Cardiovascular Implications in Preeclampsia
An Overview

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Preeclampsia is a pregnancy-specific multi-organ syndrome that affects 2% to 8% of pregnancy.[1] It is a unique condition of placental pathogenesis with acute onset of predominantly cardiovascular manifestations attributable to generalized vascular endothelial activation and vasospasm resulting in hypertension and multi-organ hypoperfusion.[2,3] The major scientific societies provide different criteria for the diagnosis of preeclampsia. Common to all diagnostic criteria is that preeclampsia is a syndrome characterized by new-onset hypertension (≥140 mm Hg systolic blood pressure [SBP] or ≥90 mm Hg diastolic blood pressure [DBP]) arising after 20 weeks of gestation with ≥1 organ system involvement[2–7] and complete resolution within 12 weeks postpartum[2–5] (Table 1). The terms "preterm" or "early-onset" preeclampsia are used to try and delineate the severity of the disease in relation to the need for iatrogenic delivery before 37 weeks (preterm preeclampsia)[8] or the time of the diagnosis at or before 34 weeks of gestational age (early-onset preeclampsia),[6,7] respectively. Although not distinct entities, it is increasingly becoming apparent that early-onset or preterm preeclampsia is especially associated with poor placentation,[9] fetal growth restriction, and worse long-term maternal cardiovascular outcomes than late-onset preeclampsia, whose pathogenesis is more related to predisposing cardiovascular or metabolic risks for endothelial dysfunction.[10] Furthermore, because the pathogenesis of preeclampsia has not been fully elucidated, the search for predictive markers and a preventative strategy remains an unfulfilled goal. Hence, clinical management is mainly symptomatic and directed to prevent maternal morbidity and mortality.[2–4] Preeclampsia is 1 of the leading causes of maternal morbidity and mortality worldwide, and delay in the treatment of severe hypertension and diagnosis of preeclampsia complications contribute significantly to maternal mortality.[11] Mortality rates have been shown to be reduced in countries such as the United States and the United Kingdom after the introduction of detailed national guidelines for the management and with increased awareness of the importance of reduction of severely raised blood pressure (BP).[12,13]

There is scant and conflicting information about the impact on the heart.[2] Previous studies on the cardiovascular changes in preeclampsia provided contradictory results mainly attributable to limitations in technology, patient selection, and data interpretation.[14] More recent studies have outlined better the cardiovascular profile in preeclampsia from the preclinical phase of the disease to the postpartum period and the cardiovascular and cardiopulmonary complications associated with this condition.[14] Multiple exceptional and exclusive changes in cardiac structure and function have been described in preeclampsia, suggesting that these women display abnormal cardiac adaptation to pregnancy.[14] These cardiac changes may be fundamental in explaining these women's increased predisposition toward preeclampsia and long-term postpartum cardiovascular disease (CVD). Indeed, the development of preeclampsia is now considered a risk factor for long-term CVD.[15] This review focuses on this recent evidence and its implication for the cardiovascular management of preeclampsia.

Preeclampsia and the Cardiovascular System

The Cardiovascular Changes in the Preclinical Phase of Preeclampsia

In the preclinical phase of preeclampsia, vascular reactivity, hemodynamic indices, and left ventricular (LV) properties are subtly impaired, especially in those women destined to develop preterm preeclampsia (Level 2 evidence).[16–26] At midgestation, there is a shift toward a low cardiac index associated with a high total vascular resistance index, increased mean arterial pressure, contracted intravascular volume, and reduced venous reserve capacity (Level 2).[16–26] In contrast, the hemodynamic profile of women destined to develop late-onset preeclampsia is not well delineated, with some authors reporting a normal cardiac index and increased total vascular resistance index at midgestation,[22] and others reporting a high cardiac output/low TVR status.[17,18,23] However, the latter authors did not normalize hemodynamic measures for body surface area or body mass index, notwithstanding the significant differences in the anthropometric parameters in the analyzed study groups. Women destined to develop preterm or term preeclampsia also show abnormal LV remodeling patterns, usually LV concentric remodeling and concentric hypertrophy.[22,23] Women destined to develop preterm preeclampsia also show evidence of LV mild diastolic dysfunction (30%) and segmental impaired myocardial relaxation (70%).[22] This diastolic impairment is associated with increased afterload and adverse LV remodeling as demonstrated by significantly higher mean arterial pressure, total vascular resistance index, relative wall thickness, and LV concentric

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Table 1. Classification and Diagnosis of Hypertensive Disorders in Pregnancy for the Major Scientific Societies

Classification	ACOG[3] (2013)	SOMANZ[5] (2008)	SOGC[6] (2008)	ASH[7] (2008)
Gestational hypertension	(1) Transient new-onset hypertension of pregnancy without proteinuria that occur after 20 wk and returns to normal by 12 wk postpartum (a retrospective diagnosis) or (2) chronic hypertension if hypertension persists. Note that the diagnosis of gestational hypertension is used during pregnancy only until a more specific diagnosis can be assigned postpartum.	BP ≥140/90 mm Hg after 20 wk of gestation without significant proteinuria, returning to normal within 12 wk postpartum	BP ≥140/90 mm Hg after 20 wk of gestation with or without comorbidities, with or without superimposed preeclampsia	BP ≥140/90 mm Hg after 20 wk of gestation; transient hypertension; BP returning to normal within 6 wk postpartum; late postpartum hypertension, with increase in BP developing weeks to 6 mo postpartum and normalized by 1 y postpartum
Preeclampsia	Increased BP (≥140 mm Hg SBP or ≥90 mm Hg DBP) on 2 occasions at least 4 h apart after 20 wk in a woman with previously normal BP plus ≥1 of the following new-onset features: proteinuria (urinary excretion of ≥0.3 g of protein in a 24-h specimen or this amount extrapolated by a timed collection or Pr/Cr ratio ≥0.3 mg/dL or dipstick reading of 1+); thrombocytopenia (platelet count <100 000 cells/mm^3); renal insufficiency (serum creatinine >1.1 mg/dL or a doubling of the serum creatinine concentrations in the absence of other renal disease); impaired liver function (elevated blood concentrations of liver transaminases to twice the normal concentration); pulmonary edema; cerebral or visual symptoms	Gestational hypertension plus ≥1 of the following: dipstick proteinuria confirmed by either random Pr/Cr ratio ≥30 mg/mmol or 0.3 g/24 h; serum or plasma creatinine >90 μmol/L; oliguria; thrombocytopenia; haemolysis; DIC; raised serum transaminases; severe epigastric or right upper quadrant pain; eclampsia; hypereflexia with sustained clonus; severe headache; persistent visual disturbances; stroke; pulmonary edema; fetal growth restriction; placental abruption	Preexisting hypertension and resistant hypertension, new proteinuria, or adverse condition*. Gestational hypertension and proteinuria (random Pr/Cr ratio ≥30 mg/mmol or 0.3 g/24 h) or adverse conditions*	Gestational hypertension or chronic hypertension and proteinuria (dipstick ≥1+, random Pr/Cr ratio ≥30 mg/mmol or 0.3 g/24 h)
Preeclampsia superimposed to chronic hypertension	The diagnosis of superimposed preeclampsia is highly likely with the following findings. (1) In women with hypertension and no proteinuria early in pregnancy (<20 wk of gestation), new-onset proteinuria. (2) In women with hypertension and proteinuria before 20 wk of gestation, any of the following are seen: (a) sudden increase in proteinuria; (b) sudden increase in BP in a woman whose hypertension has been previously well controlled; (c) thrombocytopenia (platelet count <100 000 cells/mm^3); or (d) increase in ALT or AST >70 U/L			

ACOG indicates American College of Obstetricians and Gynecologists; ALT, alanine transaminase; ASH, American Society of Hypertension; AST, aspartate transaminase; BP, blood pressure; DBP, diastolic blood pressure; DIC, disseminated intravascular coagulation; Pr/Cr, protein-to-creatinine ratio; SBP, systolic blood pressure; SOGC, Society of Obstetricians and Gynecologists of Canada; and SOMANZ, Society of Obstetric Medicine of Australia and New Zealand.

*Adverse condition: maternal symptoms or abnormal liver, kidney, or coagulation system laboratory tests or signs of fetal compromise.

hypertrophy.[22–26] Longitudinal systolic function is also reduced in the preclinical phase of the preterm disease, whereas radial systolic function is preserved.[22] These observations are supported by the finding of raised biomarkers of cardiovascular dysfunction, endothelial injury, and generalized oxidative stress in women presenting with preeclampsia.[27–29] The pattern of LV

dysfunction and remodeling seen in preeclampsia is similar to that seen in early essential hypertension in nonpregnant women and is indicative of afterload-induced impairment of subendocardial myocardial fibers.[22,30,31]

Preeclampsia is fundamentally a disease of poor placentation, which can be indirectly assessed by maternal uterine artery Doppler impedance indices in early pregnancy.[32] Several studies have assessed the relationship between the latter indices, cardiovascular profile, and the subsequent development of preeclampsia.[22–25] They uniformly show that women with both placental insufficiency and impaired LV function were more likely to develop preterm/early-onset preeclampsia, whereas those who also have placental insufficiency but normal or even enhanced LV function will be more likely to have an uncomplicated pregnancy.[22–25] Therefore, it seems that the women with abnormal uterine artery Doppler indices have different cardiovascular profiles at midgestation depending on whether they later develop preterm preeclampsia or not. From these studies, it can be speculated that maternal cardiovascular response to placental dysfunction may also play an important role in the pathogenesis of preterm preeclampsia. This supports the concept that preeclampsia is a complex disorder related not only to placental insufficiency but also to the ability of the maternal cardiovascular system to adapt to placental dysfunction.

The Cardiovascular Changes at Presentation With Preeclampsia

Women affected by preeclampsia present with different hemodynamic patterns depending on the severity of the disease, use of medication, presence of comorbidities, phase of labor, and fluid management.[14] The prevalent hemodynamic pattern is the 1 of high total vascular resistance index, partly mediated by a substantial increase in sympathetic vasoconstrictor activity,[33] and low CI, reflecting a significant burden on the heart.[34–41] Specifically, approximately half of the women affected by preterm preeclampsia present with mild-to-moderate isolated LV chamber diastolic dysfunction with preserved ejection fraction and 20% with biventricular chamber longitudinal systolic dysfunction and severe LV hypertrophy[34–40] (Figure 1; Table 2). Of the women with LV global diastolic dysfunction, half were grade I, and a quarter each had grades Ia and II.[39]

The LV remodeling/hypertrophy in preeclampsia is characteristically asymmetrical, predominantly involving the basal anteroseptum[38–40] (Figure 2). This is consistent with remodeling patterns seen in early hypertension without evidence of age or ethnic specificity in the women evaluated so far.[30] Although several other studies have also demonstrated LV dysfunction,[41–48] increased aortic stiffness,[49–51] and reduced venous capacity in preeclampsia,[52] it remains difficult to truly understand by noninvasive methods whether decreased LV performance with preeclampsia affected myocardial contractility. Indeed, each echocardiographic index is only a surrogate of the true myocardial state, and it is invariably affected by loading conditions, heart rate, and cardiac geometry in a lesser or greater extent. A number of studies attempted to overcome these limitations using relatively load-independent, heart rate–corrected wall stress or strain and strain rate indices. They found that these echocardiographic indices were not significantly different between preeclampsia patients and controls and concluded that intrinsic myocardial contractility is preserved in mainly mild or term preeclampsia when load is eliminated as a confounding factor.[38,45,53] In contrast, myocardial contractility has been showed to be significantly impaired in the more severe or preterm preeclampsia cases.[39–41] Specifically, color tissue Doppler and 2-dimensional speckle-tracking derived strain and strain rate imaging have demonstrated widespread decreased segmental myocardial systolic and diastolic deformation indices in preeclampsia (Figure 3),[39–41] indirect signs of impaired myocardial contractility and relaxation. Moreover, one fifth of women with preterm preeclampsia who exhibit biventricular chamber systolic dysfunction and severe hypertrophy also present with high-amplitude segmental postsystolic shortening at the level of the basal septum (Figure 3).[39] Although these tissue Doppler echocardiographic findings are potential markers of early subendocardial damage,[31] the plasma pro-B-type natriuretic peptide and troponin levels in this specific cohort have not been evaluated. However, plasma brain and atrial natriuretic peptides and cystatin C concentrations have been assessed and found to be increased in preeclamptic women versus pregnant controls in other studies, which also found echocardiographic features of asymptomatic LV dysfunction.[42–44] Three recent studies also found increased left atrial dimensions in preterm preeclampsia, with adverse left atrial remodeling observed only in patients with LV global diastolic dysfunction, presumably as an expression of increased left-sided chamber filling pressures.[39,40,42]

These findings, also demonstrated in essential hypertension, indicate at least that the pregnant heart in preeclampsia works at the edge of its reserve and that any additional stress could result in a significant deterioration of function and lead to overt cardiovascular and cardiopulmonary complications.

The Cardiovascular System in Postpartum Recovery From Preeclampsia

Changes in both arterial and venous systems seen in acute preeclampsia persist for the first few years postpartum and are associated with abnormal autonomic response to volume expansion and exercise.[54–59] Asymptomatic LV systolic and diastolic dysfunction, LV hypertrophy, and a prehypertension state also persists at 1 year postpartum, and it is more prevalent in preterm preeclampsia (60%) compared with term preeclampsia (15%) or matched controls (8%; Table 2).[40] More than half of preterm women with preeclampsia have asymptomatic LV cardiac dysfunction or hypertrophy (stage B heart failure) postpartum, and 40% develop essential hypertension within 1 to 2 years after pregnancy.[40] The relative risk of developing hypertension within 2 years of birth even after adjusting for confounding risk factors is increased ?15-fold if LV abnormalities are persistent after preeclampsia.[40,58] The higher prevalence of stage B heart failure in preterm than term preeclampsia or controls is consistent with the long-term outcome studies demonstrating that women with preterm preeclampsia have a higher risk of subsequent congestive heart failure and ischemic cardiac diseases compared with women with term preeclampsia or normal pregnancy.[60,61] Significantly impaired LV function and central hemodynamic properties also persist many years after delivery (Level 2).[62] There is an increasing understanding that CVDs are generally slowly progressive

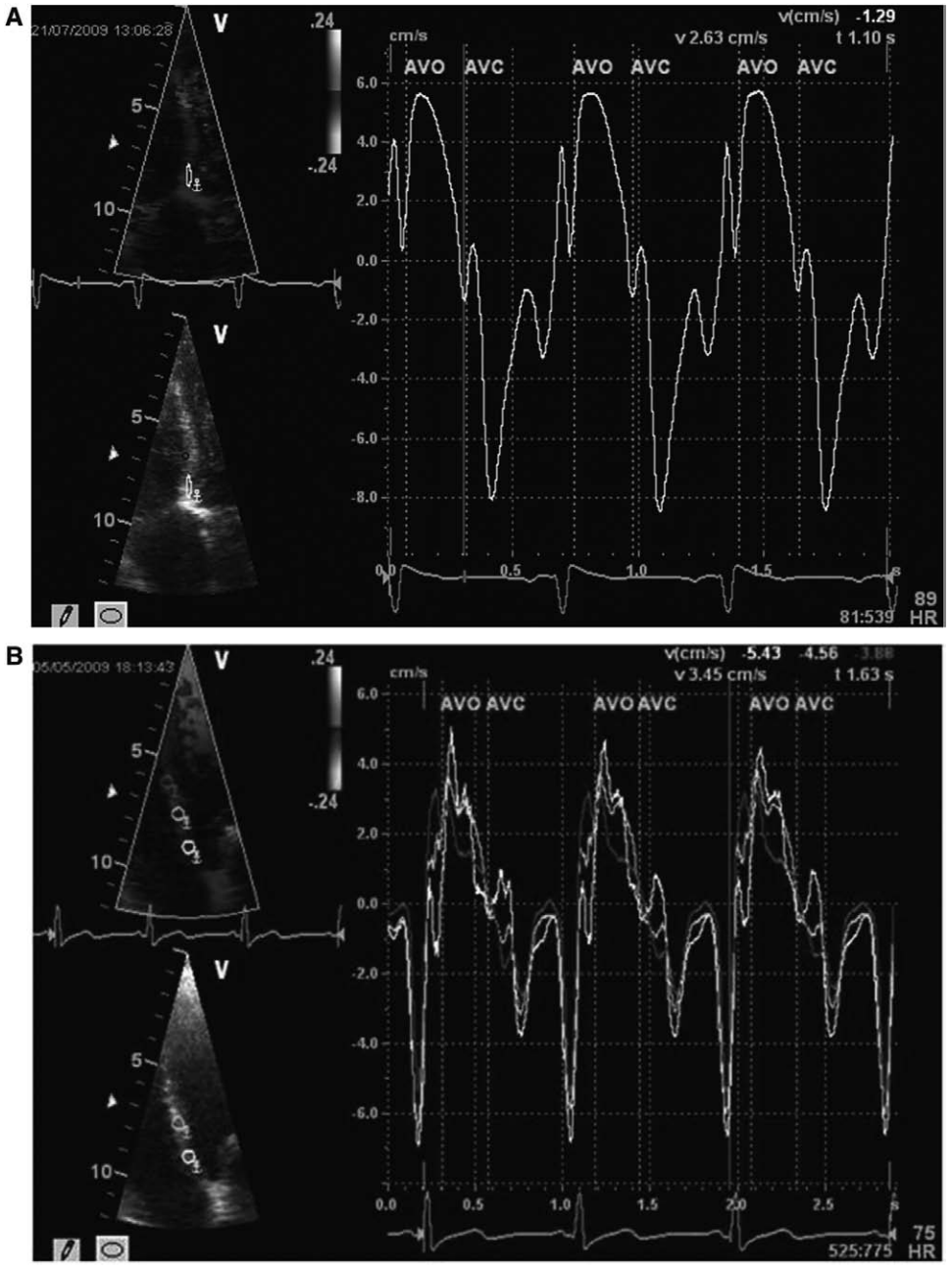

Figure 1. Color tissue Doppler (CTD) velocity curves at the level of the basal septum in a pregnant control (**A**) and at the level of multiple sites in an Asian patient with preeclampsia aged 35 years at 30 weeks of gestation (**B**). The case and control are matched for ethnicity, maternal age, and gestational age at assessment. It is possible to appreciate the early (Em) to late (Am) peak diastolic CTD velocity ratio inversions (Em/Am<1) at the level of all investigated sites in the woman with preeclampsia (**B**) vs a normal Em/Am ratio >1 in the control (**A**). This abnormal myocardial velocity pattern is suggestive of diastolic dysfunction in the woman with preeclampsia. AVC indicates aortic valve closing; and AVO, aortic valve opening.

disorders that proceed through asymptomatic to symptomatic stages.[63–65] One of the principal manifestations of this progression is the changes in the geometry and function of the left ventricle,[63–65] which have been documented widely in acute preeclampsia and several years postpartum. The diagnosis of preeclampsia in young women poses an opportunity for early identification and lifestyle and therapeutic interventions during the asymptomatic phase of cardiac impairment. This may improve the prognosis more effectively than when commenced at a more advanced or symptomatic stage.

Preeclampsia and Cardiovascular Complications in Pregnancy

Prevalence of Cardiovascular Complications in Preeclampsia

There is a high prevalence of cardiovascular and cardiopulmonary complications in women affected by preeclampsia.[66] Cardiopulmonary complications occur in as high as 6% of severe preeclampsia, increasing to 12% when preeclampsia evolves into HELLP (for hemolysis, elevated liver enzymes,

Table 2. Longitudinal Structural and Functional Cardiovascular Changes in Preterm Preeclampsia, Term Preeclampsia, and Controls From Pregnancy to 1-Year Postpartum

Abnormal Cardiac Finding	Diagnosis	Preterm Preeclampsia (n=27)	Preterm Pregnant Controls (n=54)	Term Preeclampsia (n=50)	Term Pregnant Controls (n=50)	1-Year Postpartum Preterm Preeclampsia (n=27)	1-Year Postpartum Term Preeclampsia (n=37)	1-Year Postpartum Controls (n=78)
Left heart cardiac findings								
LV alerted geometric pattern	RWT >0.42 or LVMI >95 g/m^2	81%*	13%	72%*	24%	41%†	19%	6%
LV severe hypertrophy	RWT >0.53 or LVMI >122 g/m^2	18%*	0	2%	0	11%†	0	0
LV segmental myocardial impaired relaxation	Early to late strain rate ratio <1	85%*	18%	64%*	40%	74%†‡	46%†	13%
LV segmental myocardial impaired contractility	Peak systolic strain rate 2 SDs below the expected mean for age	59%*	18%	42%	24%	52%†	16%	4%
Global diastolic dysfunction	Algorithms (combining Doppler indices using age-adjusted cutoff)	52%*	0	40%*	14%	52%†‡	16%	8%
LV radial systolic dysfunction	EF by biplane Simpson method <55%	26%*	0	4%	2%	19%†	3%	1%
Right heart cardiac findings								
RV hypertrophy	RV subcostal wall thickness >0.5 cm	48%*	9%	32%	14%	19%†	5%	1%
Diastolic dysfunction	E^1/A^1 <0.5	19%*	2%	16%*	0%	19%†‡	0%	0%
RV longitudinal systolic dysfunction	TAPSE <1.6 cm and Sm<6 cm/s or S^1 <10 cm/s	30%*	9%	4%	12%	19%†	5%	1%

Data from Melchiorre et al.[40] Values are given as percentage of women with abnormal findings. Cases and controls are matched for maternal age, ethnicity, and gestational age at assessment. A^1 indicates pulsed Doppler late diastolic velocity at the level of the right side of the tricuspid annulus; E^1, pulsed Doppler peak early diastolic velocity at the level of the right side of the tricuspid annulus; EF, ejection fraction; LV, left ventricle; LVMI, left ventricular mass normalized for body surface area; RV, right ventricle; RWT, relative wall thickness; SD, standard deviation; Sm, color tissue Doppler peak systolic velocity at the level of the basal segment of the RV free wall; S^1, pulsed Doppler peak systolic velocity at the level of the right side of the tricuspid annulus; and TAPSE, tricuspid annular plane systolic excursion.

*P values <0.05 comparing preterm preeclampsia or term preeclampsia vs matched controls.

†P values <0.05 comparing postpartum preterm preeclampsia or postpartum term preeclampsia vs postpartum matched controls.

‡P values <0.05 comparing postpartum preterm preeclampsia vs postpartum term preeclampsia.

and low platelet count) syndrome.[66] Heart failure and secondary maternal mortality/morbidity are strongly associated with preeclampsia, with the presence of comorbidities, such as advanced maternal age, contributing to the strength of this association.[67] A large well-performed population-based study conducted on a cohort of 1 132 064 maternities from 1999 to 2003 using a dataset linking birth certificates and hospital discharge data demonstrated that women with preeclampsia have a significantly higher risk of major adverse cardiovascular events (MACEs), especially myocardial infarction and stroke, during pregnancy and that their risk remains significant for ≥3 years postpartum.[68] The incidence rates of MACEs and all maternal mortality in women with preeclampsia were 16 and 40 per 100,000 patients/year, respectively.[68] Women with preeclampsia, after adjusting for socioeconomic and clinical factors, were found to have a 13-fold higher incidence of myocardial infarction, an 8-fold higher incidence of heart failure, a 14-fold higher incidence of stroke, a 13-fold higher incidence

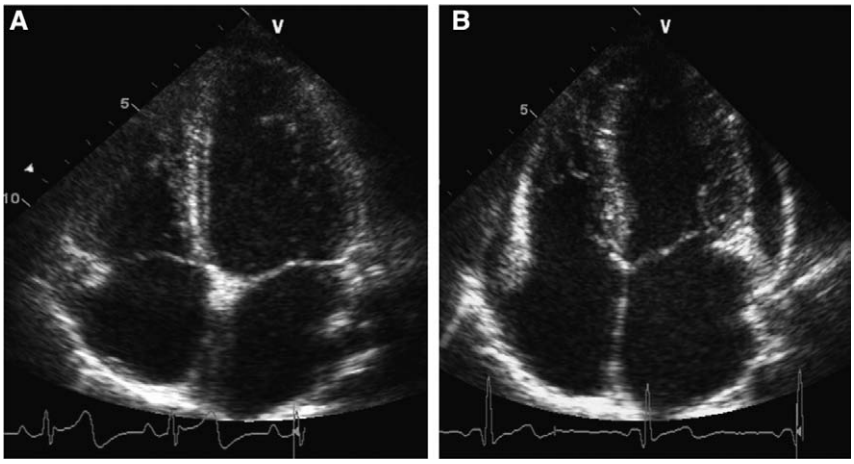

Figure 2. Two-dimensional apical 4-chamber view in a pregnant control (**A**) and a white patient with preeclampsia aged 30 years at 27 weeks of gestation (**B**). The case and control are matched for ethnicity, maternal age, and gestational age at assessment. It is possible to appreciate the left ventricle (LV) concentric remodelling and mild pericardial effusion (yellow arrow) in the patient with preeclampsia (**B**) vs a normal LV geometry in the control (**A**).

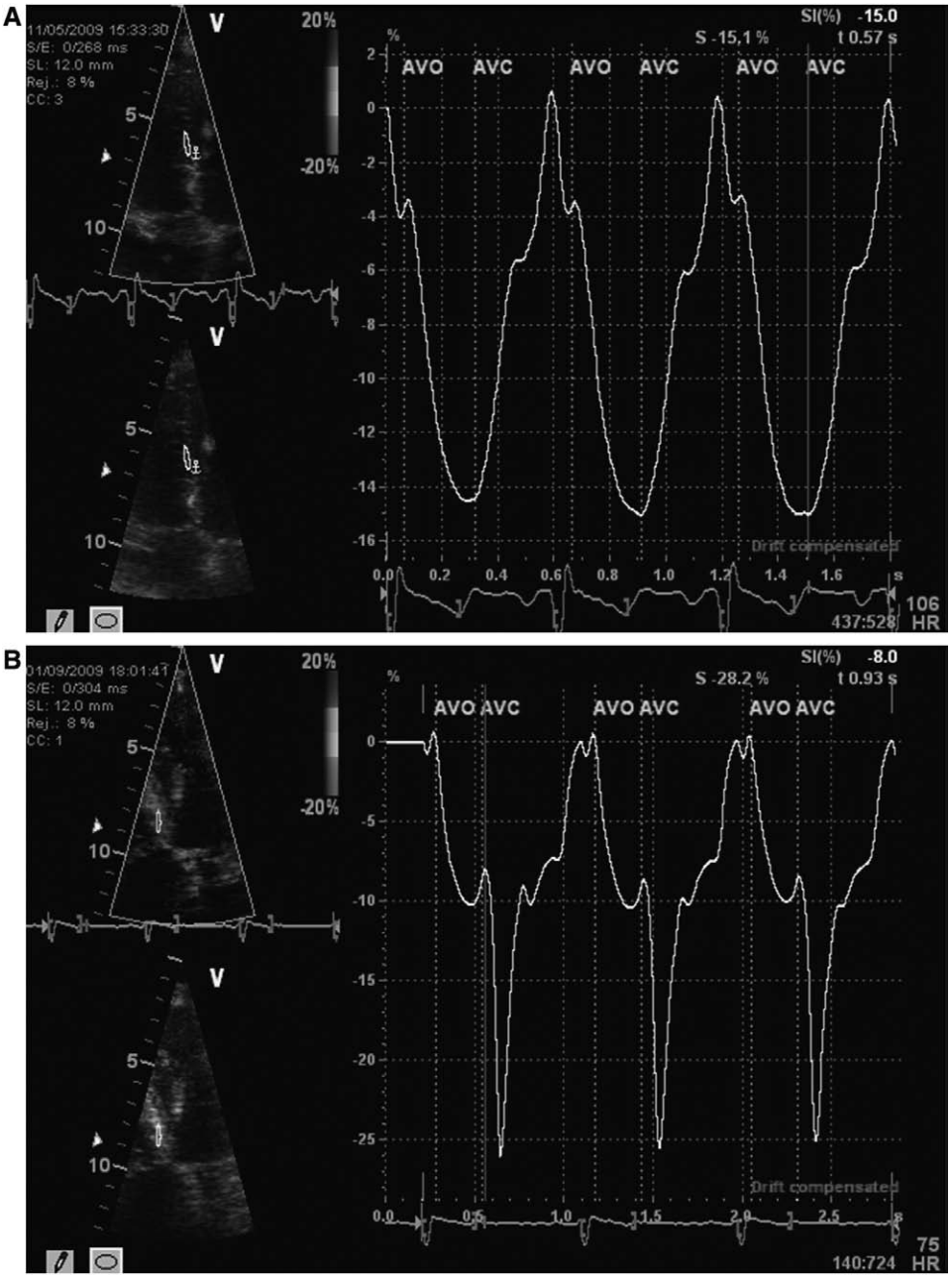

Figure 3. Color tissue Doppler (CTD)-derived strain curves at the level of the mid (**A**) and basal (**B**) septum in a pregnant control and an Afro-Caribbean patient with preeclampsia aged 26 years at 32 weeks of gestation. The case and control are matched for ethnicity, maternal age, and gestational age at assessment. It is possible to appreciate the reduced end systolic strain (10%) and the presence of high-amplitude postsystolic shortening (yellow arrow) in the woman with preeclampsia (**B**) vs a normal end systolic strain (15%) without postsystolic deformation in the control (**A**). This abnormal deformation pattern is suggestive of impaired myocardial contractility in the woman with preeclampsia. AVC indicates aortic valve closing; and AVO, aortic valve opening.

of MACEs, a 7-fold higher incidence of MACEs without stroke, a 2-fold higher incidence of MACE-related deaths, and a 6-fold higher incidence of overall death.[68] Previous autopsy data have also demonstrated that women with preeclampsia have a 10-fold higher prevalence of contraction band necrosis (35%), a reperfusion lesion after a period of no perfusion, than deaths in pregnancy from other causes (3%), suggesting the potential of more significant myocardial damage in preeclampsia than recognized previously.[69]

Preeclampsia and Peripartum Cardiovascular Management

Cardiovascular Management in Uncomplicated Preeclampsia With Severe Hypertension

The first approach in women with uncomplicated preeclampsia is the evaluation of BP profile following the American College of Obstetricians and Gynecologists, European Society of Cardiology, UK National Institute for Clinical Excellence,

Table 3. Schemes of Oral Antihypertensive Medication in Mild-to-Moderate Hypertension in Pregnancy (SBP between 140 and 159 mm Hg or DBP between 90 and 109 mm Hg)

Drug	Starting Oral Dose	Intervals	Maximum Total Dose/Die	Maternal Adverse Effects
Labetalol	100 to 400 mg	2 to 4 times daily	1200 mg/d	Headache
Alfametildopa	250 to 500 mg	2 to 4 times daily	2000 mg/d	Maternal sedation, elevated liver function enzymes, depression
Intermediate-acting nifedipine	10 to 20 mg	2 to 3 times daily	Maximum 120 mg/d	Headache
Long-acting Nifedipine	20 to 60 mg	1 time daily	Maximum 120 mg/d	Headache

In the absence of comorbidities, whether BP targets should be high normotension (85 mm Hg DBP) or nonsevere hypertension (105 mm Hg DBP) is not standardized. Data from the Cochrane Database Systematic Review on Antihypertensive drug therapy for mild-to-moderate hypertension during pregnancy (2007),[71] unless otherwise stated. The illustrated schemes of treatments are recommended by the Society of Obstetricians and Gynecologists of Canada (SOGC guidelines, 2008),[6] American College of Obstetricians and Gynecologists (ACOG guidelines, 2012),[72] and UK National Institute of Clinical Excellence (NICE guidelines, 2011)[4] with minimal differences. In particular, for ACOG 2012, the maximum total dose/die for labetalol is 2000 mg and for alfametildopa is 3000 mg/die.[72] BP indicates blood pressure; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

and the Australian and Canadian guidelines.[2–7,70] A full evaluation of kidney, liver, and coagulation system function through serial multiple laboratory tests are necessary to grade the disease and diagnose preeclampsia complications, which are usually asymptomatic in the early phase.[2–7,70] The course of preeclampsia is unpredictable, and it can evolve rapidly, requiring urgent delivery, or progress slowly over weeks, allowing for conservative management.[2–7] Therefore, most guidelines recommend immediate hospital referral for assessment of mother and fetus as soon as the diagnosis is made, with conservative management in a hospital that can handle emergency delivery and assistance for the preterm infant.[3–7] Delivery of the placenta remains the only cure for preeclampsia, but in women far from term, it has to be balanced versus the risks of severe prematurity of the infant.[2–7]

In daily practice, the antihypertensive therapy in uncomplicated preeclampsia cases is not tailored to the specific hemodynamic pattern and cardiac function of the woman who are only usually assessed in complicated preeclampsia cases or in a research setting. Although there are plenty of randomized controlled trials on the management of mild-to-moderate BP (<160 mm Hg SBP and <110 mm Hg DBP), BP treatment thresholds and goals vary in international guidelines. In favor of treatment is the potential to decrease the transition of mild-moderate to severe hypertension, and against treatment is the risk of impairment of fetal growth as a result of placental hypoperfusion and risks of fetal/neonatal drug-related adverse effects.[71] Some guidelines recommend lowering of nonsevere BP to a systolic level of 140 to 150 mm Hg and a diastolic level of 90 to 100 mm Hg because of the risk of hemorrhagic stroke in the presence of systolic hypertension.[71] However, thresholds also vary depending on the existence of comorbidities and maternal age.[71] Proposed medications differ among countries and include oral labetalol, methyldopa, nifedipine or isradipine, and some β-adrenoceptor blockers (Table 3).[71,72] Atenolol is not recommended because of its association with fetal growth restriction.[2–7] Angiotensin-converting enzyme inhibitors, angiotension receptor blockers, and direct renin inhibitors are strictly contraindicated in pregnancy because of severe fetotoxicity, particularly in the second and third trimesters (Level 3).[2–7,70–72]

There is a consensus that BP should be expeditiously treated when it is severe, defined as sustained (>15 minutes) hypertension (≥160 mm Hg SBP or ≥110 mm Hg DBP) attributable to the short-term complications related to this status, such as intracerebral hemorrhage and infarction, cardiopulmonary events, placental abruption, and stillbirth (Level 2).[2–4,6,7,73] Only the European Society of Cardiology/European School of Haematology (2011)[70] and the Society of Obstetric Medicine of Australia and New Zealand (2008)[5] guidelines define severe hypertension as ≥170 mm Hg SBP or ≥110 mm Hg DBP, which require hospitalization and treatment (Level 1C).[5,70] BP treatment is designed to minimize maternal end-organ damage and is of paramount importance to reducing maternal mortality (Level 3).[2–7,70,71,74] The goal of antihypertensive treatment is to achieve a range of 140 to 150 mm Hg SBP/80 to 100 mm Hg DBP at a rate of 10 to 20 mm Hg every 10 to 20 minutes to prevent prolonged severe systolic hypertension and its consequences on the patient.[2,4] Care should be taken to avoid abrupt falls in BP, which may induce complications as a result of end-organ hypoperfusion, including fetal death from placental hypoperfusion.[2–7,70,71,74–76] Continuous maternal and fetal monitoring should be adopted until the BP is stable.[2–7,70,71,74] The ideal antihypertensive medication should reduce BP in a controlled manner, not lower CI, reverse uteroplacental vascular constriction, or result in adverse maternal/fetal effects.[2]

The first choice of medication differs in the major international society recommendations, mainly because of known safety of use in pregnancy and historical reasons (Table 4). The National High Blood Pressure Education Program guidelines[2] suggest intramuscular or intravenous hydralazine, and the European Society of Cardiology/National Institute for Clinical Excellence recommend intravenous labetalol because of the increased incidence of adverse perinatal effects with hydralazine.[4,70] There is no clear evidence that 1 of these 2 particular antihypertensive drugs is more efficacious than the other, but each agent can be associated with adverse maternal or fetal effects, and the Cochrane review concludes that the choice should depend on the clinician's experience with a specific drug.[71] Parenteral hydralazine may increase the risk of maternal hypotension (<90 mm Hg SBP), and, to protect the fetal circulation, preloading or coadministration using no more than 500 mL of intravenous crystalloid fluid should be considered.[4] There is less justification for fluid loading postpartum for the known increased risk of pulmonary edema.[4]

Table 4. Schemes of Antihypertensive Medications in Acute, Sustained (>15[1]), Severe Hypertension in Pregnancy (SBP ≥160 mm Hg or DBP ≥110 mm Hg)

Drug	Starting Dose	Repeating Doses and Intervals if BP Is Not Controlled	Maximum Total Dose	Comments
Labetalol	20 mg i.v. over 2[1]	40 after 10,[1] 80 mg every 10[1] for 2 additional doses	220 mg	Avoid in asthma, chronic obstructive airways disease, heart failure; avoid in women of Afro-Caribbean origin*; associated with neonatal bradycardia and hypoglycemia
Hydralizine	5 mg i.v. or 10 mg i.m.	5 or 10 mg, depending on response, every 20[1]; once BP control has been achieved, repeat as needed (usually ~3 h)	20 mg i.v. or 30 mg i.m.	Risk of sudden hypotension and maternal tachycardia; may need preloading or simultaneous loading with 500 mL of fluid infusion
Short-acting nifedipine	10 mg p.o.	10 mg p.o. after 30[1]	20 mg	Not approved by the US Food and Drug Administration for management of hypertension; should be avoided in women with coronary artery disease, aortic stenosis, longstanding diabetes mellitus, and women older than 45 y because of the risks of untoward cardiovascular events†
Sodium nitroprusside	0.25 μg · kg^{-1} · min^{-1}	Maximum dose of 5 μg · kg^{-1} · min^{-1}	Fetal cyanide poisoning may occur if used for >4 h	To be used only for the extreme emergencies for the shortest time possible because of the risk of cyanide and thiocyanate toxicity for mother and infant and the risk of maternal increased intracranial pressure (ESC)
Continuous intravenous infusion of labetalol‡	Infusion of 20 mg/h	Titrated according to BP	160 mg/h	Second-line alternative after failure of both intermittent bolus of parental labetalol and hydralizine (ACOG)
Continuous intravenous infusion of nicardipine‡	Infusion of 3 mg/h	Titrated according to BP	10 mg/h	Second-line alternative after failure of both intermittent bolus of parental labetalol and hydralizine (ACOG)
Glyceryl trinitrate§	i.v. infusion of 5 μg/min	Gradually increased every 3 to 5 min	100 μg/min	Drug of choice in preeclampsia associated with pulmonary edema for ESC

Data from the Report of the American National High Blood Pressure Education Program Working Group (NHBPEPWG) on High Blood Pressure in Pregnancy (2000)[2] and American College of Obstetricians and Gynecologists guidelines (ACOG guidelines, 2011 and 2013),[3,73] unless otherwise stated. The illustrated schemes of treatments are recommended also by the Society of Obstetricians and Gynecologists of Canada (SOGC guidelines, 2008),[6] American Society of Hypertension (ASH, 2008),[7] Society of Obstetric Medicine of Australia and New Zealand (SOMANZ 2008),[5] and UK National Institute of Clinical Excellence (NICE guidelines, 2011)[4] with minimal differences. Note that, whereas the NHBPEPWG, NICE, SOGC, ACOG, and ASH consider severe hypertension in pregnancy at SBP ≥160 mm Hg or DBP ≥110 mm Hg, the SOMANZ and the European Society of Cardiology and European Society of Hypertension (ESC/European Society of Hypertension guidelines, 2011) consider severe hypertension in pregnancy as SBP ≥170 mm Hg or DBP ≥110 mm Hg. BP indicates blood pressure; DBP, diastolic blood pressure; i.m., intramuscular; i.v., intravenous; PO, per os; SBP, systolic blood pressure.

*From the guidelines of the NICE on hypertension in pregnancy (2011).[4]

†From Grossman et al. (1996).[76]

‡From the ACOG Committee Opinion on emergent therapy for acute-onset, severe hypertension with preeclampsia or eclampsia (2011).[73]

§From the ESC guidelines on the management of cardiovascular diseases during pregnancy (2011).[70]

Parenteral labetalol may cause neonatal bradycardia and is also thought to be less efficacious in Afro-Caribbean women based on information derived from studies outside pregnancy.[4] Second-line alternatives include labetalol or nicardipine by continuous infusion pump.[73,75] Sodium nitroprusside should be reserved for emergencies after failure of both labetalol and hydralizine and used for short time periods because of cyanide and thiocyanate toxicity and increased intracranial pressure effects with risk of worsening maternal cerebral edema.[2–7,73] Short-acting nifedipine (in capsules containing the liquid form), although proposed as an alternative drug by some scientific societies or groups of experts, has never been approved by the US Food and Drug Administration because of the high and uncontrolled risk of sudden hypoperfusion.[2,76] Care

should be exercised when using nifedipine or any calcium antagonist with magnesium sulfate because of the synergic effects of these drugs.[2,4–7,70] Magnesium sulfate is no longer recommended as an antihypertensive, but it is unanimously considered the drug of choice for the prevention and treatment of eclampsia in all cases of severe preeclampsia (grade A).[2–7,70] BP measurement should be monitored continually in women with severe hypertension.[4] The use of antenatal antihypertensive treatment during labor should be continuous.[4]

Cardiovascular Management in Complicated Preeclampsia

Irrespective of the gestational age, the only definite treatment for women with complicated preeclampsia is delivery of the fetus and placenta after timely stabilization of the patient.[2–7,70] The approach to the patient must be multidisciplinary, involving obstetricians, neonatologists, nephrologists, cardiologists, hematologists, and anesthetists depending on the specific preeclampsia-related complication.[2–7,70]

Pulmonary Edema

Pulmonary edema is the most common cardiopulmonary complication of preeclampsia, which occurs in up to 3% of women, mainly in the peripartum or postpartum stage, and treatment is similar to that used in the nonobstetric patients.[69,70,77,78] In hypertensive pulmonary edema, urgent reduction of critically high BP with an intravenous antihypertensive agent is necessary.[69,70,77,78] The European Society of Cardiology 2011 guidance[70] recommends intravenous nitroglycerine (glyceryl trinitrate) as the first-line choice in treatment for pulmonary edema associated with preeclampsia (Level 1C). An alternative agent, sodium nitroprusside, is recommended in severe heart failure associated with pulmonary edema and critical hypertension (Level 4), but it should be used only with caution and by experienced clinicians.[78] Intravenous furosemide is used to promote venodilation and diuresis (Level 1), whereas intravenous morphine may be given as a venodilator and anxiolytic (Level 1).[69,78] Although most patients will respond to pharmacological intervention, fluid restriction and strict fluid balance should be maintained.[69,70,77,78] Afterload reduction using vasodilators may be necessary especially in the case of LV diastolic dysfunction, and inotropic support should be given in the case of LV systolic dysfunction.[77] The majority of women would be cared for in an intensive care setting with oxygen saturation monitoring and oxygen supplementation used depending on the severity of the respiratory compromise.[7,8,69,70,77] Despite the risks of aspiration, noninvasive ventilation is preferred, because it provides increased inspired oxygen concentration, displaces fluid from the alveoli into the pulmonary circulation, decreases the work of breathing, and decreases the need/risks for tracheal intubation (Level 1).[69,77] Urine output, electrolyte balance, BP, and maternal/fetal heart rate should be closely monitored.[69,77] The woman should be positioned such that the head is elevated and antenatal uterine displacement obtained.[77]

Invasive Hemodynamic Monitoring, Fluid Balance, and Volume Expansion

Some authors recommend the use of invasive hemodynamic monitoring in the management of women with severe preeclampsia to monitor fluid therapy during plasma volume expansion, particularly in managing severe cardiac disease, pulmonary edema refractory to medical therapy, persistent oliguria unresponsive to fluid challenge, and severe hypertension unresponsive to a parental antihypertensive.[79,80] However, there is no clear evidence to support the use of invasive hemodynamic monitoring in severe preeclampsia.[79,80] With increased knowledge of echocardiographic findings in complicated preeclampsia, most women with severe, complicated preeclampsia can be managed without invasive hemodynamic monitoring.[80] There is insufficient evidence to support using pulmonary artery catheters over noninvasive methods of fluid balance management or vice versa.[79] Some observational studies showed that the use of either crystalloid or colloid solutions was associated with transient improvements in maternal cardiovascular status.[4] In contrast, a systematic review and 1 well-conducted study demonstrated no advantage to using plasma volume expansion.[4] Other studies documented that the rate of acute pulmonary edema was increased by a policy of unrestricted intravenous fluid administration (Level 3), and the Confidential Enquiry into Maternal Deaths in the United Kingdom reported 6 deaths from 1994 to 1996 as a result of adult respiratory distress syndrome related to poor fluid management in women with preeclampsia.[4] The National Institute for Clinical Excellence guidelines recommend that volume expansion (fluid loading) should be used only if hydralazine is the antenatal antihypertensive to prevent severe hypotension.[4]

Short-Term Postpartum Cardiovascular Management

Short-term postpartum management of women with preeclampsia is different depending on the severity of the disease and previous use of antihypertensive medications.[2–4] BP is monitored until it is normal after the patient is off treatment and free of symptoms of preeclampsia.[4] Typically, the latter occurs within 5 to 7 days, but some women may need prolonged antihypertensive therapy for 1 to 2 months.[4] In women with preeclampsia who did not need antihypertensive treatment, the latter is started if BP is persistently ≥150/100 mm Hg.[3,4] In women with preeclampsia who required antihypertensive treatment antenatally, the same medication is continued and gradually reduced and then interrupted until BP is normal without medication.[4] Methyldopa is usually stopped within 2 days of delivery, because postpartum use is associated with an increased likelihood of depression.[4,70,71] All women need to have a follow-up care and postnatal medical review 6 to 8 weeks postpartum, and, if the patient still requires antihypertensive medication, a cardiology consultation should be scheduled.[4] Women who had uncomplicated preeclampsia, especially preterm disease, are known to be at higher risk of premature cardiac morbidity and mortality later in life.[60,61] Those women who already experienced preeclampsia-related MACEs are especially at high risk for cardiac events within the subsequent 3 years.[68] It is yet not clear how these women should be followed-up, whether there are any biomarkers to anticipate cardiovascular events, or whether there is any treatment goal that can reduce postpartum MACEs.[68]

The new American Heart Association update on the effectiveness-based guidelines for the prevention of CVD in women includes for the first time the history of preeclampsia in the algorithm for the evaluation of the Framingham cardiovascular

risk score.[15] Importantly, it is recognized that pregnancy, because of its associated cardiovascular and metabolic stress, provides a unique opportunity to evaluate a woman's lifetime cardiovascular risk.[15,81] The development of preeclampsia is seen as a "failed test" and is an important risk factor for CVD in women.[15,81,82] The American Heart Association recommends appropriate referral postpartum by the obstetrician to a primary care physician or cardiologist so that risk factors can be carefully monitored and controlled.[15] Although some studies support the concept that the association of preeclampsia with postpregnancy cardiovascular risk may be primarily attributable to shared prepregnancy risk factors,[83,84] it must be considered that many conventional CVD risk factors are linked with aging and not yet present or routinely screened for in young women.[81] Furthermore, their effects may only become apparent at advanced stages of CVD, when intervention is less efficacious.[81] However, preeclampsia typically occurs in young women and therefore provides a unique opportunity to identify these high-risk women before other conventional cardiovascular risk factors become clinically apparent. A recent large prospective study (n=3416 women) by Fraser et al[81] assessed the associations of pregnancy complications and calculated 10-year CVD risk based on the Framingham score and a wide range of cardiovascular risk factors measured 18 years after pregnancy. Hypertensive disorders of pregnancy were associated with increased body mass index, waist circumference, BP, lipids level, and insulin level.[81] The authors suggest that preeclampsia may be the better predictor of future CVD because it was associated with a wide range of cardiovascular risk factors.[81] Importantly, by identifying pregnancy risk factors that predict subsequent CVD risk factors, the finding of Fraser et al suggest that pregnancy complications can predict CVD risk earlier than conventional CVD risk-screening protocols.[81,82] It remains unknown whether those patients with persistent LV systolic or diastolic function after preeclampsia have a worse long-term outcome than those who remodel favorably after delivery, but community echocardiography studies would suggest that they do.[85,86]

The American Heart Association recommends that clinicians who meet women for the first time should obtain a detailed history of pregnancy complications with details on their severity, gestational age at onset, concomitance of fetal growth restriction, and need for iatrogenic preterm delivery as a consequence of disease severity.[15] Early intervention, such as lifestyle modifications, healthy diet, exercise, regular BP control, and control of metabolic factors, must be recommended after delivery[3,15] and are likely to reduce complications in subsequent pregnancies and long-term cardiovascular risk more effectively than late identification and interventions.[15]

Conclusions

Recent data demonstrate a significant and previously undiscovered cardiovascular burden in pregnancy that is exacerbated if preeclampsia develops. The heart undergoes remodeling in pregnancy with increases in chamber dimensions, LV wall thickness, and mass that is consistent with a process of remodeling/hypertrophy. The likelihood of developing preeclampsia is increased by many maternal demographic and medical characteristics, such as hypertension, obesity, and age, which interestingly are also indicative of increased cardiovascular risk. This finding reinforces the hypothesis that a preexisting tendency to increased cardiovascular risk, particularly hypertension, increases a women's susceptibility to developing preeclampsia. Understanding the extent and severity of cardiovascular changes has brought new insights into the optimal management of women with preeclampsia. It is now also apparent that the postpartum recovery from preeclampsia is compromised by asymptomatic cardiovascular dysfunction. Although it is not yet evident whether preeclampsia causes permanent myocardial damage or whether the women had prepregnancy cardiovascular deficits, the development of preeclampsia represents a unique opportunity to identify women at high risk of long-term CVD before other conventional cardiovascular risk factors become clinically apparent. The optimal management of these women at high risk of long-term cardiovascular morbidity and mortality remains a considerable challenge.

The future research agenda should aim to evaluate the following: (1) the effectiveness of the new approach proposed by the American Heart Association guidelines in early identification of high-risk women; (2) the potential benefits of using new diagnostic strategies, such as conventional echocardiography and tissue Doppler techniques, in additional risk stratification and better delineation of cardiac functional and structural status; (3) the role of preventive intervention in improving clinical outcomes and then reducing the incidence of cardiovascular events or their related morbidity and mortality; and (4) the specific role of preeclampsia in damaging directly the cardiovascular system and therefore independently increasing the baseline cardiovascular risk of the women.

Disclosures

None.

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