resistance and a subsequent increase in cardiac index [141, 142]. Growing evidence supports the preferential use of vasodilators in women with elevated SVR, a group that is frequently resistant to labetalol therapy [137, 141].

Accordingly, Masini et al. suggest that the management of PE characterized by low HR, reduced CO and high SVR should be based on CCBs, for example nifedipine, nitric oxide donors and fluid administration [26]. In contrast, for women presenting with high CO and HR coupled with low SVR, alpha- and beta-blockers should be the preferred therapeutic approach [26].

Although emerging studies demonstrate the clinical benefits of this phenotype-guided strategy, further research is needed.

CONCLUSION | CONCLUSÃO

Through this review, we conclude that there are two distinct PE phenotypes characterized by opposing cardiovascular profiles that are intimately linked to the concurrent presentation of FGR. Distinguishing between these two phenotypes can ultimately help elucidate the diverse underlying pathophysiological mechanisms and advance research towards a tailored therapeutic approach to PE.

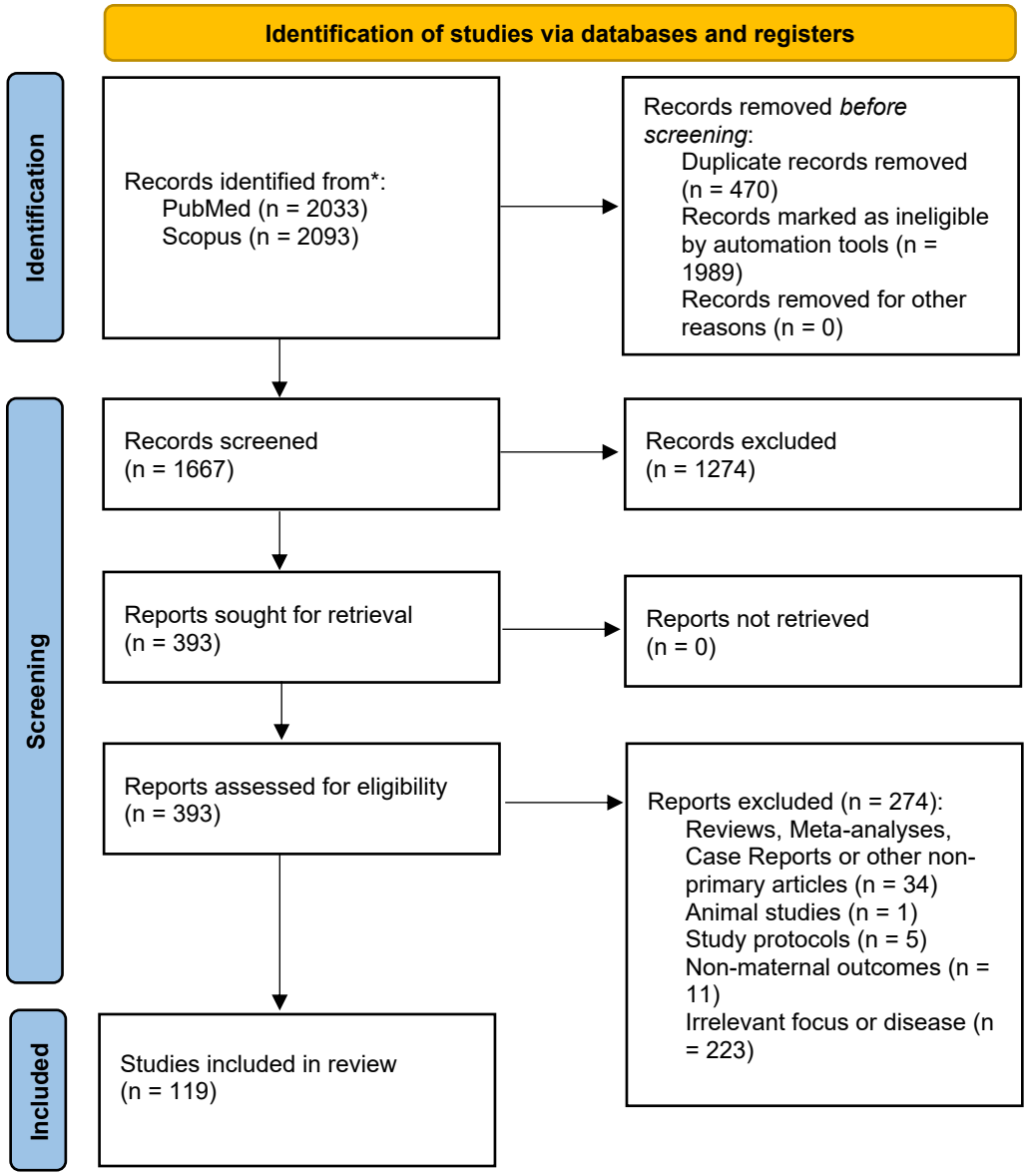


Figure 1: PRISMA 2020 flow diagram of study selection

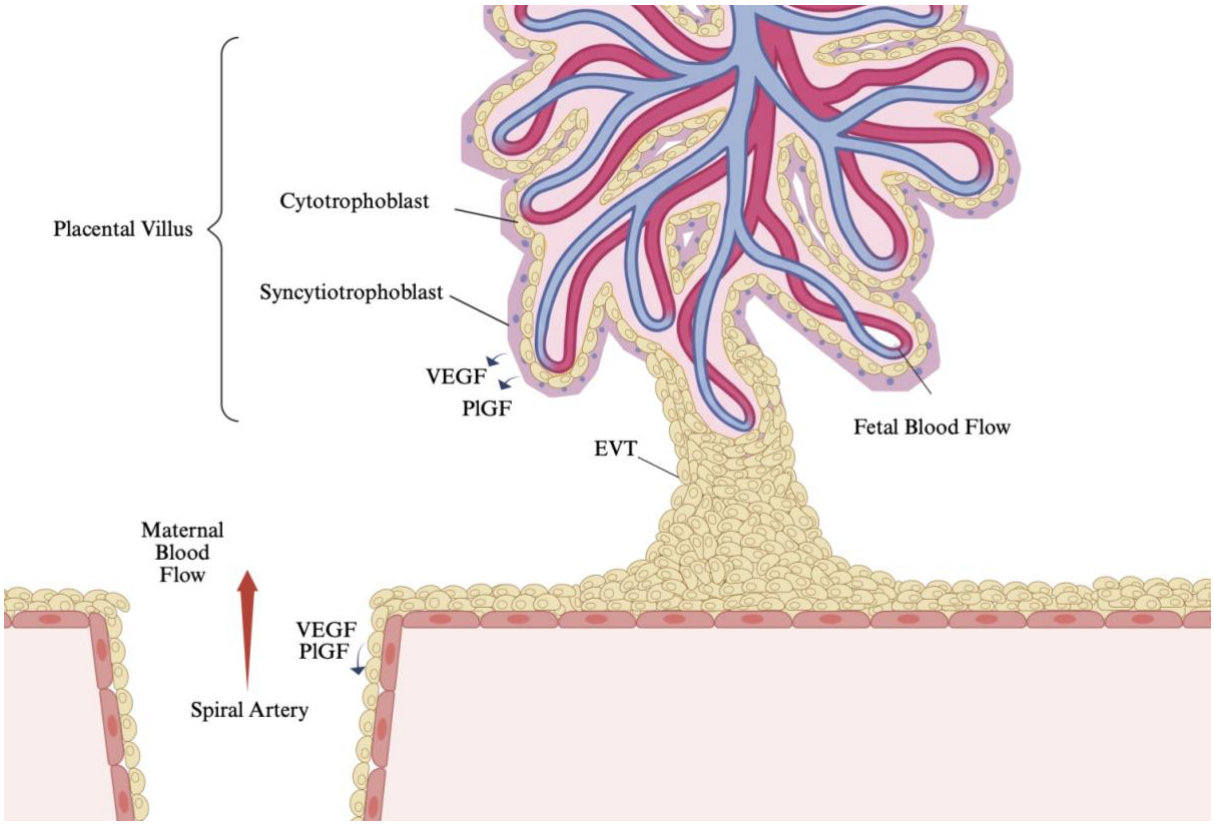


Figure 2: Placental vasculogenesis.
The syncytiotrophoblasts of the placental villus secrete VEGF and PlGF into the maternal circulation. Extravillous trophoblasts (EVT) also produce VEGF and PlGF to promote proper remodeling of the spiral arteries. Created in BioRender. Sampaio, S. (2026) https://BioRender.com/r38l89c

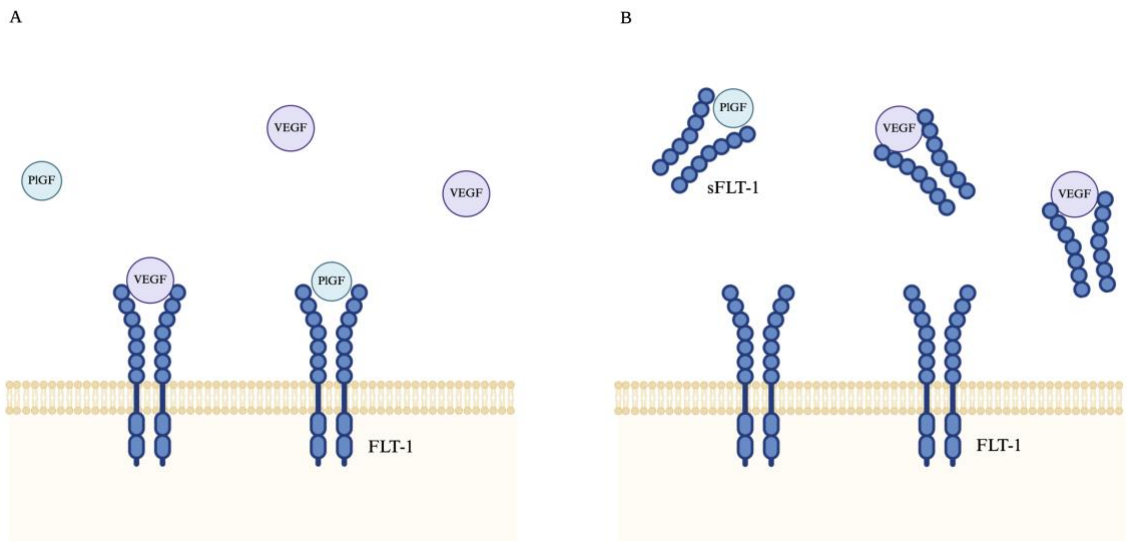


Figure 3: Maternal circulation of pro-angiogenic factors in (A) normal pregnancy and (B) preeclampsia.
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Table I: Preconception maternal cardiovascular parameters and association with PE and/or FGR.

First Author (Year)	Population	Design	Metrics	Results
Foo (2018) [15]	218 healthy women (15 PE and/or FGR)	Prospective Cohort Study	CO, CI, SV, SVR, MAP, HR	↓* CO, CI and SV and ↑* MAP and SVR in women affected by PE and/or FGR. Small negative association between HR and birth weight.
Loftness (2023) [109]	80 healthy women (10 preterm PE)	Prospective Cohort Study	CO, BP, PV, PWVs	Women with preterm PE had ↑* SBP, DBP, MAP, CO and PWVs and ↓* PV during preconception.
Bernstein (2025) [113]	124 women (81 nulliparous; 43 with prior preterm PE)	Prospective Longitudinal Cohort Study	CO, BP, HR, PV, PWVs	↑* SBP, DBP, MAP, CO, HR and PWVs in women who develop preterm PE. No significant differences found in PV.
Mahendru (2013) [115]	74 women (14 with prior PE and/or FGR)	Prospective Cohort Study	BP, HR, CO, CI, SV, SVR, PWV	↑* brachial DBP, central SBP, MAP and SVR in women with previous PE and/or FGR. No significant differences in CO, CI, SV, HR and adjusted PWV between groups.
Hale (2009) [107]	19 nulliparous women (2 PE and/or FGR)	Prospective Cohort Study	Uterine RI, volumetric UBF, CO	CO and UBF tend to be ↓ in women affected by PE. Strong negative association of uterine RI with prepregnancy UBF.
Harville (2011) [114]	1142 primiparous women	Prospective Cohort Study	BP	Women in the lowest or highest quartile of DBP were at risk for SGA.
Magnussen (2007) [105]	3494 women (133 PE)	Prospective Cohort Study	BP	Strong and linear positive association between SBP and DBP and PE.
Mukhtarova (2021) [110]	1244 women	Retrospective Cohort Study	BP	Women with prepregnancy SBP ≥130 mmHg or DBP ≥80 mmHg exhibit higher rates of BP spikes during all gestation.
Romundstad (2010) [106]	3.225 women, singleton birth	Prospective Longitudinal Cohort Study	BP	↑* prepregnancy SBP and DBP in women who developed hypertensive disorders.
Xiong (2024) [116]	567.127 women	Population-based Cohort Study	BP	Women with hypertension or ↑* BP values had a higher risk of adverse pregnancy outcomes, such as SGA.

Table I. Continued.

First Author (Year)	Population	Design	Metrics	Results
Aardenburg (2006) [117]	14 women prior PE (7 recurrent PE)	Prospective Cohort Study	PV	All women with PV below 44 mL × [lean body mass]$^{-1}$ developed recurrent hypertensive disease. Birth weight ↑* with prepregnancy PV.
Emonts (2008) [118]	151 women (50 prior PE)	Prospective Cohort Study	PV, cardiac function	↑* cardiac abnormalities, such as EF and heart size in women affected by PE. ↓* PV in PE.
Ormesher (2023) [112]	282 women with cardiac dysfunction (13 PE)	Retrospective Cohort Study	Cardiac function	↑* prevalence of preterm PE and FGR. No relation between systolic or diastolic function and pregnancy outcomes.
Rigó Jr. (2005) [111]	683 primiparous (162 severe PE)	Retrospective Cohort Study	Family history of CV disease	Family early-onset CV disorders is a predisposing factor for severe PE.
Siegmund (2019) [108]	138 women with CHD	Prospective Cohort Study	Cardiac function	Preconception RV dysfunction has an impact in placentation with a ↑* resistance in UtA flow.

Abbreviations: BP, blood pressure; CHD, congenital heart disease; CI, cardiac index; CO, cardiac output; CV, cardiovascular; DBP, diastolic blood pressure; ECG, electrocardiogram; EF, ejection fraction; FGR, fetal growth restriction; HR, heart rate; MAP, mean arterial pressure; PE, preeclampsia; PV, plasma volume; PWVs, pulse wave velocities; RI, resistance index; SBP, systolic blood pressure; SGA, small-for-gestational-age; SV, stroke volume; SVR, systemic vascular resistance; UBF, uterine blood flow; UtA, uterine artery.
*Indicates statistically significant association ($p<0.05$)

REFERENCES | REFERÊNCIAS

1. Sinkey RG, Battarbee AN, Bello NA, Ives CW, Oparil S, Tita ATN. Prevention, Diagnosis, and Management of Hypertensive Disorders of Pregnancy: a Comparison of International Guidelines. Curr Hypertens Rep. 2020;22(9):66.
2. Ives CW, Sinkey R, Rajapreyar I, Tita ATN, Oparil S. Preeclampsia—Pathophysiology and Clinical Presentations: JACC State-of-the-Art Review. Journal of the American College of Cardiology. 2020;76(14):1690–702.
3. Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin, Number 222. Obstet Gynecol. 2020;135(6):e237–e60.
4. Mahendru AA, Everett TR, Wilkinson IB, Lees CC, McEniery CM. A longitudinal study of maternal cardiovascular function from preconception to the postpartum period. J Hypertens. 2014;32(4):849–56.
5. Casanova R, Chuang A, Goepfert AR, et al. Beckmann and Ling's Obstetrics and Gynecology, 8e: Lippincott Williams & Wilkins, a Wolters Kluwer business; 2019.
6. Sanghavi M, Rutherford JD. Cardiovascular Physiology of Pregnancy. Circulation. 2014;130(12):1003–8.
7. Chapman AB, Abraham WT, Zamudio S, et al. Temporal relationships between hormonal and hemodynamic changes in early human pregnancy. Kidney Int. 1998;54(6):2056–63.
8. Brosens I, Puttemans P, Benagiano G. Placental bed research: I. The placental bed: from spiral arteries remodeling to the great obstetrical syndromes. American Journal of Obstetrics & Gynecology. 2019;221(5):437–56.
9. De Wolf F, Robertson WB, Brosens I. The ultrastructure of acute atherosis in hypertensive pregnancy. Am J Obstet Gynecol. 1975;123(2):164–74.
10. Chappell LC, Cluver CA, Kingdom J, Tong S. Pre-eclampsia. The Lancet. 2021;398(10297):341–54.
11. Aardema MW, Oosterhof H, Timmer A, van Rooy I, Aarnoudse JG. Uterine Artery Doppler Flow and Uteroplacental Vascular Pathology in Normal Pregnancies and Pregnancies Complicated by Pre-eclampsia and Small for Gestational Age Fetuses. Placenta. 2001;22(5):405–11.
12. Olofsson P, Laurini RN, Marsál K. A high uterine artery pulsatility index reflects a defective development of placental bed spiral arteries in pregnancies complicated by hypertension and fetal growth retardation. Eur J Obstet Gynecol Reprod Biol. 1993;49(3):161–8.
13. Ness RB, Roberts JM. Heterogeneous causes constituting the single syndrome of preeclampsia: A hypothesis and its implications. American Journal of Obstetrics & Gynecology. 1996;175(5):1365–70.
14. Gyselaers W. Preeclampsia Is a Syndrome with a Cascade of Pathophysiologic Events. J Clin Med. 2020;9(7).
15. Foo FL, Mahendru AA, Masini G, et al. Association Between Prepregnancy Cardiovascular Function and Subsequent Preeclampsia or Fetal Growth Restriction. Hypertension. 2018;72(2):442–50.
16. Stott D, Nzelu O, Nicolaides KH, Kametas NA. Maternal hemodynamics in normal pregnancy and in pregnancy affected by pre-eclampsia. Ultrasound Obstet Gynecol. 2018;52(3):359–64.
17. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. BMJ. 2007;335(7627):974.

18. von Dadelszen P, Magee LA, Roberts JM. Subclassification of preeclampsia. Hypertens Pregnancy. 2003;22(2):143–8.
19. Valensise H, Vasapollo B, Gagliardi G, Novelli GP. Early and late preeclampsia: two different maternal hemodynamic states in the latent phase of the disease. Hypertension. 2008;52(5):873–80.
20. Lisonkova S, Joseph KS. Incidence of preeclampsia: risk factors and outcomes associated with early- versus late-onset disease. American Journal of Obstetrics & Gynecology. 2013;209(6):544.e1–.e12.
21. Phipps EA, Thadhani R, Benzing T, Karumanchi SA. Pre-eclampsia: pathogenesis, novel diagnostics and therapies. Nat Rev Nephrol. 2019;15(5):275–89.
22. ACOG Practice Bulletin No. 204: Fetal Growth Restriction. Obstet Gynecol. 2019;133(2):e97–e109.
23. Nardozza LM, Caetano AC, Zamarian AC, et al. Fetal growth restriction: current knowledge. Arch Gynecol Obstet. 2017;295(5):1061–77.
24. Ferrazzi E, Zullino S, Stampalija T, et al. Bedside diagnosis of two major clinical phenotypes of hypertensive disorders of pregnancy. Ultrasound Obstet Gynecol. 2016;48(2):224–31.
25. Tay J, Foo L, Masini G, et al. 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. American Journal of Obstetrics & Gynecology. 2018;218(5):517.e1–.e12.
26. Masini G, Foo LF, Tay J, et al. Preeclampsia has two phenotypes which require different treatment strategies. Am J Obstet Gynecol. 2022;226(2s):S1006–s18.
27. Brosens I, Dixon HG, Robertson WB. Fetal growth retardation and the arteries of the placental bed. Br J Obstet Gynaecol. 1977;84(9):656–63.
28. Gerretsen G, Huisjes HJ, Hardonk MJ, Elema JD. Trophoblast alterations in the placental bed in relation to physiological changes in spiral arteries. Br J Obstet Gynaecol. 1983;90(1):34–9.
29. Labarrere CA, DiCarlo HL, Bammerlin E, et al. Failure of physiologic transformation of spiral arteries, endothelial and trophoblast cell activation, and acute atherosis in the basal plate of the placenta. Am J Obstet Gynecol. 2017;216(3):287.e1–.e16.
30. Brouwers L, de Gier S, Vogelvang TE, et al. Prevalence of placental bed spiral artery pathology in preeclampsia and fetal growth restriction: A prospective cohort study. Placenta. 2024;156:1–9.
31. Lyall F, Robson SC, Bulmer JN. Spiral artery remodeling and trophoblast invasion in preeclampsia and fetal growth restriction: relationship to clinical outcome. Hypertension. 2013;62(6):1046–54.
32. Sağol S, Ozkinay E, Oztekin K, Ozdemir N. The comparison of uterine artery Doppler velocimetry with the histopathology of the placental bed. Aust N Z J Obstet Gynaecol. 1999;39(3):324–9.
33. Gerretsen G, Huisjes HJ, Elema JD. Morphological changes of the spiral arteries in the placental bed in relation to pre-eclampsia and fetal growth retardation. Br J Obstet Gynaecol. 1981;88(9):876–81.
34. Sheppard BL, Bonnar J. An ultrastructural study of utero-placental spiral arteries in hypertensive and normotensive pregnancy and fetal growth retardation. Br J Obstet Gynaecol. 1981;88(7):695–705.

35. Sheppard BL, Bonnar J. THE ULTRASTRUCTURE OF THE ARTERIAL SUPPLY OF THE HUMAN PLACENTA IN PREGNANCY COMPLICATED BY FETAL GROWTH RETARDATION. BJOG: An International Journal of Obstetrics and Gynaecology. 1976;83(12):948–59.
36. Kitzmiller JL, Watt N, Driscoll SG. Decidual arteriopathy in hypertension and diabetes in pregnancy: Immunofluorescent studies. American Journal of Obstetrics and Gynecology. 1981;141(7):773–9.
37. Hustin J, Foidart JM, Lambotte R. Maternal vascular lesions in pre-eclampsia and intrauterine growth retardation: light microscopy and immunofluorescence. Placenta. 1983;4 Spec No:489–98.
38. Gosseye S, van der Veen F. HPL-positive infiltrating trophoblastic cells in normal and abnormal pregnancy. European Journal of Obstetrics and Gynecology and Reproductive Biology. 1992;44(2):85–90.
39. Zhu J, Zhong M, Pang Z, Yu Y. Dysregulated expression of matrix metalloproteinases and their inhibitors may participate in the pathogenesis of pre-eclampsia and fetal growth restriction. Early Hum Dev. 2014;90(10):657–64.
40. Huisman MA, Timmer A, Zeinstra M, et al. Matrix-metalloproteinase activity in first trimester placental bed biopsies in further complicated and uncomplicated pregnancies. Placenta. 2004;25(4):253–8.
41. Gabinskaya T, Salafia CM, Gulle VE, Holzman IR, Weintraub AS. Gestational age-dependent extravillous cytotrophoblast osteopontin immunolocalization differentiates between normal and preeclamptic pregnancies. Am J Reprod Immunol. 1998;40(5):339–46.
42. Lyall F, Simpson H, Bulmer JN, Barber A, Robson SC. Transforming growth factor-beta expression in human placenta and placental bed in third trimester normal pregnancy, preeclampsia, and fetal growth restriction. Am J Pathol. 2001;159(5):1827–38.
43. Madazli R, Benian A, Ilvan S, Calay Z. Placental apoptosis and adhesion molecules expression in the placenta and the maternal placental bed of pregnancies complicated by fetal growth restriction with and without pre-eclampsia. J Obstet Gynaecol. 2006;26(1):5–10.
44. Williams PJ, Bulmer JN, Searle RF, Innes BA, Robson SC. Altered decidual leucocyte populations in the placental bed in pre-eclampsia and foetal growth restriction: a comparison with late normal pregnancy. Reproduction. 2009;138(1):177–84.
45. Milosevic-Stevanovic J, Krstic M, Radovic-Janosevic D, Popovic J, Tasic M, Stojnev S. Number of decidual natural killer cells & macrophages in pre-eclampsia. Indian J Med Res. 2016;144(6):823–30.
46. Stallmach T, Hebisch G, Orban P, Lü X. Aberrant positioning of trophoblast and lymphocytes in the feto-maternal interface with pre-eclampsia. Virchows Archiv. 1999;434(3):207–11.
47. Vuorela P, Halmesmäki E. Vascular endothelial growth factor, its receptors, and the tie receptors in the placental bed of women with preeclampsia, diabetes, and intrauterine growth retardation. Am J Perinatol. 2006;23(4):255–63.
48. Tsatsaris V, Goffin F, Munaut C, et al. Overexpression of the soluble vascular endothelial growth factor receptor in preeclamptic patients: pathophysiological consequences. J Clin Endocrinol Metab. 2003;88(11):5555–63.
49. Barber A, Robson SC, Myatt L, Bulmer JN, Lyall F. Heme oxygenase expression in human placenta and placental bed: reduced expression of placenta endothelial HO-2 in preeclampsia and fetal growth restriction. Faseb j. 2001;15(7):1158–68.

50. Lyall F, Bulmer JN, Kelly H, Duffie E, Robson SC. Human trophoblast invasion and spiral artery transformation: the role of nitric oxide. Am J Pathol. 1999;154(4):1105–14.
51. Morris NH, Sooranna SR, Learmont JG, et al. Nitric oxide synthase activities in placental tissue from normotensive, pre-eclamptic and growth retarded pregnancies. Br J Obstet Gynaecol. 1995;102(9):711–4.
52. Ducas R, Elliott JE, Melnyk SF, et al. Cardiovascular magnetic resonance in pregnancy: Insights from the cardiac hemodynamic imaging and remodeling in pregnancy (CHIRP) study. Journal of Cardiovascular Magnetic Resonance. 2014;16(1).
53. Ekholm EMK, Antila KJ, Erkkola RU. Cardiovascular autonomic reflexes in mid-pregnancy. BJOG: An International Journal of Obstetrics & Gynaecology. 1993;100(2):177–82.
54. Estensen ME, Grindheim G, Remme EW, et al. Systemic arterial response and ventriculo-arterial interaction during normal pregnancy. American Journal of Hypertension. 2012;25(6):672–7.
55. Estensen ME, Beitnes JO, Grindheim G, et al. Altered maternal left ventricular contractility and function during normal pregnancy. Ultrasound Obstet Gynecol. 2013;41(6):659–66.
56. Geva T, Mauer MB, Striker L, Kirshon B, Pivarnik JM. Effects of physiologic load of pregnancy on left ventricular contractility and remodeling. American Heart Journal. 1997;133(1):53–9.
57. Clark SL, Cotton DB, Lee W, et al. Central hemodynamic assessment of normal term pregnancy. American Journal of Obstetrics and Gynecology. 1989;161(6 PART 1):1439–42.
58. Desai DK, Moodley J, Naidoo DP. Echocardiographic assessment of cardiovascular hemodynamics in normal pregnancy. Obstetrics and Gynecology. 2004;104(1):20–9.
59. Laird-Meeter K, van de Ley G, Bom TH, Wladimiroff JW, Roelandt J. Cardiocirculatory adjustments during pregnancy — An echocardiographic study. Clinical Cardiology. 1979;2(5):328–32.
60. Mabie WC, DiSessa TG, Crocker LG, Sibai BM, Arheart KL. A longitudinal study of cardiac output in normal human pregnancy. Am J Obstet Gynecol. 1994;170(3):849–56.
61. Mone SM, Sanders SP, Colan SD. Control mechanisms for physiological hypertrophy of pregnancy. Circulation. 1996;94(4):667–72.
62. Ogueh O, Brookes C, Johnson MR. A longitudinal study of the maternal cardiovascular adaptation to spontaneous and assisted conception pregnancies. Hypertension in Pregnancy. 2009;28(3):273–89.
63. Foo FL, Collins A, McEniery CM, Bennett PR, Wilkinson I, Lees C. Preconception and early pregnancy maternal haemodynamic changes in healthy women in relation to pregnancy viability. Human Reproduction. 2017;32(5):985–92.
64. Kager CCM, Dekker GA, Stam MC. Measurement of cardiac output in normal pregnancy by a non-invasive two-dimensional independent doppler device. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2009;49(2):142–4.
65. Volman MNM, Rep A, Kadzinska I, et al. Haemodynamic changes in the second half of pregnancy: A longitudinal, noninvasive study with thoracic electrical bioimpedance. BJOG: An International Journal of Obstetrics and Gynaecology. 2007;114(5):576–81.
66. Callaghan KM, Hennessy A, Malvisi L, Kiely M. Central haemodynamics in normal pregnancy: A prospective longitudinal study. Journal of Hypertension. 2018;36(10):2102–8.
67. Moertl MG, Ulrich D, Pickel KI, et al. Changes in haemodynamic and autonomous nervous system parameters measured non-invasively throughout normal pregnancy. European Journal of Obstetrics and Gynecology and Reproductive Biology. 2009;144(SUPPL 1):S179–S83.

68. Perry H, Stirrup O, Gutierrez J, Vinayagam D, Thilaganathan B, Khalil A. Influence of maternal characteristics and gestational age on hemodynamic indices: NICOM device-specific reference ranges. Ultrasound in Obstetrics and Gynecology. 2019;54(5):670–5.
69. van Oppen AC, van der Tweel I, Alsbach GP, Heethaar RM, Bruinse HW. A longitudinal study of maternal hemodynamics during normal pregnancy. Obstet Gynecol. 1996;88(1):40–6.
70. Varga I, Rigó J, Somos P, Joó JG, Nagy B. Analysis of maternal circulation and renal function in physiologic pregnancies; parallel examinations of the changes in the cardiac output and the glomerular filtration rate. Journal of Maternal-Fetal and Neonatal Medicine. 2000;9(2):97–104.
71. Vered Z, Poler S, Gibson P, Wlody D, Pérez JE. Noninvasive detection of the morphologic and hemodynamic changes during normal pregnancy. Clinical Cardiology. 1991;14(4):327–34.
72. Andreas M, Kuessel L, Kastl SP, et al. Bioimpedance cardiography in pregnancy: A longitudinal cohort study on hemodynamic pattern and outcome. BMC Pregnancy and Childbirth. 2016;16(1).
73. Mashini IS, Albazzaz SJ, Fadel HE, et al. Serial noninvasive evaluation of cardiovascular hemodynamics during pregnancy. American Journal of Obstetrics and Gynecology. 1987;156(5):1208–13.
74. Mesa A, Jessurun C, Hernandez A, et al. Left ventricular diastolic function in normal human pregnancy. Circulation. 1999;99(4):511–7.
75. Savu O, Jurcut R, Giuşcă S, et al. Morphological and functional adaptation of the maternal heart during pregnancy. Circulation: Cardiovascular Imaging. 2012;5(3):289–97.
76. Denolle T, Daniel JC, Calvez C, Ottavioli JN, Esnault V, Herpin D. Home blood pressure during normal pregnancy. Am J Hypertens. 2005;18(9 Pt 1):1178–80.
77. Grindheim G, Estensen ME, Langesaeter E, Rosseland LA, Toska K. Changes in blood pressure during healthy pregnancy: A longitudinal cohort study. Journal of Hypertension. 2012;30(2):342–50.
78. Tanyeri Uzel S, Kültürsay B, Karaçam M, Acar RD, Keskin B, Karagöz A. Strain-Based Echocardiographic Evaluation of Myocardial Adaptation in Normal Pregnancy: Insights into Physiological Remodeling. Turk Kardiyol Dern Ars. 2026;54(2):152–64.
79. Smith SA, Morris JM, Gallery EDM. Methods of assessment of the arterial pulse wave in normal human pregnancy. American Journal of Obstetrics and Gynecology. 2004;190(2):472–6.
80. Gomez YH, Hudda Z, Mahdi N, et al. Pulse pressure amplification and arterial stiffness in low-risk, uncomplicated pregnancies. Angiology. 2016;67(4):375–83.
81. Hermida RC, Ayala DE, Iglesias M. Predictable blood pressure variability in healthy and complicated pregnancies. Hypertension. 2001;38(3 Pt 2):736–41.
82. Gilson GJ, Samaan S, Crawford MH, Qualls CR, Curet LB. Changes in hemodynamics, ventricular remodeling, and ventricular contractility during normal pregnancy: A longitudinal study. Obstetrics and Gynecology. 1997;89(6):957–62.
83. Morris R, Sunesara I, Rush L, et al. Maternal hemodynamics by thoracic impedance cardiography for normal pregnancy and the postpartum period. Obstetrics and Gynecology. 2014;123(2):318–24.
84. Nisell H, Carlström K, Ek I, et al. The effect of pregnancy on maternal central circulation and atrial natriuretic peptide concentrations during acute plasma volume expansion. Hypertension in Pregnancy. 1993;12(3):525–32.

85. Fairlie FM, Walker JJ. Does the brachial artery doppler flow velocity waveform reflect changes in downstream impedance? American Journal of Obstetrics and Gynecology. 1991;165(6 PART 1):1741–4.
86. Robb AO, Mills NL, Din JN, et al. Influence of the menstrual cycle, pregnancy, and preeclampsia on arterial stiffness. Hypertension. 2009;53(6):952–8.
87. Melchiorre K, Sutherland GR, Liberati M, Thilaganathan B. Maternal cardiovascular impairment in pregnancies complicated by severe fetal growth restriction. Hypertension. 2012;60(2):437–43.
88. Melchiorre K, Sharma R, Khalil A, Thilaganathan B. Maternal Cardiovascular Function in Normal Pregnancy: Evidence of Maladaptation to Chronic Volume Overload. Hypertension. 2016;67(4):754–62.
89. Poppas A, Shroff SG, Korcarz CE, et al. Serial assessment of the cardiovascular system in normal pregnancy: Role of arterial compliance and pulsatile arterial load. Circulation. 1997;95(10):2407–15.
90. Sanfrutos L, Engels-Calvo V, Zapardiel I, et al. Hemodynamic changes during pregnancy and postpartum: A prospective study using thoracic electrical bioimpedance. Journal of Maternal-Fetal and Neonatal Medicine. 2011;24(11):1333–40.
91. Sowers JR, Zemel MB, Walsh MF, et al. Effects of normal pregnancy on cellular cation metabolism and peripheral vascular resistance. Am J Hypertens. 1990;3(1):16–22.
92. Valensise H, Novelli GP, Vasapollo B, et al. Maternal cardiac systolic and diastolic function: Relationship with uteroplacental resistances. A Doppler and echocardiographic longitudinal study. Ultrasound in Obstetrics and Gynecology. 2000;15(6):487–97.
93. Yarlagadda RD, Johnson J, Vårtun Å, Flo K, Acharya G. Maternal plasma pro-atrial and C-type natriuretic peptide levels and their associations with cardiovascular and renal function in the second half of normal pregnancy: a longitudinal study. BMC Pregnancy and Childbirth. 2021;21(1).
94. Fujime M, Tomimatsu T, Okaue Y, et al. Central aortic blood pressure and augmentation index during normal pregnancy. Hypertension Research. 2012;35(6):633–8.
95. Macedo ML, Luminoso D, Savvidou MD, McEniery CM, Nicolaides KH. Maternal wave reflections and arterial stiffness in normal pregnancy as assessed by applanation tonometry. Hypertension. 2008;51(4):1047–51.
96. Hart MV, Morton MJ, Hosenpud JD, Metcalfe J. Aortic function during normal human pregnancy. American Journal of Obstetrics and Gynecology. 1986;154(4):887–91.
97. Sala C, Campise M, Ambroso G, Motta T, Zanchetti A, Morganti A. Atrial natriuretic peptide and hemodynamic changes during normal human pregnancy. Hypertension. 1995;25(4 I):631–6.
98. Meah VL, Backx K, Cockcroft JR, Shave RE, Stöhr EJ. Left ventricular mechanics in late second trimester of healthy pregnancy. Ultrasound Obstet Gynecol. 2019;54(3):350–8.
99. Pandey AK, Das A, Srinivas C, et al. Maternal myocardial performance in various stages of pregnancy and post-partum. Research Journal of Cardiology. 2010;3(1):9–16.
100. Blake MJ, Martin A, Manktelow BN, et al. Changes in baroreceptor sensitivity for heart rate during normotensive pregnancy and the puerperium. Clinical Science. 2000;98(3):259–68.
101. Zentner D, Du Plessis M, Brennecke S, Wong J, Grigg L, Harrap S. Deterioration in cardiac systolic and diastolic function late in normal human pregnancy. Clinical Science. 2009;116(7):599–606.
102. Moran AM, Colan SD, Mauer MB, Geva T. Adaptive mechanisms of left ventricular diastolic function to the physiologic load of pregnancy. Clinical Cardiology. 2002;25(3):124–31.

103. Kuhn JC, Sørum Falk RS, Langesaeter E. Haemodynamic changes during labour: continuous minimally invasive monitoring in 20 healthy parturients. International Journal of Obstetric Anesthesia. 2017;31:74–83.
104. Capeless EL, Clapp JF. When do cardiovascular parameters return to their preconception values? American Journal of Obstetrics and Gynecology. 1991;165(4 PART 1):883–6.
105. Magnussen EB, Vatten LJ, Lund-Nilsen TI, Salvesen KA, Davey Smith G, Romundstad PR. Prepregnancy cardiovascular risk factors as predictors of pre-eclampsia: population based cohort study. BMJ. 2007;335(7627):978.
106. Romundstad PR, Magnussen EB, Smith GD, Vatten LJ. Hypertension in pregnancy and later cardiovascular risk: common antecedents? Circulation. 2010;122(6):579–84.
107. Hale SA, Schonberg A, Badger GJ, Bernstein IM. Relationship between prepregnancy and early pregnancy uterine blood flow and resistance index. Reprod Sci. 2009;16(11):1091–6.
108. Siegmund AS, Kampman MAM, Oudijk MA, et al. Maternal right ventricular function, uteroplacental circulation in first trimester and pregnancy outcome in women with congenital heart disease. Ultrasound in Obstetrics and Gynecology. 2019;54(3):359–66.
109. Loftness BC, Bernstein I, McBride CA, Cheney N, McGinnis EW, McGinnis RS. Preterm Preeclampsia Risk Modelling: Examining Hemodynamic, Biochemical, and Biophysical Markers Prior to Pregnancy. Annu Int Conf IEEE Eng Med Biol Soc. 2023;2023:1–4.
110. Mukhtarova N, Hetzel SJ, Johnson HM, Hoppe KK. Longitudinal blood pressure patterns of women with hypertensive disorders of pregnancy: preconception through postpartum. J Matern Fetal Neonatal Med. 2022;35(25):9023–30.
111. Rigó J, Jr., Boze T, Derzsy Z, et al. Family history of early-onset cardiovascular disorders is associated with a higher risk of severe preeclampsia. Eur J Obstet Gynecol Reprod Biol. 2006;128(1-2):148–51.
112. Ormesher L, Vause S, Higson S, et al. Prevalence of pre-eclampsia and adverse pregnancy outcomes in women with pre-existing cardiomyopathy: a multi-centre retrospective cohort study. Sci Rep. 2023;13(1):153.
113. Bernstein IM, Badger GJ, McBride CA. Prepregnancy physiology and subsequent preterm preeclampsia. Am J Obstet Gynecol. 2025;232(3):314.e1–.e12.
114. Harville EW, Viikari JS, Raitakari OT. Preconception cardiovascular risk factors and pregnancy outcome. Epidemiology. 2011;22(5):724–30.
115. Mahendru AA, Everett TR, McEniery CM, Wilkinson IB, Lees CC. Cardiovascular function in women with recurrent miscarriage, pre-eclampsia and/or intrauterine growth restriction. J Matern Fetal Neonatal Med. 2013;26(4):351–6.
116. Xiong W, Han L, Tang X, et al. Preconception Blood Pressure and Adverse Pregnancy Outcomes: A Population-Based Cohort Study. Hypertension. 2024;81(4):e31–e40.
117. Aardenburg R, Spaanderman ME, van Eijndhoven HW, de Leeuw PW, Peeters LL. A low plasma volume in formerly preeclamptic women predisposes to the recurrence of hypertensive complications in the next pregnancy. J Soc Gynecol Investig. 2006;13(8):598–603.
118. Emonts P, Seaksan S, Seidel L, et al. Prediction of maternal predisposition to preeclampsia. Hypertens Pregnancy. 2008;27(3):237–45.
119. Chen Y, Huang M, Shi D, et al. Correlation between fetal-placental doppler indices and maternal cardiac function in pregnant women with late-Onset preeclampsia or fetal growth restriction. BMC Pregnancy and Childbirth. 2025;25(1).

120. Di Martino DD, Stampalija T, Zullino S, et al. Maternal hemodynamic profile during pregnancy and in the post-partum in hypertensive disorders of pregnancy and fetal growth restriction. American Journal of Obstetrics and Gynecology MFM. 2023;5(3).
121. Di Pasquo E, Ghi T, Dall'Asta A, et al. Maternal cardiac parameters can help in differentiating the clinical profile of preeclampsia and in predicting progression from mild to severe forms. Am J Obstet Gynecol. 2019;221(6):633.e1–.e9.
122. Di Martino DD, Ferrazzi E, Garbin M, et al. Multivariable evaluation of maternal hemodynamic profile in pregnancy complicated by fetal growth restriction: prospective study. Ultrasound Obstet Gynecol. 2019;54(6):732–9.
123. Gutiérrez Henares J, Gutierrez Henares R, Perry H, Khalil A, Thilaganathan B. Maternal cardiovascular potential and kinetic energy indices in pre-eclamptic and small-for-gestational-age pregnancies. Ultrasound in Obstetrics and Gynecology. 2022;59(5):613–8.
124. Jia Rz, Liu Xm, Wang X, Wu Hq. Relationship between cardiovascular function and fetal growth restriction in women with pre-eclampsia. International Journal of Gynecology and Obstetrics. 2010;110(1):61–3.
125. Lihme F, Basit S, Persson LG, et al. Third-Trimester Cardiovascular Function and Risk of Hypertensive Disorders of Pregnancy. J Am Heart Assoc. 2024;13(20):e032673.
126. Khaw A, Kametas NA, Turan OM, Bamfo JEAK, Nicolaides KH. Maternal cardiac function and uterine artery Doppler at 11-14 weeks in the prediction of pre-eclampsia in nulliparous women. BJOG: An International Journal of Obstetrics and Gynaecology. 2008;115(3):369–76.
127. Rang S, van Montfrans GA, Wolf H. Serial hemodynamic measurement in normal pregnancy, preeclampsia, and intrauterine growth restriction. Am J Obstet Gynecol. 2008;198(5):519.e1–9.
128. Sampson R, Davis S, Wong R, Baranco N, Silverman RK. Pulse Pressure as a Hemodynamic Parameter in Preeclampsia with Severe Features Accompanied by Fetal Growth Restriction. J Clin Med. 2024;13(15).
129. Tay J, Masini G, McEniery CM, et al. Uterine and fetal placental Doppler indices are associated with maternal cardiovascular function. Am J Obstet Gynecol. 2019;220(1):96.e1–.e8.
130. Giannubilo SR, Pasculli A, Tidu E, Biagini A, Boscarato V, Ciavattini A. Relationship between maternal hemodynamics and plasma natriuretic peptide concentrations during pregnancy complicated by preeclampsia and fetal growth restriction. Journal of Perinatology. 2017;37(5):484–7.
131. Maseliene T, Zukiene G, Laurinaviciene A, Breskuviene D, Ramasauskaite D, Dzenkeviciute V. Alterations in maternal cardiovascular parameters and their impact on uterine and fetal circulation in hypertensive pregnancies and fetal growth restriction. Int J Cardiol Cardiovasc Risk Prev. 2024;22:200316.
132. Masini G, Tay J, McEniery CM, et al. Maternal Cardiovascular Dysfunction is Associated with Hypoxic Cerebral and Umbilical Doppler Changes. J Clin Med. 2020;9(9).
133. Lafuente-Ganuza P, Carretero F, Lequerica-FernÃindez P, et al. NT-proBNP levels in preeclampsia, intrauterine growth restriction as well as in the prediction on an imminent delivery. Clinical Chemistry and Laboratory Medicine. 2021;59(6):1077–85.
134. di Pasquo E, Giannubilo SR, Valentini B, et al. The "Preeclampsia and Hypertension Target Treatment" study: a multicenter prospective study to evaluate the effectiveness of the antihypertensive therapy based on maternal hemodynamic findings. Am J Obstet Gynecol MFM. 2024;6(5):101368.

135. Ogamba-Alphonso I, Miller E, Brown-Thomas TM, et al. Antihypertensive Treatment in the Postpartum Care of Preeclampsia: A Hemodynamic-Based Approach. Am J Perinatol. 2025.
136. Stott D, Bolten M, Paraschiv D, Papastefanou I, Chambers JB, Kametas NA. Longitudinal hemodynamics in acute phase of treatment with labetalol in hypertensive pregnant women to predict need for vasodilatory therapy. Ultrasound Obstet Gynecol. 2017;49(1):85–94.
137. Stott D, Papastefanou I, Paraschiv D, Clark K, Kametas NA. Serial hemodynamic monitoring to guide treatment of maternal hypertension leads to reduction in severe hypertension. Ultrasound Obstet Gynecol. 2017;49(1):95–103.
138. Carr DB, Tran LT, Brateng DA, et al. Hemodynamically-directed atenolol therapy is associated with a blunted rise in maternal sFLT-1 levels during pregnancy. Hypertens Pregnancy. 2009;28(1):42–55.
139. Chaffin DG, Webb DG. Outcomes of pregnancies at risk for hypertensive complications managed using impedance cardiography. Am J Perinatol. 2009;26(10):717–21.
140. Chen S, Wang Y, Wang Z, et al. Pre conception dyslipidemia and risk for preeclampsia in women undergoing IVF ET. Sci Rep. 2025;15(1):18454.
141. Stott D, Papastefanou I, Paraschiv D, Clark K, Kametas NA. Longitudinal maternal hemodynamics in pregnancies affected by fetal growth restriction. Ultrasound Obstet Gynecol. 2017;49(6):761–8.
142. Scardo JA, Vermillion ST, Newman RB, Chauhan SP, Hogg BB. A randomized, double-blind, hemodynamic evaluation of nifedipine and labetalol in preeclamptic hypertensive emergencies. Am J Obstet Gynecol. 1999;181(4):862–6.

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